ACT #2022 - 289

DEFENDANT'S EXHIBIT 1

SB184

216600-4

By Senators Shelnutt and Allen

RFD: Healthcare

First Read: 03-FEB-22

SB184

ENROLLED, An Act,

Relating to public health; to prohibit the performance of a medical procedure or the prescription of medication, upon or to a minor child, that is intended to alter the minor child's gender or delay puberty; to provide for exceptions; to provide for disclosure of certain information concerning students to parents by schools; and to establish criminal penalties for violations; and in connection therewith would have as its purpose or effect the requirement of a new or increased expenditure of local funds within the meaning of Amendment 621 of the Constitution of Alabama of 1901, as amended by Amendment 890, now appearing as Section 111.05 of the Official Recompilation of the Constitution of Alabama of 1901, as amended.

BE IT ENACTED BY THE LEGISLATURE OF ALABAMA:

Section 1. This act shall be known and may be cited as the Alabama Vulnerable Child Compassion and Protection Act (V-CAP).

Section 2. The Legislature finds and declares the following:

(1) The sex of a person is the biological state of being female or male, based on sex organs, chromosomes, and

endogenous hormone profiles, and is genetically encoded into a person at the moment of conception, and it cannot be changed.

(2) Some individuals, including minors, may experience discordance between their sex and their internal sense of identity, and individuals who experience severe psychological distress as a result of this discordance may be diagnosed with gender dysphoria.

(3) The cause of the individual's impression of discordance between sex and identity is unknown, and the diagnosis is based exclusively on the individual's self-report of feelings and beliefs.

(4) This internal sense of discordance is not permanent or fixed, but to the contrary, numerous studies have shown that a substantial majority of children who experience discordance between their sex and identity will outgrow the discordance once they go through puberty and will eventually have an identity that aligns with their sex.

(5) As a result, taking a wait-and-see approach to children who reveal signs of gender nonconformity results in a large majority of those children resolving to an identity congruent with their sex by late adolescence.

(6) Some in the medical community are aggressively pushing for interventions on minors that medically alter the child's hormonal balance and remove healthy external and

internal sex organs when the child expresses a desire to appear as a sex different from his or her own.

(7) This course of treatment for minors commonly begins with encouraging and assisting the child to socially transition to dressing and presenting as the opposite sex. In the case of prepubertal children, as puberty begins, doctors then administer long-acting GnRH agonist (puberty blockers) that suppress the pubertal development of the child. This use of puberty blockers for gender nonconforming children is experimental and not FDA-approved.

(8) After puberty blockade, the child is later administered "cross-sex" hormonal treatments that induce the development of secondary sex characteristics of the other sex, such as causing the development of breasts and wider hips in male children taking estrogen and greater muscle mass, bone density, body hair, and a deeper voice in female children taking testosterone. Some children are administered these hormones independent of any prior pubertal blockade.

(9) The final phase of treatment is for the individual to undergo cosmetic and other surgical procedures, often to create an appearance similar to that of the opposite sex. These surgical procedures may include a mastectomy to remove a female adolescent's breasts and "bottom surgery" that removes a minor's health reproductive organs and creates an

artificial form aiming to approximate the appearance of the genitals of the opposite sex.

(10) For minors who are placed on puberty blockers that inhibit their bodies from experiencing the natural process of sexual development, the overwhelming majority will continue down a path toward cross-sex hormones and cosmetic surgery.

(11) This unproven, poorly studied series of interventions results in numerous harmful effects for minors, as well as risks of effects simply unknown due to the new and experimental nature of these interventions.

(12) Among the known harms from puberty blockers is diminished bone density; the full effect of puberty blockers on brain development and cognition are yet unknown, though reason for concern is now present. There is no research on the long-term risks to minors of persistent exposure to puberty blockers. With the administration of cross-sex hormones comes increased risks of cardiovascular disease, thromboembolic stroke, asthma, COPD, and cancer.

(13) Puberty blockers prevent gonadal maturation and thus render patients taking these drugs infertile. Introducing cross-sex hormones to children with immature gonads as a direct result of pubertal blockade is expected to cause irreversible sterility. Sterilization is also permanent for those who undergo surgery to remove reproductive organs, and

such persons are likely to suffer through a lifetime of complications from the surgery, infections, and other difficulties requiring yet more medical intervention.

(14) Several studies demonstrate that hormonal and surgical interventions often do not resolve the underlying psychological issues affecting the individual. For example, individuals who undergo cross-sex cosmetic surgical procedures have been found to suffer from elevated mortality rates higher than the general population. They experience significantly higher rates of substance abuse, depression, and psychiatric hospitalizations.

(15) Minors, and often their parents, are unable to comprehend and fully appreciate the risk and life implications, including permanent sterility, that result from the use of puberty blockers, cross-sex hormones, and surgical procedures.

(16) For these reasons, the decision to pursue a course of hormonal and surgical interventions to address a discordance between the individual's sex and sense of identity should not be presented to or determined for minors who are incapable of comprehending the negative implications and life-course difficulties attending to these interventions.

Section 3. For the purposes of this act, the following terms shall have the following meanings:

(1) MINOR. The same meaning as in Section 43-8-1, Code of Alabama 1975.

(2) PERSON. Includes any of the following:

a. Any individual.

b. Any agent, employee, official, or contractor of any legal entity.

c. Any agent, employee, official, or contractor of a school district or the state or any of its political subdivisions or agencies.

(3) SEX. The biological state of being male or female, based on the individual's sex organs, chromosomes, and endogenous hormone profiles.

Section 4. (a) Except as provided in subsection (b), no person shall engage in or cause any of the following practices to be performed upon a minor if the practice is performed for the purpose of attempting to alter the appearance of or affirm the minor's perception of his or her gender or sex, if that appearance or perception is inconsistent with the minor's sex as defined in this act:

(1) Prescribing or administering puberty blocking medication to stop or delay normal puberty.

(2) Prescribing or administering supraphysiologic doses of testosterone or other androgens to females.

(3) Prescribing or administering supraphysiologic doses of estrogen to males.

(4) Performing surgeries that sterilize, including castration, vasectomy, hysterectomy, oophorectomy, orchiectomy, and penectomy.

(5) Performing surgeries that artificially construct tissue with the appearance of genitalia that differs from the individual's sex, including metoidioplasty, phalloplasty, and vaginoplasty.

(6) Removing any healthy or non-diseased body part or tissue, except for a male circumcision.

(b) Subsection (a) does not apply to a procedure undertaken to treat a minor born with a medically verifiable disorder of sex development, including either of the following:

(1) An individual born with external biological sex characteristics that are irresolvably ambiguous, including an individual born with 46 XX chromosomes with virilization, 46 XY chromosomes with under virilization, or having both ovarian and testicular tissue.

(2) An individual whom a physician has otherwise diagnosed with a disorder of sexual development, in which the physician has determined through genetic or biochemical testing that the person does not have normal sex chromosome structure, sex steroid hormone production, or sex steroid hormone action for a male or female.

(c) A violation of this section is a Class C felony.

Section 5. No nurse, counselor, teacher, principal, or other administrative official at a public or private school attended by a minor shall do either of the following:

(1) Encourage or coerce a minor to withhold from the minor's parent or legal guardian the fact that the minor's perception of his or her gender or sex is inconsistent with the minor's sex.

(2) Withhold from a minor's parent or legal guardian information related to a minor's perception that his or her gender or sex is inconsistent with his or her sex.

Section 6. Except as provided for in Section 4, nothing in this act shall be construed as limiting or preventing psychologists, psychological technicians, and master's level licensed mental health professionals from rendering the services for which they are qualified by training or experience involving the application of recognized principles, methods, and procedures of the science and profession of psychology and counseling.

Section 7. Nothing in this section shall be construed to establish a new or separate standard of care for hospitals or physicians and their patients or otherwise modify, amend, or supersede any provision of the Alabama Medical Liability Act of 1987 or the Alabama Medical Liability Act of 1996, or any amendment or judicial interpretation of either act.

Section 8. If any part, section, or subsection of this act or the application thereof to any person or circumstances is held invalid, the invalidity shall not affect parts, sections, subsections, or applications of this act that can be given effect without the invalid part, section, subsection, or application.

Section 9. This act does not affect a right or duty afforded to a licensed pharmacist by state law.

Section 10. Although this bill would have as its purpose or effect the requirement of a new or increased expenditure of local funds, the bill is excluded from further requirements and application under Amendment 621, as amended by Amendment 890, now appearing as Section 111.05 of the Official Recompilation of the Constitution of Alabama of 1901, as amended, because the bill defines a new crime or amends the definition of an existing crime.

Section 11. This act shall become effective 30 days following its passage and approval by the Governor, or its otherwise becoming law.

President and Presiding Officer of the Senate

Speaker of the House of Representatives

SB184

Senate 23-FEB-22

I hereby certify that the within Act originated in and passed the Senate, as amended.

Patrick Harris,
Secretary.

House of Representatives

Passed: 07-APR-22

By: Senator Shelnutt

APPROVED 4-8-2022

TIME 2:10 pm

GOVERNOR

Alabama Secretary Of State

Act Num....: 2022-289
Bill Num...: S-184

Recv'd 04/08/22 02:23pmSLF

SPONSOR

1 Shelnutt

CO-SPONSORS

2 Allen

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I hereby certify that the Resolution as required in Section C of Act No. 81-889 was adopted and is attached to the Bill, SB 184.

yeas 24 nays 4 abstain 0

PATRICK HARRIS,
Secretary

I hereby certify that the notice & proof is attached to the Bill, SB _____ as required in the General Acts of Alabama, 1975 Act No. 919.

PATRICK HARRIS,
Secretary

CONFERENCE COMMITTEE

Senate Conferees _____

_____

_____

DATE: 2-24

RD 1 RFD Judy

REPORT OF STANDING COMMITTEE

This bill having been referred by the House to its standing committee on _____ was acted upon by such committee in session, and returned therefrom to the House with the recommendation that it be Passed, w/amend(s) _____ w/sub _____.

This 2 day of March, 2022.

_____, Chairperson

DATE: 3-2

RF **RD 2**

DATE:

RE-REFERRED ☐ RE-COMMITTED ☐

Committee _____

I hereby certify that the Resolution as required in Section C of Act No. 81-889 was adopted and is attached to the Bill, SB _____.

YEAS _____ **NAYS** _____

JEFF WOODARD,
Clerk

FURTHER HOUSE ACTION (OVER)

DEFENDANT'S EXHIBIT 2

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER, *et al.*,	)	
Plaintiffs,	)	
v.	)	No. 2:22-cv-00184-LCB-SRW
KAY IVEY, in her official capacity as Governor of the State of Alabama, *et al.*,	)	
Defendants.	)	

DECLARATION OF DR. JAMES CANTOR

My name is James Michael Cantor. I am over the age of 19, I am qualified to give this declaration, and, I have personal knowledge of the matters set forth herein.

My CV is attached to this declaration. Recent publications are listed on my CV.

In the past four years, I have provided expert testimony in the following cases:

2022	Hersom & Doe v WVa Health & Human Services	Southern Dist, West Virginia
2022	BPJ v WVa Board of Education	Southern Dist, West Virginia
2021	Cross et al. v Loudoun School Board	Loudoun, Virginia
2021	Allan M. Josephson v Neeli Bendapudi	Western District of Kentucky
2021	Re Commitment of Michael Hughes (Frye Hearing)	Cook County, Illinois
2019	US vs Peter Bright	Southern Dist, NY, NY
2019	Probate and Family Court (Custody Hearing)	Boston, Massachusetts
2019	Re Commitment of Steven Casper (Frye Hearing)	Kendall County, Illinois
2019	Re Commitment of Inger (Frye Hearing)	Poughkeepsie, New York
2018	Re Commitment of Fernando Little (Frye Hearing)	Utica, New York
2018	Canada vs John Fitzpatrick (Sentencing Hearing)	Toronto, Ontario, Canada

I am compensated a the rate of $400 per hour for my work on this matter. My compensation is not dependent upon the substance of my opinions or the outcome of the case.

TABLE OF CONTENTS

I. Introduction

A. Background & Credentials

1. I am a clinical psychologist and Director of the Toronto Sexuality Centre in Canada. For my education and training, I received my Bachelor of Science degree from Rensselaer Polytechnic Institute, where I studied mathematics, physics, and computer science. I received my Master of Arts degree in psychology from Boston University, where I studied neuropsychology. I earned my Doctoral degree in psychology from McGill University, which included successfully defending my doctoral dissertation studying the effects of psychiatric medication and neurochemical changes on sexual behavior, and included a clinical internship assessing and treating people with a wide range of sexual and gender identity issues.

2. Over my academic career, my posts have included Psychologist and Senior Scientist at the Centre for Addiction and Mental Health (CAMH) and Head of Research for CAMH's Sexual Behaviour Clinic, Associate Professor of Psychiatry on the University of Toronto Faculty of Medicine, and Editor-in-Chief of the peer reviewed journal, *Sexual Abuse*. That journal is one of the top-impact, peer-reviewed journals in sexual behavior science and is the official journal of the Association for the Treatment of Sexual Abusers. In that appointment, I was charged to be the final arbiter for impartially deciding which contributions from other scientists in my field merited publication. I believe that appointment indicates not only my extensive experience evaluating scientific claims and methods, but also the faith put in me by the other scientists in my field. I have also served on the Editorial Boards of the *Journal of Sex Research*, the *Archives of Sexual Behavior*, and *Journal of Sexual Aggression*. Thus, although I cannot speak for other scientists, I regularly interact with and am routinely exposed to the views and opinions of most of the scientists active in our field today, within the United States and throughout the world.

3. My scientific expertise spans the biological and non-biological development

of human sexuality, the classification of sexual interest patterns, the assessment and treatment of atypical sexualities, and the application of statistics and research methodology in sex research. I am the author of over 50 peer-reviewed articles in my field, spanning the development of sexual orientation, gender identity, hypersexuality, and atypical sexualities collectively referred to as *paraphilias*. I am the author of the past three editions of the gender identity and atypical sexualities chapter of the *Oxford Textbook of Psychopathology*. These works are now routinely cited in the field and are included in numerous other textbooks of sex research.

4. I began providing clinical services to people with gender dysphoria in 1998. I trained under Dr. Ray Blanchard of CAMH and have participated in the assessment of treatment of over one hundred individuals at various stages of considering and enacting both transition and detransition, including its legal, social, and medical (both cross-hormonal and surgical) aspects. My clinical experience includes the assessment and treatment of several thousand individuals experiencing other atypical sexuality issues. I am regularly called upon to provide objective assessment of the science of human sexuality by the courts (prosecution and defense), professional media, and mental health care providers.

5. I have served as an expert witness in 11 cases in the past five years. These are listed on my *curriculum vitae*, attached here as Appendix 1.

6. A substantial proportion of the existing research on gender dysphoria comes from two clinics, one in Canada and one in the Netherlands. The CAMH gender clinic (previously, Clarke Institute of Psychiatry) was in operation for several decades, and its research was directed by Dr. Kenneth Zucker. I was employed by CAMH between 1998 and 2018. I was a member of the hospital's adult forensic program. However, I was in regular contact with members of the CAMH child psychiatry program (of which Dr. Zucker was a member), and we collaborated on multiple projects.

7. For my work in this case, I am being compensated at the hourly rate of $400

per hour. My compensation does not change based on the conclusions and opinions that I provide here or later in this case or on the outcome of this lawsuit.

B. Overview

8. The principal opinions that I offer and explain in detail in this report include that:

a. A ban on medical transition services for youth under age 18 is consistent with international standards;

b. The large majority of gender dysphoric, pre-pubescent youth cease to feel gender dysphoric by puberty;

c. Among youth under age 18, follow-up studies show positive results in association with psychotherapy, not medically aided transition; and

d. Follow-up studies of medical transition have shown positive results only in samples of adults ages 18 and older.

9. To prepare the present report, I reviewed the following resources related to this litigation:

a. Text of Alabama Bill SB-184;

b. Memorandum in support of plaintiffs' motion for temporary restraining order & preliminary injunction;

c. Declaration of Linda A. Hawkins, Ph.D., LPC in support of plaintiffs' motion for temporary restraining order & preliminary injunction;

d. Declaration of Morissa J. Ladinsky, MD, FAAP, in support of plaintiffs' motion for temporary restraining order & preliminary injunction;

e. Declaration of Stephen Rosenthal, MD, in support of plaintiffs' motion for temporary restraining order & preliminary injunction.

II. Fact-Check of Assertions of Plaintiffs' Experts' Reports

10. I have reviewed the memorandum supporting the plaintiffs' motion, including its declarations by Drs. Hawkins, Ladinsky, and Rosenthal, and compared

its claims with the published, peer-reviewed scientific literature of gender dysphoria, its treatment and outcomes. The motion and all three experts asserted very many very bold claims, but vanishingly little citation of any objective science at all. Of the many hundred relevant, peer-reviewed research articles on this topic, Dr. Hawkins cited three, Dr. Ladinsky cited none at all, and Dr. Rosenthal cited eight, four of which were from the same research team, also cited by Dr. Hawkins. As demonstrated in the following, that small set of articles represents a highly cherry-picked misrepresentation of the relevant body of science, failing to reflect the consensus of the research literature. Their declarations not only fail to reflect the consensus of the science, but also repeatedly assert claims in direct opposition to that science. A comprehensive summary of the research literature on gender dysphoria is provided herein.

A. Professional and International Standards of Care

11. The claims expressed in the plaintiffs' documents largely rely on their claims of professional standards, citing the American Association of Pediatrics (AAP), the World Professional Association for Transgender Health (WPATH), and the Endocrine Society. In so doing, the plaintiffs provided only misleading half-truths, yielding only an incomplete and inaccurate portrayal of the field. Missing from the plaintiffs documentation were that these that these standards have repeatedly been found to be wanting, that their application has failed to produce improvement among patients, and that it is these U.S.-based associations that are out of line with the international consensus of health care experts.

12. First, the plaintiffs' documentation misrepresents the contents of the associations' policies themselves. With the broad exception of the AAP, their statements repeatedly noted instead that:

- Desistance of gender dysphoria occurs in the majority of prepubescent children.

- Mental health issues need to be assessed as potentially contributing factors and need to be addressed before transition.
- Puberty-blocking medication is an experimental, not a routine, treatment.
- Social transition is not generally recommended until after puberty.

Although some other associations have published broad statements of moral support for sexual minorities and against discrimination, they did not include any specific standards or guidelines regarding medical- or transition-related care.

13. Second, the WPATH and the Endocrine Society guidelines have both been subjected to standardized evaluation, the Appraisal of Guidelines for Research and Evaluation ("AGREE II") method, as part of an appraisal of all published CPGs regarding sex and gender minority healthcare.[1] Utilizing community stakeholders to set domain priorities for the evaluation, the assessment concluded that the guidelines regarding HIV and its prevention were of high quality, but that "[t]ransition-related CPGs tended to lack methodological rigour and rely on patchier, lower-quality primary research."[2] Neither the Endocrine Society's or WPATH's guidelines were recommended for use. Indeed, the WPATH guidelines received unanimous ratings of "Do not recommend."[3] Thus, despite the exuberant adjectives offered in the plaintiffs' experts' reports, objective analysis yields the opposite conclusion.

14. The AAP differed from the other (U.S.-based) associations in outlining far less conservative clinical decision-making, but only in contradiction with the published research. Immediately following the publication of the AAP policy, I conducted a point-by-point fact-check of the claims it asserted and the references it cited in support. I submitted that to the *Journal of Sex & Marital Therapy*, a well-known research journal of my field, where it underwent blind peer review and was published. I append that article as part of this report. *See* Appendix 1. A great deal of published attention ensued; however, the AAP has yet to respond to the errors I

[1] Dahlen, *et al.*, 2021.
[2] Dahlen, *et al.*, 2021, at 6.
[3] Dahlen, *et al.*, 2021, at 7.

demonstrated its policy contained. Writing for *The Economist* about the use of puberty blockers, Helen Joyce asked AAP directly, "Has the AAP responded to Dr Cantor? If not, have you any response now?" The AAP Media Relations Manager, Lisa Black, responded: "We do not have anyone available for comment."

15. Finally, the opinions of these U.S.-based associations are in stark opposition to international standards: Public healthcare systems throughout the world have instead been withdrawing their earlier support for childhood transition, responding to the increasingly recognized risks associated with hormonal interventions and the now clear lack of evidence that medical transition was benefitting most children, as opposed to the mental health counseling accompanying transition. These have included the United Kingdom[4], Finland,[5] Sweden[6], and France[7].

B. Claims attributed to Olson and Durwood, *et al.*

16. The Hawkins and Rosenthal reports both cited Olson, *et al.* (2016), claiming it to demonstrate that transition reduce risk of mental illness. That claim entirely misrepresents, indeed reverses, the state of the scientific literature. Although Olson, *et al.* (2016) did indeed report that gender dysphoric children showed no mental health differences from the non-transgender control groups, that report turned out to be incorrect: Not pointed out by Drs Hawkins or Rosenthal is that the Olson data were subsequently subjected to a re-analysis and that, after correcting for statistical errors in the original analysis, the data instead showed that the gender dysphoric children under Olson's care *did,* in fact, exhibit significantly lower mental health[8].

17. I conducted an electronic search of the research literature to identify any

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4 U.K. National Institute for Health and Care Excellence, 2020.
5 Council for Choices in Health Care in Finland, 2020.
6 Swedish National Board of Health and Welfare, 2022.
7 Académie Nationale de Médecine, 2022, Feb. 25.
8 Schumm & Crawford, 2020; Schumm, *et al.,* 2019.

responses from the Olson team regarding the Schumm and Crawford re-analysis of the Olson data and was not able to locate any. I contacted Professor Schumm by email on August 22, 2021 to verify that conclusion, to which he wrote there has been: "No response [from Olson]"[9].

18. Rosenthal also cited a retrospective study from the Olson team, published as Durwood et al., 2017. That study surveyed children in the TransYouth Project—people who have socially transitioned, their families, and any contacts they had, by word of mouth. This method is referred to as "convenience sampling," and differs from genuinely representative samples in applying to means of ensuring study participants accurately represent the population being studied. There were three groups of children for comparison: (i) children who had already socially transitioned, (ii) their siblings, and (iii) children in a university database of families interested in participating in child development research. As noted by the study authors, "For the first time, this article reports on socially transitioned gender children's mental health as reported by the children."[10] Reports from parents were also recorded.[11] In contrast, no reports or ratings were provided by any mental health care professional or researcher at all. That is, although adding self-assessments to the professional assessments might indeed provide novel insights, this project did not add self-assessment to professional assessment. Rather, it replaced professional assessment with self-assessment. Moreover, as already noted, Olson's data did not show what the Olson team claimed.[12] The dataset was subsequently re-analyzed, and "[T]o the contrary, the transgender children, even when supported by their parents, had significantly lower average scores on anxiety and self-worth."[13]

19. It is well established in the field of psychology that participant self-

9 Schumm, email communication, Aug. 22, 2021 (on file with author).
10 Durwood, *et al.*, 2017, at 121 (italics added).
11 *See* Olson, *et al.*, 2016.
12 Schumm, *et al.,* 2019.
13 Schumm & Crawford, 2020, p. 9

assessment can be severely unreliable for multiple reasons. For example, one well-known phenomenon in psychological research is known as "socially desirable responding"—the tendency of subjects to give answers that they believe will make themselves look good, rather than accurate answers. Specifically, subjects' reports that they are enjoying good mental health and functioning well could reflect the subjects' desire to be *perceived* as healthy and as having made good choices, rather than reflecting their actual mental health.

20. In their analyses, the study reported finding no significant differences between the transgender children, their non-transgender siblings, or the community controls. As the authors noted, "[t]hese findings are in striking contrast to previous work with gender-nonconforming children who had not socially transitioned, which found very high rates of depression and anxiety."[14] The authors are correct to note that their result contrasts with the previous research, but they do not discuss that this could reflect a problem with the novel research design they used: The subjective self-reports of the children and their parents' reports may not be reflecting reality objectively, as careful professional researchers would. Because the study did not employ any method to detect and control for participants indulging in "socially desirable responding" or acting under other biasing motivations, this possibility cannot be assessed or ruled out.

21. Because this was a single-time study relying on self-reporting, rather than a before-and-after transition study relying on professional evaluation, it is not possible to know if the children reported as well-functioning are in fact well-functioning, nor if so whether they are well-functioning because they were permitted to transition, or whether instead the fact is that they were already well-functioning and therefore permitted to transition. Finally, because the TransYouth project lacks a prospective design, it cannot be known how many cases attempted transition,

[14] Durwood, *et al.*, 2017, at 116.

reacted poorly, and then detransitioned, thus never having entered into the study in the first place.

C. Claims attributed to de Vries, et al.

22. Drs. Hawkins and Rosenthal both cited de Vries, *et al.* (2014) to support their assertion that medical transition of minors improved their mental health. It is not possible for one to come to that conclusion from that study, however. The clinic treating these children (the originators of "The Dutch Protocol"[15]) provides psychotherapy together with medical services. In research science, this situation is called a "confound." It is not possible to distinguish whether any changes were due to the medical services, the psychotherapy, or an interaction between them. Nonetheless, another study, left uncited by the plaintiff's experts, demonstrated that improvements in mental health are associated with receiving psychotherapy rather than medical services. As detailed later in this report, Costa*, et al.,* (2015) conducted a follow-up study of youth in the U.K., one group receiving only psychotherapy, and one group first receiving only psychotherapy and then receiving both psychotherapy and medical services. Both groups improved, and the group receiving medical services failed to show significant differences from the group who received only psychotherapy throughout.

D. Claims attributed to Spack.

23. Dr. Rosenthal also misrepresented the views of Dr. Norman Spack. The article Rosenthal cited—Spack, 2012—repeatedly emphasized that children with gender dysphoria exhibit very many symptoms of mental illnesses. Spack asserted unambiguously that "Gender dysphoric children who do not receive *counseling* have a high risk of behavioural and emotional problems and psychiatric diagnoses"[16]. Dr. Rosenthal's context misrepresents Spack so as to suggest Spack was advocating for

[15] de Vries*, et al.,* 2011.
[16] Spack, *et al.,* 2012, at 422, italics added.

medical transition to treat the gender dysphoria rather than counseling to treat suicidality and any other mental health issues. Moreover still, missing from the Rosenthal report was Spack's conclusion that "[m]ental health intervention should persist for the long term, even after surgery, *as patients continue to be at mental health risk, including for suicide.* While the causes of suicide are multifactorial, the possibility cannot be ruled out that some patients unrealistically believe that surgery(ies) solves their psychological distress."[17] Whereas Rosenthal (selectively) cited Spack to support the insinuation that medical transition relieves distress, Spack instead explicitly warned against drawing exactly that conclusion.

E. Other claims

24. Rosenthal cited Green*, et al.,* (2021) and Turban*, et al.* (2021) to assert that "hormone therapy usage is significantly related to lower rates of depression and suicidality" [Rosenthal, paragraph 45]. In coming to that conclusion, Dr. Rosenthal violates a well-known principal of science: Correlation does not imply causation. That is, this very pattern is what one would predict from clinical gate-keeping: Mental health constitute exclusion criteria by clinical guidelines. Thus, samples of those receiving hormone therapy would necessarily have passed that criterion, whereas the non-medical group would contain those with already identifiable mental health concerns.

25. The plaintiff's experts indicated medical services to alleviate mental health distress; however, people with gender dysphoria continue to experience those mental health symptoms even transition, including a 19 times greater risk of death from suicide.[18] It is this consistent finding in the research literature conclusion that yielded clinical guidelines repeatedly to indicate that mental health issues should be resolved *before* any transition.

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[17] Spack, 2013, at 484, italics added
[18] Dhejne, *et al.*, 2011.

III. Science of Gender Dysphoria and Transsexualism

26. One of the most widespread public misunderstandings about transsexualism and people with gender dysphoria is that all cases of gender dysphoria represent the same phenomenon; however, the clinical science has long and consistently demonstrated that gender dysphoric children (cases of *early-onset* gender dysphoria) do not represent the same phenomenon as adult gender dysphoria (cases of *late-onset* gender dysphoria),[19] merely attending clinics at younger ages. That is, gender dysphoric children are not simply younger versions of gender dysphoric adults. They differ in every known regard, from sexual interest patterns, to responses to treatments. A third presentation has recently become increasingly observed among people presenting to gender clinics: These cases appear to have an onset in adolescence in the absence of any childhood history of gender dysphoria. Such cases have been called adolescent-onset or "rapid-onset" gender dysphoria (ROGD).

27. In the context of the present proceedings, the adult-onset phenomenon would not seem relevant; however, very many public misunderstandings and expert misstatements come from misattributing evidence or personal experience from one of these types to the other. For example, there exist only very few cases of transition regret among *adult* transitioners, whereas the research has unanimously shown that the majority of children with gender dysphoria desist—that is, they cease to experience such dysphoria by or during puberty. A brief summary of the adult-onset phenomenon is therefore included here to facilitate distinguishing features which are unique to each type of gender dysphoria.

A. Adult-Onset Gender Dysphoria

28. People with adult-onset gender dysphoria typically attend clinics requesting transition services in mid-adulthood, usually in their 30s or 40s. Such individuals are nearly exclusively male.[20] They typically report being sexually

[19] Blanchard, 1985.
[20] Blanchard, 1990, 1991.

attracted to women and sometimes to both men and women. Some cases profess asexuality, but very few indicate any sexual interest in or behavior involving men.[21] Cases of adult-onset gender dysphoria are typically associated with a sexual interest pattern (medically, a *paraphilia*) involving themselves in female form.[22]

1. Outcome Studies of Transition in Adult-Onset Gender Dysphoria

29. Clinical research facilities studying gender dysphoria have repeatedly reported low rates of regret (less than 3%) among adult-onset patients who underwent complete transition (*i.e.*, social, plus hormonal, plus surgical transition). This has been widely reported by clinics in Canada,[23] Sweden,[24] and the Netherlands.[25]

30. Importantly, each of the Canadian, Swedish, and Dutch clinics for adults with gender dysphoria all performed "gate-keeping" procedures, disqualifying from medical services people with mental health or other contraindications. One would not expect the same results to emerge in the absence of such gate-keeping or when gate-keepers apply only minimal standards or cursory assessment.

2. Mental Health Issues in Adult-Onset Gender Dysphoria

31. The research evidence on mental health issues in gender dysphoria indicates it to be different between adult-onset versus adolescent-onset versus prepubescent-onset types. The co-occurrence of mental illness with gender dysphoria in adults is widely recognized and widely documented.[26] A research team in 2016 published a comprehensive and systematic review of all studies examining rates of mental health issues in transgender adults.[27] There were 38 studies in total. The review indicated that many studies were methodologically weak, but nonetheless

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21 Blanchard, 1988.
22 Blanchard 1989a, 1989b, 1991.
23 Blanchard, *et al.*, 1989.
24 Dhejneberg, *et al.*, 2014.
25 Wiepjes, *et al.*, 2018.
26 *See, e.g.*, Hepp, *et al.*, 2005.
27 Dhejne, *et al.*, 2016.

demonstrated (1) that rates of mental health issues among people are highly elevated both before and after transition, (2) but that rates were less elevated among those who completed transition. Analyses were not conducted in a way so as to compare the elevation in mental health issues observed among people newly attending clinics to improvement after transition. Also, several studies showed more than 40% of patients becoming "lost to follow-up." With attrition rates that high, it is unclear to what extent the information from the available participants genuinely reflects the whole sample. The very high rate of "lost to follow-up" leaves open the possibility of considerably more negative results overall.

32. An important caution applies to interpreting these results: These very high proportions of mental health issues come from people who are attending a clinic for the first time and are undergoing assessment. Clinics serving a "gate-keeper" role divert candidates with mental health issues away from medical intervention. The side-effect of removing these people from the samples of transitioners is that if a researcher compared the average mental health of individuals coming into the clinic with the average mental health of individuals going through medical transition, then the post-transition group would appear to show a substantial improvement, even though transition had *no effect at all*: The removal of people with poorer mental health created the statistical illusion of improvement among the remaining people.

33. The long-standing and consistent finding that gender dysphoric adults have high rates of mental health issues both before and after transition and the finding that those mental health issues cause the gender dysphoria (the epiphenomenon) rather than the other way around indicate a critical point: To the extent that gender dysphoric children resemble adults, we should not expect mental health to improve as a result of transition. Mental health issues should be resolved before any transition.

B. Childhood Onset (Pre-Puberty) Gender Dysphoria

1. Prospective Studies of Childhood-Onset Gender Dysphoria Show that Most Children Desist in the "Natural Course" by Puberty

34. The large majority of childhood onset cases of gender dysphoria occur in biological males, with clinics reporting 2–6 biological male children to each female.[28]

35. Prepubescent children (and their parents) have been approaching mental health professionals for help with their unhappiness with their sex and belief they would be happier living as the other for many decades. Projects following-up and reporting on such cases began being published in the 1970s, with subsequent generations of research employing increasingly sophisticated methods studying the outcomes of increasingly large samples. In total, there have now been 11 such outcomes studies, listed as Appendix 2.

36. In sum, despite coming from a variety of countries, conducted by a variety of labs, using a variety of methods, all spanning four decades, every study without exception has come to the identical conclusion: Among prepubescent children who feel gender dysphoric, the majority cease to want to be the other gender over the course of puberty—ranging from 61–88% desistance across the large, prospective studies. Such cases are often referred to as "desisters," whereas children who continue to feel gender dysphoria are often called "persisters."

37. Notably, in most cases, these children were receiving professional psychosocial support across the study period aimed not at affirming cross-gender identification, but at resolving stressors and issues potentially interfering with desistance. While beneficial to these children and their families, the inclusion of therapy in the study protocol represents a complication for the interpretation of the results: That is, it is not possible to know to what extent the observed outcomes (predominant desistance, with a small but consistent occurrence of persistence) were

[28] Cohen-Kettenis, *et al.*, 2003; Steensma, *et al.,* 2018; Wood, *et al.*, 2013.

influenced by the psychosocial support, or would have emerged regardless. It can be concluded only that prepubescent children who suffer gender dysphoria and receive psychosocial support focused on issues other than "affirmation" of cross-gender identification do in fact desist in suffering from gender dysphoria, at high rates, over the course of puberty.

38. While the absolute number of those who present as prepubescent children with gender dysphoria and "persist" through adolescence is very small in relation to the total population, persistence in some subjects was observed in each of these studies. Thus, the clinician cannot take either outcome for granted.

39. It is because of this long-established and invariably consistent research finding that desistance is probable, but not inevitable, that the "watchful waiting" method became the standard approach for assisting gender dysphoric children. The balance of potential risks to potential benefits is very different for groups likely to desist versus groups unlikely to desist: If a child is very likely to persist, then taking on the risks of medical transition might be more worthwhile than if that child is very likely to desist in transgender feelings.

40. The consistent observation of high rates of desistance among pre-pubertal children who present with gender dysphoria demonstrates a pivotally important—yet often overlooked—feature: because gender dysphoria so often desists on its own, clinical researchers cannot assume that therapeutic intervention cannot facilitate or speed desistance for at least some patients. Such is an empirical question, and there has not yet been any such study.

41. It is also important to note that research has not yet identified any reliable procedure for discerning which children who present with gender dysphoria will persist, as against the majority who will desist, absent transition and "affirmation." Such a method would be valuable, as the more accurately that potential persisters can be distinguished from desisters, the better the risks and benefits of options can

be weighted. Such "risk prediction" and behavioral "test construction" are standard components of applied statistics in the behavioral sciences. Multiple research teams have reported that, on average, groups of persisters are somewhat more gender non-conforming than desisters, but not so different as to usefully predict the course of a particular child.[29]

42. In contrast, a single research team (the aforementioned Olson group) claimed the opposite, asserting that they developed a method of distinguishing persisters from desisters, using a single composite score representing a combination of children's "peer preference, toy preference, clothing preference, gender similarity, and gender identity."[30] The reported a statistical association (mathematically equivalent to a correlation) between that composite score and the probability of persistence. As they indicated, "Our model predicted that a child with a gender-nonconformity score of .50 would have roughly a .30 probability . . . of socially transitioning. By contrast, a child with gender-nonconformity score of .75 would have roughly a .48 probability."[31] Although the Olson team declared that "social transitions may be predictable from gender identification and preferences,"[32] their actual results suggest the opposite: The gender-nonconforming group who went on to transition (socially) had a mean composite score of .73 (which is less than .75), and the gender-nonconforming group who did not transition had a mean composite score of .61, also less than .75.[33] Both of those are lower than the value of .75, so both of those would be more likely than not to desist, rather than to proceed to transition. That is, Olson's model does not distinguish likely from unlikely to transition; rather, it distinguishes unlikely from even less likely to transition.

43. Although it remains possible for some future finding to yield a method to

[29] Singh, *et al.* (2021); Steensma *et al.*, 2013.
[30] Rae, *et al.*, 2019, at 671.
[31] Rae, *et al.*, 2019, at 673.
[32] Rae, *et al.*, 2019, at 669.
[33] Rae, *et al.*, 2019, Supplemental Material at 6, Table S1, bottom line.

identify with sufficient accuracy which gender dysphoric children will persist, there does not exist such a method at the present time. Moreover, in the absence of long-term follow-up, it cannot be known what proportions come to regret having transitioned and then *de*transition. Because only a minority of gender dysphoric children persist in feeling gender dysphoric in the first place, "transition-on-demand" increases the probably of unnecessary transition and unnecessary medical risks.

2. "Watchful Waiting" and "The Dutch Approach"

44. It was this state of the science—that the majority of prepubescent children will desist in their feelings of gender dysphoria and that we lack an accurate method of identifying which children will persist—that led to the development of a clinical approach, often called "The Dutch Approach" (referring to The Netherlands clinic where it was developed) including "Watchful Waiting" periods. Internationally, the Dutch Approach is currently the most widely respected and utilized method for treatment of children who present with gender dysphoria.

45. The purpose of these methods was to compromise the conflicting needs among: clients' desires upon assessment, the long-established and repeated observation that those preferences will change in the majority of (but not all) childhood cases, and that cosmetic aspects of medical transition are perceived to be better when they occur earlier rather than later.

46. The Dutch Approach (also called the "Dutch Protocol") was developed over many years by the Netherlands' child gender identity clinic, incorporating the accumulating findings from their own research as well as those reported by other clinics working with gender dysphoric children. They summarized and explicated the approach in their peer-reviewed report, *Clinical management of gender dysphoria in children and adolescents: The Dutch Approach* (de Vries & Cohen-Kettenis, 2012). The components of the Dutch Approach are:

- no social transition at all considered before age 12 (watchful waiting

period),

- no puberty blockers considered before age 12,
- cross-sex hormones considered only after age 16, and
- resolution of mental health issues before any transition.

47. For youth under age 12, "the general recommendation is watchful waiting and carefully observing how gender dysphoria develops in the first stages of puberty."[34]

48. The age cut-offs of the Dutch Approach authors were not based on any research demonstrating their superiority over other potential age cut-off's. Rather, they were chosen to correspond to ages of consent to medical procedures under Dutch law. But whatever their original rationale, the data from this clinic simply contains no information about safety or efficacy of these measures at younger ages.

49. The authors of the Dutch Approach repeatedly and consistently emphasize the need for extensive mental health assessment, including clinical interviews, formal psychological testing with validated psychometric instruments, and multiple sessions with the child and the child's parents.

50. Within the Dutch approach, there is no social transition before age twelve. That is, social affirmation of the new gender may not begin until age 12—as desistance is less likely to occur past that age. "Watchful Waiting" refers to a child's developmental period up to that age. Watchful waiting does not mean do nothing but passively observe the child. Such children and families typically present with substantial distress involving both gender and non-gender issues. It is during the watchful waiting period that a child (and other family members as appropriate) would undergo therapy, resolving other issues which may be exacerbating psychological stress or dysphoria. As noted by the Dutch clinic, "[T]he adolescents in this study received extensive family or other social support . . . [and they] were all regularly seen by one of the clinic's psychologists or psychiatrists."[35] One is actively treating

[34] de Vries & Cohen-Kettenis, 2012, at 301.
[35] de Vries, *et al.*, 2011, at 2280-81.

the person, while carefully "watching" the dysphoria.

51. The inclusion of psychotherapy and support during the watchful waiting period is, clinically, a great benefit to the gender dysphoric children and their parents. The inclusion of psychotherapy and support poses a scientific complication, however: It becomes difficult to know to what extent the outcomes of these cases might be related to receiving psychotherapy received versus being "spontaneous" desistance, which would have occurred on its own anyway. This situation is referred to in science as a "confound."

3. Studies of Transition Outcomes: Overview

52. Very many strong claims have appeared in the media and on social media asserting that transition results in improved mental health or, contradictorily, in decreased mental health. In the highly politicized context of gender and transgender research, many authors have cited only the findings which appear to support one side, cherry-picking from the complete set of research reports. Seemingly contradictory findings are common in science with on-going research projects. When considered together, however, the full set of relevant reports show that a coherent pattern and conclusion has emerged over time, as detailed in the following sections. Initial optimism was suggested by reports of improvements in mental health.[36] Upon continued analysis, these seeming successes turned out to be illusory, however: The Bränström and Pachankis (2019) finding has been retracted.[37] The greater mental health among transitioners reported by Costa, *et al.* (2015) was noted to be because the control group consisted of cases excluded from hormone eligibility exactly because they showed poor mental health to begin with.[38] The improvements reported by the de Vries studies from the Dutch Clinic themselves appear genuine; however, because that clinic also provides psychotherapy to all cases receiving puberty-blockers, it

[36] Bränström & Pachankis 2019; Costa, *et al.*, 2015; de Vries, *et al.*, 2011; de Vries, *et al.*, 2014.
[37] Kalin, 2020.
[38] Biggs, 2019.

remains entirely plausible that the psychotherapy and not the puberty blockers caused the improvements.[39] New studies continue to appear an accelerating rate, repeatedly reporting deteriorations or lacks of improvement in mental health[40] or lack of improvement beyond psychotherapy alone,[41] and other studies continue to report on only the combined effect of both psychotherapy and hormone treatment together.[42]

a. Outcomes of The Dutch Approach (studies from before 2017): Mix of positive, negative, and neutral outcomes

53. The research confirms that some, but not all, adolescents improve on some, but not all, indicators of mental health and that those indicators are inconsistent across studies. Thus, the balance of potential benefits to potential risks differs across cases, and thus suggests different courses of treatment across cases.

54. The Dutch clinical research team followed up 70 youth undergoing puberty suppression at their clinic.[43] The youth improved on several variables upon follow-up as compared to pre-suppression measurement, including depressive symptoms and general functioning. No changes were detected in feelings of anxiety or anger or in gender dysphoria as a result of puberty suppression; however, natal females using puberty suppression suffered *increased* body dissatisfaction both with their secondary sex characteristics and with nonsexual characteristics.[44]

55. As the report authors noted, while it is possible that the improvement on some variables was due to the puberty-blockers, it is also possible that the improvement was due to the mental health support, and it is possible that the improvement occurred only on its own with natural maturation. So any conclusion that puberty blockers improved the mental health of the treated children is not

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39 Biggs, 2020.
40 Carmichael, *et al.*, 2021; Hisle-Gorman, *et al.*, 2021; Kaltiala, *et al.*, 2020.
41 Achille, *et al.*, 2020.
42 Kuper, *et al.*, 2020; van der Miesen, *et al.*, 2020, at 703.
43 de Vries, *et al.* 2011.
44 Biggs, 2020.

justified by the data. Because this study did not include a control group (another group of adolescents matching the first group, but *not* receiving medical or social support), these possibilities cannot be distinguished from each other, representing a confound. The authors of the study were explicit in noting this themselves: "All these factors may have contributed to the psychological well-being of these gender dysphoric adolescents."[45]

56. The authors were careful not to overstate the implications of their results, "We *cautiously* conclude that puberty suppression *may be* a valuable *element* in clinical management of adolescent gender dysphoria."[46]

57. Costa, *et al.* (2015) reported on preliminary outcomes from the Tavistock and Portman NHS Foundation Trust clinic in the UK. They compared the psychological functioning of one group of youth receiving psychological support with a second group receiving both psychological support as well as puberty blocking medication. Both groups improved in psychological functioning over the course of the study, but no statistically significant differences between the groups was detected at any point.[47] As those authors concluded, "Psychological support and puberty suppression were both associated with an improved global psychosocial functioning in GD adolescence. Both these interventions may be considered effective in the clinical management of psychosocial functioning difficulties in GD adolescence."[48] Because psychological support does not pose the physical health risks that hormonal interventions or surgery does (such as loss of reproductive function), one cannot justify taking on the greater risks of social transition, puberty blockers or surgery without evidence of such treatment producing superior results. Such evidence does not exist.

b. Clinicians and advocates have invoked the Dutch Approach

[45] de Vries, *et al.* 2011, at 2281.
[46] de Vries, *et al.* 2011, at 2282, italics added.
[47] Costa, *et al.*, at 2212 Table 2.
[48] Costa, *et al.*, at 2206.

while departing from its protocols in important ways.

58. The reports of partial success contained in de Vries, *et al.* 2011 called for additional research, both to confirm those results and to search for ways to maximize beneficial results and minimize negative outcomes. Instead, many other clinics and clinicians proceeded on the basis of the positives only, broadened the range of people beyond those represented in the research findings, and removed the protections applied in the procedures that led to those outcomes. Many clinics and individual clinicians have reduced the minimum age for transition to 10 instead of 12. While the Dutch Protocol involves interdisciplinary teams of clinicians, many clinics now rely on a single assessor, in some cases one without adequate professional training in childhood and adolescent mental health. Comprehensive, longitudinal assessments (*e.g.*, one and a half *years*[49]) became approvals after one or two assessment sessions. Validated, objective measures of youths' psychological functioning were replaced with clinicians' subjective (and first) opinions, often reflecting only the clients' own self-report. Systematic recordings of outcomes, so as to allow for detection and correction of clinical deficiencies, were eliminated.

59. Notably, Dr. Thomas Steensma, central researcher of the Dutch clinic, has decried other clinics for "blindly adopting our research" despite the indications that those results may not actually apply: "We don't know whether studies we have done in the past are still applicable to today. Many more children are registering, and also a different type."[50] Steensma opined that "every doctor or psychologist who is involved in transgender care should feel the obligation to do a good pre- and post-test." But few if any are doing so.

c. Studies by other clinicians in other countries have failed to reliably replicate the positive components of the results reported by the Dutch clinicians in de Vries et al. 2011.

60. The indications of potential benefit from puberty suppression in at least

[49] de Vries, *et al.*, 2011.
[50] Tetelepta, 2021.

some cases has led some clinicians to attempt to replicate the positive aspects of those findings. These efforts have not succeeded.

61. The Tavistock and Portman clinic in the U.K. recently released its findings, attempting to replicate the outcomes reported by the Dutch clinic.[51] Study participants were ages 12–15 (Tanner stages 3 for natal males, Tanner 2 for natal females) and were repeatedly tested before beginning puberty-blocking medications and then every six months thereafter. Cases exhibiting serious mental illnesses (*e.g.*, psychosis, bipolar disorder, anorexia nervosa, severe body-dysmorphic disorder unrelated to gender dysphoria) were excluded. Relative to the time point before beginning puberty suppression, there were *no* significant changes in any psychological measure, from either the patients' or their parents' perspective.

62. A multidisciplinary team from Dallas published a prospective follow-up study which included 25 youths as they began puberty suppression.[52] (The other 123 study participants were undergoing cross-sex hormone treatment.) Interventions were administered according to "Endocrine Society Clinical Practice Guidelines."[53] Their analyses found *no statistically significant changes* in the group undergoing puberty suppression on any of the nine measures of wellbeing measured, spanning tests of body satisfaction, depressive symptoms, or anxiety symptoms.[54] (Although the authors reported detecting some improvements, these were only found when the large group undergoing cross-sex hormone treatment were added in.) Although the Dutch Approach includes age 12 as a minimum for puberty suppression treatment, this team provided such treatment beginning at age 9.8 years (full range: 9.8–14.9 years).[55]

63. Achille, *et al.* (2020) at Stony Brook Children's Hospital in New York treated a sample of 95 youth with gender dysphoria, providing follow-up data on 50

[51] Carmichael, *et al.*, 2021.
[52] Kuper, *et al.*, 2020, at 5.
[53] Kuper, *et al.*, 2020, at 3, referring to Hembree, *et al.*, 2017.
[54] Kuper, *et al.*, 2020, at Table 2.
[55] Kuper, *et al.*, 2020, at 4.

of them. (The report did not indicate how these 50 were selected from the 95.) As well as receiving puberty blocking medications, "Most subjects were followed by mental health professionals. Those that were not were encouraged to see a mental health professional."[56] The puberty blockers themselves "were introduced in accordance with the Endocrine Society and the WPATH guidelines."[57] Upon follow-up, some incremental improvements were noted; however, after statistically adjusting for psychiatric medication and engagement in counselling, "*most predictors did not reach statistical significance*."[58] That is, puberty blockers did not improve mental health any more than did mental health care on its own.

64. In a recent update, the Dutch clinic reported continuing to find improvement in transgender adolescents' psychological functioning, reaching age-typical levels, "after the start of specialized transgender care involving puberty suppression."[59] Unfortunately, because the transgender care method of that clinic involves both psychosocial support and puberty suppression, it cannot be known which of those (or their combination) is driving the improvement. Also, the authors indicate that the changing demographic and other features among gender dysphoric youth might have caused the treated group to differ from the control group in unknown ways. As the study authors themselves noted, "The present study can, therefore, not provide evidence about the direct benefits of puberty suppression over time and long-term mental health outcomes."[60]

65. It has not yet been determined why the successful outcomes reported by the Dutch child gender clinic a decade ago failed to emerge when applied by others more recently. It is possible that:

(1) The Dutch Approach itself does *not* work and that their originally successful results were a fluke;

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56 Achille, *et al.*, 2020, at 2.
57 Achille, *et al.*, 2020, at 2.
58 Achille, *et al.*, 2020, at 3 (italics added).
59 van der Miesen, *et al.*, 2020, at 699.
60 van der Miesen, *et al.*, 2020, at 703.

(2) The Dutch Approach *does* work, but only in the Netherlands, with local cultural, genetic, or other unrecognized factors that do not generalize to other countries;

(3) The Dutch Approach itself *does* work, but other clinics and individual clinicians are removing safeguards and adding short-cuts to the approach, and those changes are hampering success.

(4) The Dutch Approach *does* work, but the cause of the improvement is the psychosocial support, rather than any medical intervention, which other clinics are *not* providing.

66. The failure of other clinics to repeat the already very qualified success of the Dutch clinic demonstrates the need for still greater caution before endorsing transition and the greater need to resolve potential mental health obstacles before doing so.

4. Mental Health Issues in Childhood-Onset Gender Dysphoria

67. As shown by the outcomes studies, there is no statistically significant evidence that transition reduces the presence of mental illness among transitioners. As shown repeatedly by clinical guidelines from multiple professional associations, mental health issues are expected or required to be resolved *before* undergoing transition. The reasoning behind these conclusions is that children may be expressing gender dysphoria, not because they are experiencing what gender dysphoric adults report, but because they mistake what their experiences indicate or to what they might lead. For example, a child experiencing depression from social isolation might develop hope—and the unrealistic expectation—that transition will help them fit in, this time as and with the other sex.

68. If a child undergoes transition, discovering only then that their mental health or social situations will not in fact change, the medical risks and side-effects (such as sterilization) will have been borne for no reason. If, however, a child resolves the mental health issues first with the gender dysphoria resolving with it (which the research literature shows to be the case in the large majority), then the child need not undergo transition at all, but yet still retains the opportunity to do so later.

69. Elevated rates of multiple mental health issues among gender dysphoric

children are reported throughout the research literature. A formal analysis of children (ages 4–11) undergoing assessment at the Dutch child gender clinic showed 52% fulfilled criteria for a DSM axis-I disorder.[61] A comparison of the children attending the Canadian versus Dutch child gender dysphoria clinic showed only few differences between them, but a large proportion in both groups were diagnosable with clinically significant mental health issues. Results of standard assessment instruments (Child Behavior Check List, or CBCL) demonstrated that the average score was in the clinical rather than healthy range, among children in both clinics.[62] When expressed as percentages, among 6–11-year-olds, 61.7% of the Canadian and 62.1% of the Dutch sample were in the clinical range.

70. A systematic, comprehensive review of all studies of Autism Spectrum Disorders (ASDs) and Attention-Deficit Hyperactivity Disorder (ADHD) among children diagnosed with gender dysphoria was recently conducted. It was able to identify a total of 22 studies examining the prevalence of ASD or ADHD I youth with gender dysphoria. Studies reviewing medical records of children and adolescents referred to gender clinics showed 5–26% to have been diagnosed with ASD.[63] Moreover, those authors gave specific caution on the "considerable overlap between symptoms of ASD and symptoms of gender variance, exemplified by the subthreshold group which may display symptoms which could be interpreted as either ASD or gender variance. Overlap between symptoms of ASD and symptoms of GD may well confound results."[64] When two or more issues are present at the same time (in this case, gender dysphoria present at the same time as ADHD or ASD), researchers cannot distinguish when a result is associated with or caused by the issue of interest (gender dysphoria itself) or one of the side issues, called *confounds* (ADHD or ASD,

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61 Wallien, *et al.*, 2007.
62 Cohen-Kettenis, *et al.*, 2003, at 46.
63 Thrower, *et al.*, 2020.
64 Thrower, *et al.*, 2020, at 703.

in the present case).[65] The rate of ADHD among children with GD was 8.3–11%. Conversely, in data from children (ages 6–18) with Autism Spectrum Disorders (ASDs) show they are more than seven times more likely to have parent-reported "gender variance."[66]

C. Adolescent-Onset Gender Dysphoria

1. Features of Adolescent-Onset Gender Dysphoria

71. In the social media age, a third profile has recently begun to present to clinicians or socially, characteristically distinct from the previously identified ones.[67] Unlike adult-onset gender dysphoria and unlike childhood-onset, this group is predominately biologically female. This group first presents in adolescence, but lacks the history of cross-gender behavior in childhood like the childhood-onset cases have. It is this feature which led to the term Rapid Onset Gender Dysphoria (ROGD).[68] The majority of cases appear to occur within clusters of peers and in association with increased social media use[69] and especially among people with autism or other neurodevelopmental or mental health issues.[70]

72. It cannot be easily determined whether the self-reported gender dysphoria is a result of other underlying issues or if those mental health issues are the result of the stresses of being a sexual minority, as some writers are quick to assume.[71] (The science of the *Minority Stress Hypothesis* appears in its own section.) Importantly, and unlike other presentations of gender dysphoria, people with rapid-onset gender dysphoria often (47.2%) experienced *declines* rather than improvements in mental health when they publicly acknowledged their gender status.[72] Although long-term outcomes have not yet been reported, these distinctions demonstrate that one cannot

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65 Cohen-Kettenis *et al.,* 2003, at 51; Skelly *et al.,* 2012.
66 Janssen, *et al.*, 2016.
67 Kaltiala-Heino, *et al.*, 2015; Littman, 2018.
68 Littman, 2018.
69 Littman, 2018.
70 Kaltiala-Heino, *et al.*, 2015; Littman, 2018; Warrier, *et al.*, 2020.
71 Boivin, *et al.*, 2020.
72 Biggs, 2020; Littman, 2018.

apply findings from the other types of gender dysphoria to this type. That is, in the absence of evidence, researchers cannot assume that the pattern found in childhood-onset or adult-onset gender dysphoria also applies to rapid-onset (aka adolescent-onset) gender dysphoria. The group differences already observed argue against the conclusion that any given feature would be present, in general, throughout all types of gender dysphoria.

2. Prospective Studies of Social Transition and Puberty Blockers in Adolescence

73. There do not yet exist prospective outcomes studies either for social transition or for medical interventions for people whose gender dysphoria began in adolescence. That is, instead of taking a sample of individuals and following them forward over time (thus permitting researchers to account for people dropping out of the study, people misremembering the order of events, etc.), all studies have thus far been *retrospective*. It is not possible for such studies to identify what factors caused what outcomes. No study has yet been organized in such a way as to allow for an analysis of the adolescent-onset group, as distinct from childhood-onset or adult-onset cases. Many of the newer clinics (not the original clinics which systematically tracked and reported on their cases' results) fail to distinguish between people who had childhood-onset gender dysphoria and have aged into adolescence and people whose onset was not until adolescence. Similarly, there are clinics failing to distinguish people who had adolescent-onset gender dysphoria and aged into adulthood from adult-onset gender dysphoria. Studies selecting groups according to their current age instead of their ages of onset can produce only confounded results, representing unclear mixes according to how many of each type of case wound up in the final sample.

3. Mental Illness in Adolescent-Onset Gender Dysphoria

74. In 2019, a Special Section of the *Archives of Sexual Behavior* was published:

"Clinical Approaches to Adolescents with Gender Dysphoria." It included this brief yet thorough summary of rates of mental health issues among adolescents expressing gender dysphoria by Dr. Aron Janssen of the Department of Child and Adolescent Psychiatry of New York University:[73] The literature varies in the range of percentages of adolescents with co-occurring disorders. The range for depressive symptoms ranges was 6–42%,[74] with suicide attempts ranging 10 to 45%.[75] Self-injurious thoughts and behaviors range 14–39%.[76] Anxiety disorders and disruptive behavior difficulties including Attention Deficit/Hyperactivity Disorder are also prevalent.[77] Gender dysphoria also overlaps with Autism Spectrum Disorder.[78]

75. Of particular concern in the context of adolescent onset gender dysphoria is *Borderline Personality Disorder* (BPD). The DSM-5-TR criteria for BPD are[79]:

> A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:
>
> 1. Frantic efforts to avoid real or imagined abandonment. (Note: Do not include suicidal or self-mutilating behaviour covered in Criterion 5.)
> 2. A pattern of unstable and intense interpersonal relationship characterized by alternating between extremes of idealization and devaluation.
> 3. *Identity disturbance: markedly and persistently unstable self-image or sense of self.*
> 4. Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating). (Note: Do not include suicidal or self-mutilating behavior covered in Criterion 5.)
> 5. *Recurrent suicidal behaviour, gestures, or threats, or self-mutilating behavior.*
> 6. Affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days).

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73 Janssen, *et al.*, 2019.
74 Holt, *et al.*, 2016; Skagerberg, *et al.*, 2013; Wallien, *et al.*, 2007.
75 Reisner, *et al.,* 2015.
76 Holt, *et al.*, 2016; Skagerberg, *et al.*, 2013.
77 de Vries, *et al.*, 2011; Mustanski, *et al.*, 2010; Wallien, *et al.*, 2007.
78 de Vries, *et al.*, 2010; Jacobs, *et al.*, 2014; Janssen, *et al.*, 2016; May, *et al.*, 2016; Strang, *et al.*, 2014, 2016.
79 American Psychiatric Association, 2022, pp. 752–753, italics added.

7. Chronic feelings of emptiness.
8. Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights).
9. Transient, stress-related paranoid ideation or severe dissociative symptoms.

(Italics added.)

76. It is increasingly hypothesized that very many cases appearing to be adolescent-onset gender dysphoria are actually cases of BPD.[80] That is, some people may be misinterpreting their experiences to represent a gender identity issue, when it instead represents the "identity disturbance" noted in symptom Criterion 3. Like adolescent-onset gender dysphoria, BPD begins to manifest in adolescence, is substantially more common among biological females than males, and occurs in 2–3% of the population, rather than 1-in-5,000 people (*i.e.*, 0.02%). Thus, if even only a portion of people with BPD had an 'identity disturbance' that focused on gender identity and were mistaken for transgender, they could easily overwhelm the number of genuine cases of gender dysphoria.

77. A primary cause for concern is symptom Criterion 5: recurrent suicidality. Regarding the provision of mental health care, this is a crucial distinction: A person with BPD going undiagnosed will not receive the appropriate treatments (the currently most effective of which is Dialectical Behavior Therapy). A person with a cross-gender identity would be expected to feel relief from medical transition, but someone with BPD would not: The problem was not about *gender* identity, but about having an *unstable* identity. Moreover, after a failure of medical transition to provide relief, one would predict for these people increased levels of hopelessness and increased risk of suicidality. One would predict also that misdiagnoses would occur more often if one reflexively dismissed or discounted symptoms of BPD as responses to "minority stress." The Minority Stress Hypothesis is discussed in its own section

[80] *E.g.*, Anzani, *et al.,* 2020; Zucker, 2019.

herein.

78. Regarding research, there have now been several attempts to document rates of suicidality among gender dysphoric adolescents (reviewed in its own section herein). The scientific concern presented by BPD is that it poses a potential confound: samples of gender dysphoric adolescents could appear to have elevated rates of suicidality, not because of the gender dysphoria (or transphobia in society), but because of the number of people with BPD in the sample.

IV. Other Scientific Claims Assessed

A. Conversion Therapy

79. Activists and social media increasingly, but erroneously, apply the term "conversion therapy" moving farther and farther from what the research has reported. "Conversion therapy" (or "reparative therapy" and other names) was the attempt to change a person's sexual orientation; however, with the public more frequently accustomed to "LGB" being expanded to "LGBTQ+", the claims relevant only to sexual orientation are being misapplied to gender identity. The research has repeatedly demonstrated that once one explicitly acknowledges being gay or lesbian, this is only very rarely are mistaken. That is entirely unlike gender identity, wherein the great majority of children who declare cross-gender identity cease to do so by puberty, as shown unanimously by every follow-up study ever published. As the field grows increasingly polarized, any therapy failing to provide affirmation-on-demand is mislabeled "conversion therapy."[81] Indeed, even actions of non-therapists, unrelated to any therapy have been labelled conversion therapy, including the prohibition of biological males competing on female teams.[82]

B. Assessing Claims of Suicidality

80. In the absence of scientific evidence associating improvement with

[81] D'Angelo, *et al.,* 2021.
[82] Turban, 2021, March 16.

transition among youth, demands for transition are increasingly accompanied by hyperbolic warnings of suicide should there be delay or obstacle to affirmation-on-demand. Social media circulate claims of extreme suicidality accompanied by declarations that "I'd rather have a trans daughter than a dead son." Such claims convey only grossly misleading misrepresentations of the research literature, however.

81. Despite that the media treat them as near synonyms, suicide and suicidality are distinct phenomena. They represent different behaviors with different motivations, with different mental health issues, and with differing clinical needs. *Suicide* refers to completed suicides and the sincere intent to die. It is substantially associated with impulsivity, using more lethal means, and being a biological male.[83] *Suicidality* refers to parasuicidal behaviors, including suicidal ideation, threats, and gestures. These typically represent cries for help rather than an intent to die and are more common among biological females. Suicidal threats can indicate any of many problems or represent emotional blackmail, as typified in "If you leave me, I will kill myself." Professing suicidality is also used for attention- seeking or for the support or sympathy it evokes from others, indicating distress much more frequently than an intent to die.

82. The scientific study of suicide is inextricably linked to that of mental illness. For example, as noted in the preceding, suicidality is a well-documented symptom of Borderline Personality Disorder (as are chronic identity issues), and personality disorders are highly elevated among transgender populations, especially adolescent-onset. Thus, the elevations of suicidality among gender dysphoric adolescents may not be a result of anything related to transition (or lack of transition), but to the overlap with mental illness of which suicidality is a substantial part. Conversely,

[83] Freeman, *et al.,* 2017.

improvements in suicidality reported in some studies may not be the result of anything related to transition, but rather to the concurrent general mental health support which is reported by the clinical reported prospective outcomes. Studies that include more than one factor at the same time without accounting for each other represent a "confound," and it cannot be known which factor (or both) is the one causing the effects observed. That is, when a study provides both mental health services and medical transition services at the same time, it cannot be known which (or both) is what caused any changes.

83. A primary criterion for readiness for transition used by the clinics demonstrating successful transition is the absence or resolution of other mental health concerns, such as suicidality. In the popular media, however, indications of mental health concerns are instead often dismissed as an expectable result caused by Sexual Minority Stress (SMS). It is generally implied that such symptoms will resolve upon transition and integration into an affirming environment.

84. Despite that mental health issues, including suicidality, are repeatedly required by clinical standards of care to be resolved before transition, threats of suicide are instead oftentimes used as the very justification for labelling transition a 'medical necessity'. However plausible it might seem that failing to affirm transition causes suicidality, the epidemiological evidence indicates that hypothesis to be incorrect: Suicide rates remains elevated even after complete transition, as shown by a comprehensive review of 17 studies of suicidality in gender dysphoria.[84]

85. Of particular relevance in the present context is suicidality as a well-documented symptom of Borderline Personality Disorder (BPD) and that very many cases appearing to be adolescent-onset gender dysphoria actually represent cases of BPD. [See full DSM-5-TR criteria already listed herein.] That is, some people may be

[84] McNeil, *et al.,* 2017.

misinterpreting their experiencing of the broader "identity disturbance" of symptom Criterion 3 to represent a gender identity issue specifically. Like adolescent-onset gender dysphoria, BPD begins to manifest in adolescence and occurs in 2–3% of the population, rather than 1-in-5,000 people. (Thus, if even only a portion of people with BPD experienced an identity disturbance that focused on gender identity and were mistaken for transgender, they could easily overwhelm the number of genuine cases of gender dysphoria.)

86. Rates of completed suicide are elevated among post-transition transsexuals, but are nonetheless rare,[85] and BPD is repeatedly documented to be greatly elevated among sexual minorities[86]. Overall, rates of suicidal ideation and suicidal attempts appear to be related—not to transition status—but to the social support received: The research evidence shows that support decreases suicidality, but that transition itself does not. Indeed, in some situations, social support was associated with increased suicide attempts, suggesting the reported suicidality may represent attempts to evoke more support.[87]

C. Assessing Demands for Social Transition and Affirmation-Only or Affirmation-on-Demand Treatment in Pre-Pubertal Children.

87. Colloquially, affirmation refers broadly to any actions that treat the person as belonging to a new gender. In different contexts, that could apply to social actions (use of a new name and pronouns), legal actions (changes to birth certificates), or medical actions (hormonal and surgical interventions). That is, social transition, legal transition, and medical transition (and subparts thereof) need not, and rarely do, occur at the same time. In practice, there are cases in which a child has socially only partially transitioned, such as presenting as one gender at home and another at school or presenting as one gender with one custodial parent and another gender with

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85 Wiepjes, *et al.,* 2020.
86 Reuter, *et al.,* 2016; Rodriguez-Seiljas, *et al.,* 2021; Zanarni, *et al.,* 2021.
87 Bauer, *et al*., 2015; Canetto, et al., 2021.

the other parent.

88. Referring to "affirmation" as a treatment approach is ambiguous: Although often used in public discourse to take advantage of the positive connotations of the term, it obfuscates what exactly is being affirmed. This often leads to confusion, such as quoting a study of the benefits and risks of social affirmation in a discussion of medical affirmation, where the appearance of the isolated word "affirmation" refers to entirely different actions.

89. It is also an error to divide treatment approaches into affirmative versus non-affirmative. As noted already, the widely adopted Dutch Approach (and the guidelines of the multiple professional associations based on it) cannot be said to be either: It is a staged set of interventions, wherein social transition (and puberty blocking) may not begin until age 12 and cross-sex hormonal and other medical interventions, later.

90. Formal clinical approaches to helping children expressing gender dysphoria employ a gate-keeper model, with decision trees to help clinicians decide when and if the potential benefits of affirmation of the new gender would outweigh the potential risks of doing so. Because the gate-keepers and decision-trees generally include the possibility of affirmation in at least some cases, it is misleading to refer to any one approach as "the affirmation approach." The most extreme decision-tree would be accurately called affirmation-*on-demand,* involving little or no opportunity for children to explore at all whether the distress they feel is due to some other, less obvious, factor, whereas more moderate gate-keeping would endorse transition only in select situations, when the likelihood of regretting transition is minimized.

91. Many outcomes studies have been published examining the results of gate-keeper models, but no such studies have been published regarding affirmation-on-demand with children. Although there have been claims that affirmation-on-demand causes mental health or other improvement, these have been the result only of

"retrospective" rather than "prospective" studies. That is, such studies did not take a sample of children and follow them up over time, to see how many dropped out altogether, how many transitioned successfully, and how many transitioned and regretted it or detransitioned. Rather, such studies took a sample of successfully transitioned adults and asked them retrospective questions about their past. In such studies, it is not possible to know how many other people dropped out or regretted transition, and it is not possible to infer causality from any of the correlations detected, despite authors implying and inferring causality.

D. Assessing the "Minority Stress Hypothesis"

92. The elevated levels of mental health problems among lesbian, gay, and bisexual populations is a well-documented phenomenon, and the idea that it is caused by living within a socially hostile environment is called the *Minority Stress Hypothesis*.[88] The association is not entirely straight-forward, however. For example, although lesbian, gay, and bisexual populations are more vulnerable to suicide ideation overall, the evidence specifically on adult lesbian and bisexual women is unclear. Meyer did not include transgender populations in originating the hypothesis, and it remains a legitimate question to what extent and in what ways it might apply to gender identity.

93. Minority stress is associated, in large part, with being a visible minority. There is little evidence that transgender populations show the patterns suggested by the hypothesis. For example, the minority stress hypothesis would predict differences according to how visibly a person is discernable as a member of the minority, which often changes greatly upon transition. Biological males who are very effeminate stand out throughout childhood, but in some cases can successfully blend in as adult females; whereas the adult-onset transitioners blend in very much as heterosexual cis-gendered males during their youth and begin visibly to stand out in adulthood,

[88] Meyer, 2003.

only for the first time.

94. Also suggesting minority stress cannot be the full story is that the mental health symptoms associated with minority stress do not entirely correspond with those associated with gender dysphoria. The primary symptoms associated with minority stress are depressive symptoms, substance use, and suicidal ideation.[89] The symptoms associated with gender dysphoria indeed include depressive symptoms and suicidal ideation, but also include anxiety symptoms, Autism Spectrum Disorders, and personality disorders.

V. Assessing Statements from Professional Associations

A. Understanding the Value of Statements from Professional Associations

95. The value of position statements from professional associations should be neither over- nor under-estimated. In the ideal, an organization of licensed health care professionals would convene a panel of experts who would systematically collect all the available evidence about an issue, synthesizing it into recommendations or enforceable standards for clinical care, according to the quality of the evidence for each alternative. For politically neutral issues, with relevant expertise contained among association members, this ideal can be readily achievable. For controversial issues with no clear consensus, the optimal statement would summarize each perspective and explicate the strengths and weaknesses of each, providing relatively reserved recommendations and suggestions for future research that might resolve the continuing questions. Several obstacles can hinder that goal, however. Committees within professional organizations are typically volunteer activities, subject to the same internal politics of all human social structures. That is, committee members are not necessarily committees of experts on a topic—they are often committees of generalists handling a wide variety of issues or members of an interest group who

[89] Meyer, 2003.

feel strongly about political implications of an issue, instead of scientists engaged in the objective study of the topic.

96. Thus, documents from professional associations may represent required standards, the violation of which may merit sanctions, or may represent only recommendations or guidelines. A document may represent the views of an association's full membership or only of the committee's members (or majorities thereof). Documents may be based on systematic, comprehensive reviews of the available research or selected portions of the research. In sum, the weight best placed on any association's statement is the amount by which that association employed evidence versus other considerations in its process.

B. Misrepresentations of statements of professional associations.

97. In the presently highly politicized context, official statements of professional associations have been widely misrepresented. In preparing the present report, I searched the professional research literature for documentation of statements from these bodies and from my own files, for which I have been collecting such information for many years. I was able to identify statements from six such organizations. Although not strictly a medical association, the World Professional Association for Transgender Health (WPATH) also distributed a set of guidelines in wide use and on which other organizations' guidelines are based.

98. Notably, despite that all these medical associations reiterate the need for mental health issues to be resolved before engaging in medical transition, only the AACAP members have medical training in mental health. The other medical specialties include clinical participation with this population, but their assistance in transition generally assumes the mental health aspects have already been assessed and treated beforehand.

1. World Professional Association for Transgender Health (WPATH)

99. The WPATH standards as they relate to prepubescent children begin with the acknowledgement of the known rates of desistance among gender dysphoric children:

> [I]n follow-up studies of prepubertal children (mainly boys) who were referred to clinics for assessment of gender dysphoria, the dysphoria persisted into adulthood for only 6–23% of children (Cohen-Kettenis, 2001; Zucker & Bradley, 1995). Boys in these studies were more likely to identify as gay in adulthood than as transgender (Green, 1987; Money & Russo, 1979; Zucker & Bradley, 1995; Zuger, 1984). Newer studies, also including girls, showed a 12–27% persistence rate of gender dysphoria into adulthood (Drummond, Bradley, Peterson-Badali, & Zucker, 2008; Wallien & Cohen-Kettenis, 2008).[90]

100. That is, "In most children, gender dysphoria will disappear before, or early in, puberty."[91]

101. Although WPATH does not refer to puberty blocking medications as "experimental," the document indicates the non-routine, or at least inconsistent availability of the treatment:

> Among adolescents who are referred to gender identity clinics, the number considered eligible for early medical treatment—starting with GnRH analogues to suppress puberty in the first Tanner stages—differs among countries and centers. Not all clinics offer puberty suppression. If such treatment is offered, the pubertal stage at which adolescents are allowed to start varies from Tanner stage 2 to stage 4 (Delemarre, van de Waal & Cohen-Kettenis, 2006; Zucker et al., [2012]).[92]

102. WPATH neither endorses nor proscribes social transitions before puberty, instead recognizing the diversity among families' decisions:

> Social transitions in early childhood do occur within some families with early success. This is a controversial issue, and divergent views are held by health professionals. The current evidence base is insufficient to predict the long-term outcomes of completing a gender role transition during early childhood.[93]

103. It does caution, however, "Relevant in this respect are the previously described relatively low persistence rates of childhood gender dysphoria."[94]

2. Endocrine Society (ES)

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90 Coleman, *et al.*, 2012, at 172.
91 Coleman, *et al.*, 2012, at 173.
92 Coleman, *et al.*, 2012, at 173.
93 Coleman, *et al.*, 2012, at 176.
94 Coleman, *et al.*, 2012, at 176 (quoting Drummond, *et al.*, 2008; Wallien & Cohen-Kettenis, 2008).

104. The 150,000-member Endocrine Society appointed a nine-member task force, plus a methodologist and a medical writer, who commissioned two systematic reviews of the research literature and, in 2017, published an update of their 2009 recommendations, based on the best available evidence identified. The guideline was co-sponsored by the American Association of Clinical Endocrinologists, American Society of Andrology, European Society for Paediatric Endocrinology, European Society of Endocrinology, Pediatric Endocrine Society (PES), and the World Professional Association for Transgender Health (WPATH).

105. The document acknowledged the frequency of desistance among gender dysphoric children:

> Prospective follow-up studies show that childhood GD/gender incongruence does not invariably persist into adolescence and adulthood (so-called "desisters"). Combining all outcome studies to date, the GD/gender incongruence of a minority of prepubertal children appears to persist in adolescence. . . . In adolescence, a significant number of these desisters identify as homosexual or bisexual.[95]

106. The statement similarly acknowledges inability to predict desistance or persistence, "With current knowledge, we cannot predict the psychosexual outcome for any specific child."[96]

107. Although outside their area of professional expertise, mental health issues were also addressed by the Endocrine Society, repeating the need to handle such issues before engaging in transition, "In cases in which severe psychopathology, circumstances, or both seriously interfere with the diagnostic work or make satisfactory treatment unlikely, clinicians should assist the adolescent in managing these other issues."[97] This ordering—to address mental health issues before embarking on transition—avoids relying on the unproven belief that transition will solve such issues.

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[95] Hembree, *et al.*, 2017, at 3876.
[96] Hembree, *et al.*, 2017, at 3876.
[97] Hembree, *et al.*, 2017, at 3877.

108. The Endocrine Society did not endorse any affirmation-only approach. The guidelines were neutral with regard to social transitions before puberty, instead advising that such decisions be made only under clinical supervision: "We advise that decisions regarding the social transition of prepubertal youth are made with the assistance of a mental health professional or similarly experienced professional."[98]

109. The Endocrine Society guidelines make explicit that, after gathering information from adolescent clients seeking medical interventions and their parents, the clinician "provides correct information to prevent unrealistically high expectations [and] assesses whether medical interventions may result in unfavorable psychological and social outcomes."[99]

3. Pediatric Endocrine Society and Endocrine Society (ES/PES)

110. In 2020, the 1500-member Pediatric Endocrine Society partnered with the Endocrine Society to create and endorse a brief, two-page position statement.[100] Although strongly worded, the document provided no specific guidelines, instead deferring to the Endocrine Society guidelines.[101]

111. It is not clear to what extent this endorsement is meaningful, however. According to the PES, the Endocrine Society "recommendations include evidence that treatment of gender dysphoria/gender incongruence is medically necessary and should be covered by insurance."[102] However, the Endocrine Society makes neither statement. Although the two-page PES document mentioned insurance coverage four times, the only mention of health insurance by the Endocrine Society was: "If GnRH analog treatment is not available (insurance denial, prohibitive cost, or other reasons), postpubertal, transgender female adolescents may be treated with an

98 Hembree, *et al.*, 2017, at 3872.
99 Hembree, *et al.*, 2017, at 3877.
100 PES, online; Pediatric Endocrine Society & Endocrine Society, Dec. 2020.
101 Pediatric Endocrine Society & Endocrine Society, Dec. 2020, at 1; Hembree, *et al.*, 2017.
102 Pediatric Endocrine Society & Endocrine Society, Dec. 2020, at 1.

antiandrogen that directly suppresses androgen synthesis or action."[103] Despite the PES asserting it as "medically necessary," the Endocrine Society stopped short of that. Its only use of that phrase was instead limiting: "We recommend that a patient pursue genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically necessary and would benefit the patient's overall health and/or well-being."[104]

4. American Academy of Child & Adolescent Psychiatry (AACAP)

112. The 2012 statement of the American Academy of Child & Adolescent Psychiatry (AACAP) is not an affirmation-only policy. It notes:

> Just as family rejection is associated with problems such as depression, suicidality, and substance abuse in gay youth, the proposed benefits of treatment to eliminate gender discordance in youth must be carefully weighed against such possible deleterious effects. . . . In general, it is desirable to help adolescents who may be experiencing gender distress and dysphoria to defer sex reassignment until adulthood, or at least until the wish to change sex is unequivocal, consistent, and made with appropriate consent.[105]

113. The AACAP's language repeats the description of the use of puberty blockers only as an exception: "For situations in which deferral of sex reassignment decisions until adulthood is *not clinically feasible*, one approach that has been described in case series is sex hormone suppression under endocrinological management with psychiatric consultation using gonadotropin-releasing hormone analogues."[106]

114. The AACAP statement acknowledges the long-term outcomes literature for gender dysphoric children: "In follow-up studies of prepubertal boys with gender discordance—including many without any mental health treatment—the cross gender wishes usually fade over time and do not persist into adulthood,"[107] adding that "[c]linicians should be aware of current evidence on the natural course of gender

[103] Hembree, *et al.* 2017, at 3883.
[104] Hembree, *et al.*, 2017 at 3872, 3894.
[105] Adelson & AACAP, 2012, at 969.
[106] Adelson & AACAP, 2012, at 969 (italics added).
[107] Adelson & AACAP, 2012, at 963.

discordance and associated psychopathology in children and adolescents in choosing the treatment goals and modality."[108]

115. The policy similarly includes a provision for resolving mental health issues: "Gender reassignment services are available in conjunction with mental health services focusing on exploration of gender identity, cross-sex treatment wishes, counseling during such treatment if any, and *treatment of associated mental health problems*."[109] The document also includes minority stress issues and the need to deal with mental health aspects of minority status (*e.g.*, bullying).[110]

116. Rather than endorse social transition for prepubertal children, the AACAP indicates: "There is similarly no data at present from controlled studies to guide clinical decisions regarding the risks and benefits of sending gender discordant children to school in their desired gender. Such decisions must be made based on clinical judgment, bearing in mind the potential risks and benefits of doing so."[111]

5. American College of Obstetricians & Gynecologists (ACOG)

117. The American College of Obstetricians & Gynecologists (ACOG) published a "Committee Opinion" expressing recommendations in 2017. The statement indicates it was developed by the ACOG's Committee on Adolescent Health Care, but does not indicate participation based on professional expertise or a systematic method of objectively assessing the existing research. It includes the disclaimer: "This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed."[112]

118. Prepubertal children do not typically have clinical contact with gynecologists, and the ACOG recommendations include that the client additionally

[108] Adelson & AACAP, 2012, at 968.
[109] Adelson & AACAP, 2012, at 970 (italics added).
[110] Adelson & AACAP, 2012, at 969.
[111] Adelson & AACAP, 2012, at 969.
[112] ACOG, 2017, at 1.

have a primary health care provider.[113]

119. The ACOG statement cites the statements made by other medical associations—European Society for Pediatric Endocrinology (ESPE),, PES, and the Endocrine Society—and by WPATH.[114] It does not cite any professional association of *mental* health care providers, however. The ACOG recommendations repeat the previously mentioned eligibility/readiness criteria of having no mental illness that would hamper diagnosis and no medical contraindications to treatment. It notes: "*Before* any treatment is undertaken, the patient must display eligibility and readiness (Table 1), meaning that the adolescent has been evaluated by a mental health professional, has no contraindications to therapy, and displays an understanding of the risks involved."[115]

120. The "Eligibility and Readiness Criteria" also include, "Diagnosis established for gender dysphoria, transgender, transsexualism."[116] This standard, requiring a formal diagnosis, forestalls affirmation-on-demand because self-declared self-identification is not sufficient for DSM diagnosis.

121. ACOG's remaining recommendations pertain only to post-transition, medically oriented concerns. Pre-pubertal social transition is not mentioned in the document, and the outcomes studies of gender dysphoric (prepubescent) children are not cited.

6. American College of Physicians (ACP)

122. The American College of Physicians published a position paper broadly expressing support for the treatment of LGBT patients and their families, including nondiscrimination, antiharassment, and defining "family" by emotional rather than biological or legal relationships in visitation policies, and the inclusion of transgender

[113] ACOG, 2017, at 1.
[114] ACOG, 2017, at 1, 3.
[115] ACOG, 2017, at 1, 3 (citing the Endocrine Society guidelines) (italics added).
[116] ACOG, 2017, at 3 Table 1.

health care services in public and private health benefit plans.[117]

123. ACP did not provide guidelines or standards for child or adult gender transitions. The policy paper opposed attempting "reparative therapy;" however, the paper confabulated sexual orientation with gender identity in doing so. That is, on the one hand, ACP explicitly recognized that "[s]exual orientation and gender identity are inherently different."[118] It based this statement on the fact that "the American Psychological Association conducted a literature review of 83 studies on the efficacy of efforts to change *sexual orientation*."[119] The APA's document, entitled "Report of the American Psychological Task Force on appropriate therapeutic responses to *sexual orientation*" does not include or reference research on gender identity.[120] Despite citing no research about transgenderism, the ACP nonetheless included in its statement: "Available research does not support the use of reparative therapy as an effective method in the treatment of LGB*T* persons."[121] That is, the inclusion of "T" with "LGB" is based on something other than the existing evidence.

124. There is another statement,[122] which was funded by ACP and published in the Annals of Internal Medicine under its "*In the Clinic*" feature, noting that "'In the Clinic' does not necessarily represent official ACP clinical policy."[123] The document discusses medical transition procedures for adults rather than for children, except to note that "[n]o medical intervention is indicated for prepubescent youth,"[124] that a "mental health provider can assist the child and family with identifying an appropriate time for a social transition,"[125] and that the "child should be assessed and managed for coexisting mood disorders during this period because risk for suicide is

117 Daniel & Butkus, 2015a, 2015b.
118 Daniel & Butkus, 2015b, at 2.
119 Daniel & Butkus, 2015b, at 8 (italics added).
120 APA, 2009 (italics added).
121 Daniel & Butkus, 2015b, at 8 (italics added).
122 Safer & Tangpricha, 2019.
123 Safer & Tangpricha, 2019, at ITC1.
124 Safer & Tangpricha, 2019, at ITC9.
125 Safer & Tangpricha, 2019, at ITC9.

higher than in their cisgender peers."[126]

7. American Academy of Pediatrics (AAP)

125. The policy of the American Academy of Pediatrics (AAP) is unique among the major medical associations in being the only one to endorse an affirmation-on-demand policy, including social transition before puberty without any watchful waiting period. Although changes in recommendations can obviously be appropriate in response to new research evidence, the AAP provided none. Rather, the research studies AAP cited in support of its policy simply did not say what AAP claimed they did. In fact, the references that AAP cited as the basis of their policy instead outright contradicted that policy, repeatedly endorsing watchful waiting.[127] Moreover, of all the outcomes research published, the AAP policy cited *one*, and that without mentioning the outcome data it contained.[128].

8. The ESPE-LWPES GnRH Analogs Consensus Conference Group

126. Included in the interest of completeness, there was also a collaborative report in 2009, between the European Society for Pediatric Endocrinology (ESPE) and the Lawson Wilkins Pediatric Endocrine Society (LWPES).[129] Thirty experts were convened, evenly divided between North American and European labs and evenly divided male/female, who comprehensively rated the research literature on gonadotropin-release hormone analogs in children.

127. The effort concluded that "[u]se of gonadotropin-releasing hormone analogs for conditions other than central precocious puberty requires additional investigation and cannot be suggested routinely."[130] However, gender dysphoria was not explicitly mentioned as one of those other conditions.

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126 Safer & Tangpricha, 2019, at ITC9.
127 Cantor, 2020.
128 Cantor, 2020, at 1.
129 Carel et al., 2009.
130 Carel et al. 2009, at 752.

C. International Health Care Consensus

1. United Kingdom

128. The National Health Service (NHS) of the United Kingdom centralizes gender counselling and transitioning services in a single clinic, the Gender Identity Development Service (GIDS) of the Tavistock and Portman NHS Foundation Trust. Between 2008 and 2018, the number of referrals to the clinic had increased by a factor of 40, leading to a government inquiry into the causes[131]. The GIDS was repeatedly accused of over-diagnosing and permitting transition in cases despite indicators against patient transition, including by 35 members of the GIDS staff, who resigned by 2019[132].

129. The NHS appointed Dr. Hilary Cass, former President of the Royal College of Paediatrics and Child Health, to conduct an independent review[133]. That review included a systematic consolidation of all the research evidence, following established procedures for preventing the "cherry-picking" or selective citation favouring or down-playing any one conclusion[134]. The review's results were unambiguous: "The critical outcomes for decision making are the impact on gender dysphoria, mental health and quality of life. The quality of evidence for these outcomes was assessed as very low"[135], again using established procedures for assessing clinical research evidence (called GRADE). The review also assessed as "very low" the quality of evidence regarding "body image, psychosocial impact, engagement with health care services, impact on extent of an satisfaction with surgery and stopping treatment"[136]. The report concluded that of the existing research, "The studies included in this evidence review are all small, uncontrolled observational studies, which are subject to bias and confounding….They suggest little change with GnRH analogues [puberty

131 Marsh, 2020; Rayner, 2018.
132 BBC, 2021; Donnelly, 2019.
133 National Health Service, 2020, Sept. 22.
134 National Institute for Health and Care Excellence, 2020.
135 National Institute for Health and Care Excellence, 2020, p. 4.
136 National Institute for Health and Care Excellence, 2020, p. 5.

blockers] from baseline to follow-up"[137].

2. Finland

130. In Finland, the assessments of mental health and preparedness of minors for transition services are centralized by law into two research clinics, Helsinki University Central Hospital and Tampere University Hospital. The eligibility of minors began in 2011. In 2019, Finnish researchers published an analysis of the outcomes of adolescents diagnosed with transsexualism and receiving cross-sex hormone treatment[138]. That study showed that despite the purpose of medical transition to improve mental health: "Medical gender reassignment is not enough to improve functioning and relieve psychiatric comorbidities among adolescents with gender dysphoria. Appropriate interventions are warranted for psychiatric comorbidities and problems in adolescent development"[139]. The patients who were functioning well after transition were those who were already functioning well before transition, and those who were functioning poorly, continued to function poorly after transition.

131. Consistent with the evidence, Finland's health care service (Council for Choices in Health Care in Finland—COHERE) thus ended the surgical transition of minors, ruling in 2020 that "Surgical treatments are not part of the treatment methods for dysphoria caused by gender-related conflicts in minors" (COHERE, 2020). The review of the research concluded that "[N]o conclusions can be drawn on the stability of gender identity during the period of disorder caused by a psychiatric illness with symptoms that hamper development." COHERE also greatly restricted access to puberty-blocking and other hormonal treatments, indicating they "may be considered if the need for it continues *after* the other psychiatric symptoms have

[137] National Institute for Health and Care Excellence, 2020, p. 13.
[138] Kaltiala et al., 2020.
[139] Kaltiala et al., 2020, p. 213.

ceased and adolescent development is progressing normally"[140]. The council was explicit in noting the lack of research needed for decision-making, "There is also a need for more information on the *disadvantages* of procedures and on people who regret them"[141].

3. Sweden

132. Sweden's national health care policy regarding trans issues has developed quite similarly to that of the UK. Already in place 20 years ago, Swedish health care policy permitted otherwise eligible minors to receive puberty-blockers beginning at age 14 and cross-sex hormones at age 16.) At that time, only small numbers of minors sought medical transition services. An explosion of referrals ensued in 2013–2014. Sweden's Board of Health and Welfare reported that, in 2018, the number of diagnoses of gender dysphoria was 15 times higher than 2008 among girls ages 13–17.

133. Sweden has long been very accepting with regard to sexual and gender diversity. In 2018, a law was proposed to lower the age of eligibility for ?surgical care from age 18 to 15, remove the requirement for parental consent, and lower legal change of gender to age 12. A series of cases of regret and suicide were reported in the Swedish media, leading to questions of mental health professionals failing to consider. In 2019, the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) therefore conducted its own comprehensive review of the research[142]. Like the UK, the Swedish investigation employed methods to ensure the encapsulation of the all the relevant evidence[143].

134. The SBU report came to the same conclusions as the UK commission. From 2022 forward, the Swedish National Board or Health and Welfare therefore

[140] Council for Choices in Health Care in Finland, 2020; italics added.
[141] Council for Choices in Health Care in Finland, 2020; italics added.
[142] Orange, 2020, Feb 22.
[143] Swedish Agency for Health Technology Assessment and Assessment of Social Services, 2019.

"recommends restraint when it comes to hormone treatment…Based on the results that have emerged, the National Board of Health and Welfare's overall conclusion is that the risks of anti-puberty and sex-confirming hormone treatment for those under 18 currently outweigh the possible benefits for the group as a whole"[144]. Neither puberty blockers nor cross-sex hormones would be provided under age 16, and patients ages 16–18 would receive such treatments only within research settings (clinical trials monitored by the appropriate Swedish research ethics board).

4. France

135. In 2022, the Académie Nationale de Médecine of France issued a strongly worded statement, citing the Swedish ban on hormone treatments. "[A] great medical caution must be taken in children and adolescents, given the vulnerability, particularly psychological, of this population and the many undesirable effects, and even serious complications, that some of the available therapies can cause…such as impact on growth, bone fragility, risk of sterility, emotional and intellectual consequences and, for girls, symptoms reminiscent of menopause"[145]. For hormones, the Académie concluded "the greatest reserve is required in their use," and for surgical treatments, "[T]heir irreversible nature must be emphasized." The Académie did not outright ban medical interventions, but warned "the risk of over-diagnosis is real, as shown by the increasing number of transgender young adults wishing to "detransition". Rather than medical interventions, it advised health care providers "to extend as much as possible the psychological support phase." The Académie reviewed and emphasized the evidence indicating the very large and very sudden increase in youth requesting medical transition. It attributed the change, not to society now being more accepting of sexual diversity, but to social media, "underlining the addictive character of excessive consultation of social networks which is both

144 Swedish National Board of Health and Welfare, 2022.
145 Académie Nationale de Médecine, 2022, Feb. 25.

harmful to the psychological development of young people and responsible, for a very important part, of the growing sense of gender incongruence."

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APPENDICES

Appendix 1

Curriculum Vita

Appendix 2

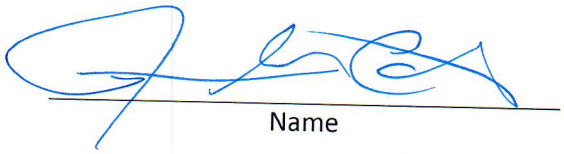
Peer-reviewed article:

Cantor, J. M. (2020). Transgender and gender diverse children and adolescents: Fact-checking of AAP policy. *Journal of Sex & Marital Therapy, 46,* 307–313. doi: 10.1080/0092623X.2019.1698481

Appendix 3

The Outcomes Studies of Childhood-Onset Gender Dysphoria

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct. Executed on 30 April, 2022.



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EDUCATION

Postdoctoral Fellowship Jan., 2000–May, 2004
Centre for Addiction and Mental Health • Toronto, Canada

Doctor of Philosophy Sep., 1993–Jun., 2000
Psychology • McGill University • Montréal, Canada

Master of Arts Sep., 1990–Jan., 1992
Psychology • Boston University • Boston, MA

Bachelor of Science Sep. 1984–Aug., 1988
Interdisciplinary Science • Rensselaer Polytechnic Institute • Troy, NY
Concentrations: Computer science, mathematics, physics

EMPLOYMENT HISTORY

Director Feb., 2017–Present
Toronto Sexuality Centre • Toronto, Canada

Senior Scientist (Inaugural Member) Aug., 2012–May, 2018
Campbell Family Mental Health Research Institute
Centre for Addiction and Mental Health • Toronto, Canada

Senior Scientist Jan., 2012–May, 2018
Complex Mental Illness Program
Centre for Addiction and Mental Health • Toronto, Canada

Head of Research Nov., 2010–Apr. 2014
Sexual Behaviours Clinic
Centre for Addiction and Mental Health • Toronto, Canada

Research Section Head Dec., 2009–Sep. 2012
Law & Mental Health Program
Centre for Addiction and Mental Health • Toronto, Canada

Psychologist May, 2004–Dec., 2011
Law & Mental Health Program
Centre for Addiction and Mental Health • Toronto, Canada

Clinical Psychology Intern Sep., 1998–Aug., 1999
Centre for Addiction and Mental Health • Toronto, Canada

Teaching Assistant Sep., 1993–May, 1998
Department of Psychology
McGill University • Montréal, Canada

Pre-Doctoral Practicum Sep., 1993–Jun., 1997
Sex and Couples Therapy Unit
Royal Victoria Hospital • Montréal, Canada

Pre-Doctoral Practicum May, 1994–Dec., 1994
Department of Psychiatry
Queen Elizabeth Hospital • Montréal, Canada

ACADEMIC APPOINTMENTS

Associate Professor Jul., 2010–May, 2019
Department of Psychiatry
University of Toronto Faculty of Medicine • Toronto, Canada

Adjunct Faculty Aug. 2013–Jun., 2018
Graduate Program in Psychology
York University • Toronto, Canada

Associate Faculty (Hon) Oct., 2017–Dec., 2017
School of Behavioural, Cognitive & Social Science
University of New England • Armidale, Australia

Assistant Professor Jun., 2005–Jun., 2010
Department of Psychiatry
University of Toronto Faculty of Medicine • Toronto, Canada

Adjunct Faculty Sep., 2004–Jun., 2010
Clinical Psychology Residency Program
St. Joseph's Healthcare • Hamilton, Canada

PUBLICATIONS

1. Cantor, J. M. (2020). Transgender and gender diverse children and adolescents: Fact-checking of AAP policy. *Journal of Sex & Marital Therapy, 46,* 307–313. doi: 10.1080/0092623X.2019.1698481
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PUBLICATIONS

LETTERS AND COMMENTARIES

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9. Cantor, J. M. (2011). New MRI studies support the Blanchard typology of male-to-female transsexualism [Letter to the Editor]. *Archives of Sexual Behavior, 40*, 863–864. doi: 10.1007/s10508-011-9805-6
10. Zucker, K. J., Bradley, S. J., Own-Anderson, A., Kibblewhite, S. J., & Cantor, J. M. (2008). Is gender identity disorder in adolescents coming out of the closet? *Journal of Sex and Marital Therapy, 34,* 287–290.
11. Cantor, J. M. (2003, Summer). Review of the book *The Man Who Would Be Queen* by J. Michael Bailey. *Newsletter of Division 44 of the American Psychological Association, 19*(2), 6.
12. Cantor, J. M. (2003, Spring). What are the hot topics in LGBT research in psychology? *Newsletter of Division 44 of the American Psychological Association, 19*(1), 21–24.
13. Cantor, J. M. (2002, Fall). Male homosexuality, science, and pedophilia. *Newsletter of Division 44 of the American Psychological Association, 18*(3), 5–8.
14. Cantor, J. M. (2000). Review of the book *Sexual Addiction: An Integrated Approach. Journal of Sex and Marital Therapy, 26*, 107–109.

EDITORIALS

1. Cantor, J. M. (2012). Editorial. *Sexual Abuse: A Journal of Research and Treatment, 24*.

2. Cantor, J. M. (2011). Editorial note. *Sexual Abuse: A Journal of Research and Treatment, 23,* 414.
3. Barbaree, H. E., & Cantor, J. M. (2010). Performance indicates for *Sexual Abuse: A Journal of Research and Treatment* (SAJRT) [Editorial]. *Sexual Abuse: A Journal of Research and Treatment, 22,* 371–373.
4. Barbaree, H. E., & Cantor, J. M. (2009). *Sexual Abuse: A Journal of Research and Treatment* performance indicators for 2007 [Editorial]. *Sexual Abuse: A Journal of Research and Treatment, 21,* 3–5.
5. Zucker, K. J., & Cantor, J. M. (2009). Cruising: Impact factor data [Editorial]. *Archives of Sexual Research, 38,* 878–882.
6. Barbaree, H. E., & Cantor, J. M. (2008). Performance indicators for *Sexual Abuse: A Journal of Research and Treatment* [Editorial]. *Sexual Abuse: A Journal of Research and Treatment, 20,* 3–4.
7. Zucker, K. J., & Cantor, J. M. (2008). The *Archives* in the era of online first ahead of print[Editorial]. *Archives of Sexual Behavior, 37,* 512–516.
8. Zucker, K. J., & Cantor, J. M. (2006). The impact factor: The *Archives* breaks from the pack [Editorial]. *Archives of Sexual Behavior, 35,* 7–9.
9. Zucker, K. J., & Cantor, J. M. (2005). The impact factor: “Goin’ up” [Editorial]. *Archives of Sexual Behavior, 34,* 7–9.
10. Zucker, K., & Cantor, J. M. (2003). The numbers game: The impact factor and all that jazz [Editorial]. *Archives of Sexual Behavior, 32,* 3–5.

FUNDING HISTORY

Principal Investigators:	Doug VanderLaan, Meng-Chuan Lai
Co-Investigators:	James M. Cantor, Megha Mallar Chakravarty, Nancy Lobaugh, M. Palmert, M. Skorska
Title:	*Brain function and connectomics following sex hormone treatment in adolescents experience gender dysphoria*
Agency:	Canadian Institutes of Health Research (CIHR), Behavioural Sciences-B-2
Funds:	$650,250 / 5 years (July, 2018)
Principal Investigator:	Michael C. Seto
Co-Investigators:	Martin Lalumière , James M. Cantor
Title:	*Are connectivity differences unique to pedophilia?*
Agency:	University Medical Research Fund, Royal Ottawa Hospital
Funds:	$50,000 / 1 year (January, 2018)
Principal Investigator:	Lori Brotto
Co-Investigators:	Anthony Bogaert, James M. Cantor, Gerulf Rieger
Title:	*Investigations into the neural underpinnings and biological correlates of asexuality*
Agency:	Natural Sciences and Engineering Research Council (NSERC), Discovery Grants Program
Funds:	$195,000 / 5 years (April, 2017)
Principal Investigator:	Doug VanderLaan
Co-Investigators:	Jerald Bain, James M. Cantor, Megha Mallar Chakravarty, Sofia Chavez, Nancy Lobaugh, and Kenneth J. Zucker
Title:	*Effects of sex hormone treatment on brain development: A magnetic resonance imaging study of adolescents with gender dysphoria*
Agency:	Canadian Institutes of Health Research (CIHR), Transitional Open Grant Program
Funds:	$952,955 / 5 years (September, 2015)
Principal Investigator:	James M. Cantor
Co-Investigators:	Howard E. Barbaree, Ray Blanchard, Robert Dickey, Todd A. Girard, Phillip E. Klassen, and David J. Mikulis
Title:	*Neuroanatomic features specific to pedophilia*
Agency:	Canadian Institutes of Health Research (CIHR)
Funds:	$1,071,920 / 5 years (October, 2008)
Principal Investigator:	James M. Cantor
Title:	*A preliminary study of fMRI as a diagnostic test of pedophilia*
Agency:	Dean of Medicine New Faculty Grant Competition, Univ. of Toronto
Funds:	$10,000 (July, 2008)

Principal Investigator:	James M. Cantor
Co-Investigator:	Ray Blanchard
Title:	*Morphological and neuropsychological correlates of pedophilia*
Agency:	Canadian Institutes of Health Research (CIHR)
Funds:	$196,902 / 3 years (April, 2006)

KEYNOTE AND INVITED ADDRESSES

1. Cantor, J. M. (2021, September 28). *No topic too tough for this expert panel: A year in review.* Plenary Session for the 40th Annual Research and Treatment Conference, Association for the Treatment of Sexual Abusers.
2. Cantor, J. M. (2019, May 1). *Introduction and Q&A for 'I, Pedophile.'* StopSO 2nd Annual Conference, London, UK.
3. Cantor, J. M. (2018, August 29). *Neurobiology of pedophilia or paraphilia? Towards a 'Grand Unified Theory' of sexual interests.* Keynote address to the International Association for the Treatment of Sexual Offenders, Vilnius, Lithuania.
4. Cantor, J. M. (2018, August 29). *Pedophilia and the brain: Three questions asked and answered.* Preconference training presented to the International Association for the Treatment of Sexual Offenders, Vilnius, Lithuania.
5. Cantor, J. M. (2018, April 13). *The responses to* I, Pedophile *from We, the people.* Keynote address to the Minnesota Association for the Treatment of Sexual Abusers, Minneapolis, Minnesota.
6. Cantor, J. M. (2018, April 11). *Studying atypical sexualities: From vanilla to* I, Pedophile. Full day workshop at the Minnesota Association for the Treatment of Sexual Abusers, Minneapolis, Minnesota.
7. Cantor, J. M. (2018, January 20). *How much sex is enough for a happy life?* Invited lecture to the University of Toronto Division of Urology Men's Health Summit, Toronto, Canada.
8. Cantor, J. M. (2017, November 2). Pedophilia as a phenomenon of the brain: Update of evidence and the public response. Invited presentation to the 7th annual SBC education event, Centre for Addiction and Mental Health, Toronto, Canada.
9. Cantor, J. M. (2017, June 9). Pedophilia being in the brain: The evidence and the public's reaction. Invited presentation to *SEXposium at the ROM: The science of love and sex,* Toronto, Canada.
10. Cantor, J. M., & Campea, M. (2017, April 20). *"I, Pedophile" showing and discussion.* Invited presentation to the 42nd annual meeting of the Society for Sex Therapy and Research, Montréal, Canada.
11. Cantor, J. M. (2017, March 1). *Functional and structural neuroimaging of pedophilia: Consistencies across methods and modalities.* Invited lecture to the Brain Imaging Centre, Royal Ottawa Hospital, Ottawa, Canada.
12. Cantor, J. M. (2017, January 26). *Pedophilia being in the brain: The evidence and the public reaction.* Inaugural keynote address to the University of Toronto Sexuality Interest Network, Toronto, Ontario, Canada.
13. Cantor, J. M. (2016, October 14). *Discussion of CBC's "I, Pedophile."* Office of the Children's Lawyer Educational Session, Toronto, Ontario, Canada.
14. Cantor, J. M. (2016, September 15). *Evaluating the risk to reoffend: What we know and what we don't.* Invited lecture to the Association of Ontario Judges, Ontario Court of Justice Annual Family Law Program, Blue Mountains, Ontario, Canada. [Private link only: https://vimeo.com/239131108/3387c80652]
15. Cantor, J. M. (2016, April 8). *Pedophilia and the brain: Conclusions from the second generation of research.* Invited lecture at the 10th annual Risk and Recovery Forensic Conference, Hamilton, Ontario.

16. Cantor, J. M. (2016, April 7). *Hypersexuality without the hyperbole.* Keynote address to the 10th annual Risk and Recovery Forensic Conference, Hamilton, Ontario.
17. Cantor, J. M. (2015, November). *No one asks to be sexually attracted to children: Living in Daniel's World.* Grand Rounds, Centre for Addiction and Mental Health. Toronto, Canada.
18. Cantor, J. M. (2015, August). *Hypersexuality: Getting past whether "it" is or "it" isn't.* Invited address at the 41st annual meeting of the International Academy of Sex Research. Toronto, Canada.
19. Cantor, J. M. (2015, July). *A unified theory of typical and atypical sexual interest in men: Paraphilia, hypersexuality, asexuality, and vanilla as outcomes of a single, dual opponent process.* Invited presentation to the 2015 Puzzles of Sexual Orientation conference, Lethbridge, AL, Canada.
20. Cantor, J. M. (2015, June). *Hypersexuality.* Keynote Address to the Ontario Problem Gambling Provincial Forum. Toronto, Canada.
21. Cantor, J. M. (2015, May). *Assessment of pedophilia: Past, present, future.* Keynote Address to the International Symposium on Neural Mechanisms Underlying Pedophilia and Child Sexual Abuse (NeMUP). Berlin, Germany.
22. Cantor, J. M. (2015, March). *Prevention of sexual abuse by tackling the biggest stigma of them all: Making sex therapy available to pedophiles.* Keynote address to the 40th annual meeting of the Society for Sex Therapy and Research, Boston, MA.
23. Cantor, J. M. (2015, March. *Pedophilia: Predisposition or perversion?* Panel discussion at Columbia University School of Journalism. New York, NY.
24. Cantor, J. M. (2015, February). *Hypersexuality.* Research Day Grand Rounds presentation to Ontario Shores Centre for Mental Health Sciences, Whitby, Ontario, Canada.
25. Cantor, J. M. (2015, January). *Brain research and pedophilia: What it means for assessment, research, and policy.* Keynote address to the inaugural meeting of the Netherlands Association for the Treatment of Sexual Abusers, Utrecht, Netherlands.
26. Cantor, J. M. (2014, December). *Understanding pedophilia and the brain: Implications for safety and society.* Keynote address for The Jewish Community Confronts Violence and Abuse: Crisis Centre for Religious Women, Jerusalem, Israel.
27. Cantor, J. M. (2014, October). *Understanding pedophilia & the brain.* Invited full-day workshop for the Sex Offender Assessment Board of Pennsylvania, Harrisburg, PA.
28. Cantor, J. M. (2014, September). *Understanding neuroimaging of pedophilia: Current status and implications.* Invited lecture presented to the Mental Health and Addition Rounds, St. Joseph's Healthcare, Hamilton, Ontario, Canada.
29. Cantor, J. M. (2014, June). *An evening with Dr. James Cantor.* Invited lecture presented to the Ontario Medical Association, District 11 Doctors' Lounge Program, Toronto, Ontario, Canada.
30. Cantor, J. M. (2014, April). *Pedophilia and the brain.* Invited lecture presented to the University of Toronto Medical Students lunchtime lecture. Toronto, Ontario, Canada.
31. Cantor, J. M. (2014, February). *Pedophilia and the brain: Recap and update.* Workshop presented at the 2014 annual meeting of the Washington State Association for the Treatment of Sexual Abusers, Cle Elum, WA.
32. Cantor, J. M., Lafaille, S., Hannah, J., Kucyi, A., Soh, D., Girard, T. A., & Mikulis, D. M. (2014, February). *Functional connectivity in pedophilia.* Neuropsychiatry Rounds, Toronto Western Hospital, Toronto, Ontario, Canada.

33. Cantor, J. M. (2013, November). *Understanding pedophilia and the brain: The basics, the current status, and their implications.* Invited lecture to the Forensic Psychology Research Centre, Carleton University, Ottawa, Canada.
34. Cantor, J. M. (2013, November). *Mistaking puberty, mistaking hebephilia.* Keynote address presented to the 32nd annual meeting of the Association for the Treatment of Sexual Abusers, Chicago, IL.
35. Cantor, J. M. (2013, October). *Understanding pedophilia and the brain: A recap and update.* Invited workshop presented at the 32nd annual meeting of the Association for the Treatment of Sexual Abusers, Chicago, IL.
36. Cantor, J. M. (2013, October). *Compulsive-hyper-sex-addiction: I don't care what we all it, what can we* do*?* Invited address presented to the Board of Examiners of Sex Therapists and Counselors of Ontario, Toronto, Ontario, Canada.
37. Cantor, J. M. (2013, September). *Neuroimaging of pedophilia: Current status and implications.* McGill University Health Centre, Department of Psychiatry Grand Rounds presentation, Montréal, Québec, Canada.
38. Cantor, J. M. (2013, April). *Understanding pedophilia and the brain.* Invited workshop presented at the 2013 meeting of the Minnesota Association for the Treatment of Sexual Abusers, Minneapolis, MN.
39. Cantor, J. M. (2013, April). *The neurobiology of pedophilia and its implications for assessment, treatment, and public policy.* Invited lecture at the 38th annual meeting of the Society for Sex Therapy and Research, Baltimore, MD.
40. Cantor, J. M. (2013, April). *Sex offenders: Relating research to policy.* Invited roundtable presentation at the annual meeting of the Academy of Criminal Justice Sciences, Dallas, TX.
41. Cantor, J. M. (2013, March). *Pedophilia and brain research: From the basics to the state-of-the-art.* Invited workshop presented to the annual meeting of the Forensic Mental Health Association of California, Monterey, CA.
42. Cantor, J. M. (2013, January). *Pedophilia and child molestation.* Invited lecture presented to the Canadian Border Services Agency, Toronto, Ontario, Canada.
43. Cantor, J. M. (2012, November). *Understanding pedophilia and sexual offenders against children: Neuroimaging and its implications for public safety.* Invited guest lecture to University of New Mexico School of Medicine Health Sciences Center, Albuquerque, NM.
44. Cantor, J. M. (2012, November). *Pedophilia and brain research.* Invited guest lecture to the annual meeting of the Circles of Support and Accountability, Toronto, Ontario, Canada.
45. Cantor, J. M. (2012, January). *Current findings on pedophilia brain research.* Invited workshop at the San Diego International Conference on Child and Family Maltreatment, San Diego, CA.
46. Cantor, J. M. (2012, January). *Pedophilia and the risk to re-offend.* Invited lecture to the Ontario Court of Justice Judicial Development Institute, Toronto, Ontario, Canada.
47. Cantor, J. M. (2011, November). *Pedophilia and the brain: What it means for assessment, treatment, and policy.* Plenary Lecture presented at the Association for the Treatment of Sexual Abusers, Toronto, Ontario, Canada.
48. Cantor, J. M. (2011, July). *Towards understanding contradictory findings in the neuroimaging of pedophilic men.* Keynote address to 7th annual conference on Research in Forensic Psychiatry, Regensberg, Germany.

49. Cantor, J. M. (2011, March). *Understanding sexual offending and the brain: Brain basics to the state of the art.* Workshop presented at the winter conference of the Oregon Association for the Treatment of Sexual Abusers, Oregon City, OR.
50. Cantor, J. M. (2010, October). *Manuscript publishing for students.* Workshop presented at the 29th annual meeting of the Association for the Treatment of Sexual Abusers, Phoenix, AZ.
51. Cantor, J. M. (2010, August). *Is sexual orientation a paraphilia?* Invited lecture at the International Behavioral Development Symposium, Lethbridge, Alberta, Canada.
52. Cantor, J. M. (2010, March). *Understanding sexual offending and the brain: From the basics to the state of the art.* Workshop presented at the annual meeting of the Washington State Association for the Treatment of Sexual Abusers, Blaine, WA.
53. Cantor, J. M. (2009, January). *Brain structure and function of pedophilia men.* Neuropsychiatry Rounds, Toronto Western Hospital, Toronto, Ontario.
54. Cantor, J. M. (2008, April). *Is pedophilia caused by brain dysfunction?* Invited address to the University-wide Science Day Lecture Series, SUNY Oswego, Oswego, NY.
55. Cantor, J. M., Kabani, N., Christensen, B. K., Zipursky, R. B., Barbaree, H. E., Dickey, R., Klassen, P. E., Mikulis, D. J., Kuban, M. E., Blak, T., Richards, B. A., Hanratty, M. K., & Blanchard, R. (2006, September). *MRIs of pedophilic men.* Invited presentation at the 25th annual meeting of the Association for the Treatment of Sexual Abusers, Chicago.
56. Cantor, J. M., Blanchard, R., & Christensen, B. K. (2003, March). *Findings in and implications of neuropsychology and epidemiology of pedophilia.* Invited lecture at the 28th annual meeting of the Society for Sex Therapy and Research, Miami.
57. Cantor, J. M., Christensen, B. K., Klassen, P. E., Dickey, R., & Blanchard, R. (2001, July). *Neuropsychological functioning in pedophiles.* Invited lecture presented at the 27th annual meeting of the International Academy of Sex Research, Bromont, Canada.
58. Cantor, J. M., Blanchard, R., Christensen, B., Klassen, P., & Dickey, R. (2001, February). *First glance at IQ, memory functioning and handedness in sex offenders.* Lecture presented at the Forensic Lecture Series, Centre for Addiction and Mental Health, Toronto, Ontario, Canada.
59. Cantor, J. M. (1999, November). *Reversal of SSRI-induced male sexual dysfunction: Suggestions from an animal model.* Grand Rounds presentation at the Allan Memorial Institute, Royal Victoria Hospital, Montréal, Canada.

PAPER PRESENTATIONS AND SYMPOSIA

1. Cantor, J. M. (2020, April). "I'd rather have a trans kid than a dead kid": Critical assessment of reported rates of suicidality in trans kids. *Paper presented at the annual meeting of the Society for the Sex Therapy and Research.* Online in lieu of in person meeting.
2. Stephens, S., Lalumière, M., Seto, M. C., & Cantor, J. M. (2017, October). *The relationship between sexual responsiveness and sexual exclusivity in phallometric profiles.* Paper presented at the annual meeting of the Canadian Sex Research Forum, Fredericton, New Brunswick, Canada.
3. Stephens, S., Cantor, J. M., & Seto, M. C. (2017, March). *Can the SSPI-2 detect hebephilic sexual interest?* Paper presented at the annual meeting of the American-Psychology Law Society Annual Meeting, Seattle, WA.
4. Stephens, S., Seto, M. C., Goodwill, A. M., & Cantor, J. M. (2015, October). *Victim choice polymorphism and recidivism.* Symposium Presentation. Paper presented at the 34th annual meeting of the Association for the Treatment of Sexual Abusers, Montréal, Canada.
5. McPhail, I. V., Hermann, C. A., Fernane, S. Fernandez, Y., Cantor, J. M., & Nunes, K. L. (2014, October). *Sexual deviance in sexual offenders against children: A meta-analytic review of phallometric research.* Paper presented at the 33rd annual meeting of the Association for the Treatment of Sexual Abusers, San Diego, CA.
6. Stephens, S., Seto, M. C., Cantor, J. M., & Goodwill, A. M. (2014, October). *Is hebephilic sexual interest a criminogenic need?: A large scale recidivism study.* Paper presented at the 33rd annual meeting of the Association for the Treatment of Sexual Abusers, San Diego, CA.
7. Stephens, S., Seto, M. C., Cantor, J. M., & Lalumière, M. (2014, October). *Development and validation of the Revised Screening Scale for Pedophilic Interests (SSPI–2).* Paper presented at the 33rd annual meeting of the Association for the Treatment of Sexual Abusers, San Diego, CA.
8. Cantor, J. M., Lafaille, S., Hannah, J., Kucyi, A., Soh, D., Girard, T. A., & Mikulis, D. M. (2014, September). *Pedophilia and the brain: White matter differences detected with DTI.* Paper presented at the 13th annual meeting of the International Association for the Treatment of Sexual Abusers, Porto, Portugal.
9. Stephens, S., Seto, M., Cantor, J. M., Goodwill, A. M., & Kuban, M. (2014, March). *The role of hebephilic sexual interests in sexual victim choice.* Paper presented at the annual meeting of the American Psychology and Law Society, New Orleans, LA.
10. McPhail, I. V., Fernane, S. A., Hermann, C. A., Fernandez, Y. M., Nunes, K. L., & Cantor, J. M. (2013, November). *Sexual deviance and sexual recidivism in sexual offenders against children: A meta-analysis.* Paper presented at the 32nd annual meeting of the Association for the Treatment of Sexual Abusers, Chicago, IL.
11. Cantor, J. M. (2013, September). *Pedophilia and the brain: Current MRI research and its implications.* Paper presented at the 21st annual World Congress for Sexual Health, Porto Alegre, Brazil. [Featured among Best Abstracts, top 10 of 500.]
12. Cantor, J. M. (Chair). (2012, March). *Innovations in sex research.* Symposium conducted at the 37th annual meeting of the Society for Sex Therapy and Research, Chicago.
13. Cantor, J. M., & Blanchard, R. (2011, August). fMRI versus phallometry in the diagnosis of pedophilia and hebephilia. In J. M. Cantor (Chair), *Neuroimaging of men's object*

preferences. Symposium presented at the 37th annual meeting of the International Academy of Sex Research, Los Angeles, USA.

14. Cantor, J. M. (Chair). (2011, August). *Neuroimaging of men's object preferences.* Symposium conducted at the 37th annual meeting of the International Academy of Sex Research, Los Angeles.
15. Cantor, J. M. (2010, October). A meta-analysis of neuroimaging studies of male sexual arousal. In S. Stolerú (Chair), *Brain processing of sexual stimuli in pedophilia: An application of functional neuroimaging.* Symposium presented at the 29th annual meeting of the Association for the Treatment of Sexual Abusers, Phoenix, AZ.
16. Chivers, M. L., Seto, M. C., Cantor, J. C., Grimbos, T., & Roy, C. (April, 2010). *Psychophysiological assessment of sexual activity preferences in women.* Paper presented at the 35th annual meeting of the Society for Sex Therapy and Research, Boston, USA.
17. Cantor, J. M., Girard, T. A., & Lovett-Barron, M. (2008, November). *The brain regions that respond to erotica: Sexual neuroscience for dummies.* Paper presented at the 51st annual meeting of the Society for the Scientific Study of Sexuality, San Juan, Puerto Rico.
18. Barbaree, H., Langton, C., Blanchard, R., & Cantor, J. M. (2007, October). *The role of age-at-release in the evaluation of recidivism risk of sexual offenders.* Paper presented at the 26th annual meetingof the Association for the Treatment of Sexual Abusers, San Diego.
19. Cantor, J. M., Kabani, N., Christensen, B. K., Zipursky, R. B., Barbaree, H. E., Dickey, R., Klassen, P. E., Mikulis, D. J., Kuban, M. E., Blak, T., Richards, B. A., Hanratty, M. K., & Blanchard, R. (2006, July). *Pedophilia and brain morphology.* Abstract and paper presented at the 32nd annual meeting of the International Academy of Sex Research, Amsterdam, Netherlands.
20. Seto, M. C., Cantor, J. M., & Blanchard, R. (2006, March). *Child pornography offending is a diagnostic indicator of pedophilia*. Paper presented at the 2006 annual meeting of the American Psychology-Law Society Conference, St. Petersburg, Florida.
21. Blanchard, R., Cantor, J. M., Bogaert, A. F., Breedlove, S. M., & Ellis, L. (2005, August). *Interaction of fraternal birth order and handedness in the development of male homosexuality.* Abstract and paper presented at the International Behavioral Development Symposium, Minot, North Dakota.
22. Cantor, J. M., & Blanchard, R. (2005, July). *Quantitative reanalysis of aggregate data on IQ in sexual offenders.* Abstract and poster presented at the 31st annual meeting of the International Academy of Sex Research, Ottawa, Canada.
23. Cantor, J. M. (2003, August). *Sex reassignment on demand: The clinician's dilemma.* Paper presented at the 111th annual meeting of the American Psychological Association, Toronto, Canada.
24. Cantor, J. M. (2003, June). *Meta-analysis of VIQ–PIQ differences in male sex offenders.* Paper presented at the Harvey Stancer Research Day, Toronto, Ontario, Canada.
25. Cantor, J. M. (2002, August). *Gender role in autogynephilic transsexuals: The more things change…* Paper presented at the 110th annual meeting of the American Psychological Association, Chicago.

26. Cantor, J. M., Christensen, B. K., Klassen, P. E., Dickey, R., & Blanchard, R. (2001, June). *IQ, memory functioning, and handedness in male sex offenders.* Paper presented at the Harvey Stancer Research Day, Toronto, Ontario, Canada.
27. Cantor, J. M. (1998, August). *Convention orientation for lesbian, gay, and bisexual students*. Papers presented at the 106th annual meeting of the American Psychological Association.
28. Cantor, J. M. (1997, August). *Discussion hour for lesbian, gay, and bisexual students*. Presented at the 105th annual meeting of the American Psychological Association.
29. Cantor, J. M. (1997, August). *Convention orientation for lesbian, gay, and bisexual students*. Paper presented at the 105th annual meeting of the American Psychological Association.
30. Cantor, J. M. (1996, August). *Discussion hour for lesbian, gay, and bisexual students*. Presented at the 104th annual meeting of the American Psychological Association.
31. Cantor, J. M. (1996, August). *Symposium: Question of inclusion: Lesbian and gay psychologists and accreditation*. Paper presented at the 104th annual meeting of the American Psychological Association, Toronto.
32. Cantor, J. M. (1996, August). *Convention orientation for lesbian, gay, and bisexual students*. Papers presented at the 104th annual meeting of the American Psychological Association.
33. Cantor, J. M. (1995, August). *Discussion hour for lesbian, gay, and bisexual students*. Presented at the 103rd annual meeting of the American Psychological Association.
34. Cantor, J. M. (1995, August). *Convention orientation for lesbian, gay, and bisexual students*. Papers presented at the 103rd annual meeting of the American Psychological Association.
35. Cantor, J. M. (1994, August). *Discussion hour for lesbian, gay, and bisexual students*. Presented at the 102nd annual meeting of the American Psychological Association.
36. Cantor, J. M. (1994, August). *Convention orientation for lesbian, gay, and bisexual students*. Papers presented at the 102nd annual meeting of the American Psychological Association.
37. Cantor, J. M., & Pilkington, N. W. (1992, August). *Homophobia in psychology programs: A survey of graduate students.* Paper presented at the Centennial Convention of the American Psychological Association, Washington, DC. (ERIC Document Reproduction Service No. ED 351 618)
38. Cantor, J. M. (1991, August). *Being gay and being a graduate student: Double the memberships, four times the problems*. Paper presented at the 99th annual meeting of the American Psychological Association, San Francisco.

POSTER PRESENTATIONS

1. Klein, L., Stephens, S., Goodwill, A. M., Cantor, J. M., & Seto, M. C. (2015, October). *The psychological propensities of risk in undetected sexual offenders.* Poster presented at the 34th annual meeting of the Association for the Treatment of Sexual Abusers, Montréal, Canada.
2. Pullman, L. E., Stephens, S., Seto, M. C., Goodwill, A. M., & Cantor, J. M. (2015, October). *Why are incest offenders less likely to recidivate?* Poster presented at the 34th annual meeting of the Association for the Treatment of Sexual Abusers, Montréal, Canada.
3. Seto, M. C., Stephens, S. M., Cantor, J. M., Lalumiere, M. L., Sandler, J. C., & Freeman, N. A. (2015, August). *The development and validation of the Revised Screening Scale for Pedophilic Interests (SSPI-2).* Poster presentation at the 41st annual meeting of the International Academy of Sex Research. Toronto, Canada.
4. Soh, D. W., & Cantor, J. M. (2015, August). *A peek inside a furry convention.* Poster presentation at the 41st annual meeting of the International Academy of Sex Research. Toronto, Canada.
5. VanderLaan, D. P., Lobaugh, N. J., Chakravarty, M. M., Patel, R., Chavez, S. Stojanovski, S. O., Takagi, A., Hughes, S. K., Wasserman, L., Bain, J., Cantor, J. M., & Zucker, K. J. (2015, August). *The neurohormonal hypothesis of gender dysphoria: Preliminary evidence of cortical surface area differences in adolescent natal females.* Poster presentation at the 31st annual meeting of the International Academy of Sex Research. Toronto, Canada.
6. Cantor, J. M., Lafaille, S. J., Moayedi, M., Mikulis, D. M., & Girard, T. A. (2015, June). *Diffusion tensor imaging (DTI) of the brain in pedohebephilic men: Preliminary analyses.* Harvey Stancer Research Day, Toronto, Ontario Canada.
7. Newman, J. E., Stephens, S., Seto, M. C., & Cantor, J. M. (2014, October). *The validity of the Static-99 in sexual offenders with low intellectual abilities.* Poster presentation at the 33rd annual meeting of the Association for the Treatment of Sexual Abusers, San Diego, CA.
8. Lykins, A. D., Walton, M. T., & Cantor, J. M. (2014, June). *An online assessment of personality, psychological, and sexuality trait variables associated with self-reported hypersexual behavior.* Poster presentation at the 30th annual meeting of the International Academy of Sex Research, Dubrovnik, Croatia.
9. Stephens, S., Seto, M. C., Cantor, J. M., Goodwill, A. M., & Kuban, M. (2013, November). *The utility of phallometry in the assessment of hebephilia.* Poster presented at the 32nd annual meeting of the Association for the Treatment of Sexual Abusers, Chicago.
10. Stephens, S., Seto, M. C., Cantor, J. M., Goodwill, A. M., & Kuban, M. (2013, October). *The role of hebephilic sexual interests in sexual victim choice.* Poster presented at the 32nd annual meeting of the Association for the Treatment of Sexual Abusers, Chicago.
11. Fazio, R. L., & Cantor, J. M. (2013, October). *Analysis of the Fazio Laterality Inventory (FLI) in a population with established atypical handedness.* Poster presented at the 33rd annual meeting of the National Academy of Neuropsychology, San Diego.
12. Lafaille, S., Hannah, J., Soh, D., Kucyi, A., Girard, T. A., Mikulis, D. M., & Cantor, J. M. (2013, August). *Investigating resting state networks in pedohebephiles.* Poster presented at the 29th annual meeting of the International Academy of Sex Research, Chicago.

13. McPhail, I. V., Lykins, A. D., Robinson, J. J., LeBlanc, S., & Cantor, J. M. (2013, August). *Effects of prescription medication on volumetric phallometry output.* Poster presented at the 29th annual meeting of the International Academy of Sex Research, Chicago.
14. Murray, M. E., Dyshniku, F., Fazio, R. L., & Cantor, J. M. (2013, August). *Minor physical anomalies as a window into the prenatal origins of pedophilia.* Poster presented at the 29th annual meeting of the International Academy of Sex Research, Chicago.
15. Sutton, K. S., Stephens, S., Dyshniku, F., Tulloch, T., & Cantor, J. M. (2013, August). *Pilot group treatment for "procrasturbation."* Poster presented at 39th annual meeting of the International Academy of Sex Research, Chicago.
16. Sutton, K. S., Pytyck, J., Stratton, N., Sylva, D., Kolla, N., & Cantor, J. M. (2013, August). *Client characteristics by type of hypersexuality referral: A quantitative chart review.* Poster presented at the 39th annual meeting of the International Academy of Sex Research, Chicago.
17. Fazio, R. L., & Cantor, J. M. (2013, June). *A replication and extension of the psychometric properties of the Digit Vigilance Test.* Poster presented at the 11th annual meeting of the American Academy of Clinical Neuropsychology, Chicago.
18. Lafaille, S., Moayedi, M., Mikulis, D. M., Girard, T. A., Kuban, M., Blak, T., & Cantor, J. M. (2012, July). *Diffusion Tensor Imaging (DTI) of the brain in pedohebephilic men: Preliminary analyses.* Poster presented at the 38th annual meeting of the International Academy of Sex Research, Lisbon, Portugal.
19. Lykins, A. D., Cantor, J. M., Kuban, M. E., Blak, T., Dickey, R., Klassen, P. E., & Blanchard, R. (2010, July). *Sexual arousal to female children in gynephilic men.* Poster presented at the 38th annual meeting of the International Academy of Sex Research, Prague, Czech Republic.
20. Cantor, J. M., Girard, T. A., Lovett-Barron, M., & Blak, T. (2008, July). *Brain regions responding to visual sexual stimuli: Meta-analysis of PET and fMRI studies.* Abstract and poster presented at the 34th annual meeting of the International Academy of Sex Research, Leuven, Belgium.
21. Lykins, A. D., Blanchard, R., Cantor, J. M., Blak, T., & Kuban, M. E. (2008, July). *Diagnosing sexual attraction to children: Considerations for DSM-V.* Poster presented at the 34th annual meeting of the International Academy of Sex Research, Leuven, Belgium.
22. Cantor, J. M., Blak, T., Kuban, M. E., Klassen, P. E., Dickey, R. and Blanchard, R. (2007, October). *Physical height in pedophilia and hebephilia.* Poster presented at the 26th annual meeting of the Association for the Treatment of Sexual Abusers, San Diego.
23. Cantor, J. M., Blak, T., Kuban, M. E., Klassen, P. E., Dickey, R. and Blanchard, R. (2007, August). *Physical height in pedophilia and hebephilia.* Abstract and poster presented at the 33rd annual meeting of the International Academy of Sex Research, Vancouver, Canada.
24. Puts, D. A., Blanchard, R., Cardenas, R., Cantor, J., Jordan, C. L., & Breedlove, S. M. (2007, August). *Earlier puberty predicts superior performance on male-biased visuospatial tasks in men but not women.* Abstract and poster presented at the 33rd annual meeting of the International Academy of Sex Research, Vancouver, Canada.
25. Seto, M. C., Cantor, J. M., & Blanchard, R. (2005, November). *Possession of child pornography is a diagnostic indicator of pedophilia.* Poster presented at the 24th annual meeting of the Association for the Treatment of Sexual Abusers, New Orleans.

26. Blanchard, R., Cantor, J. M., Bogaert, A. F., Breedlove. S. M., & Ellis, L. (2005, July). *Interaction of fraternal birth order and handedness in the development of male homosexuality.* Abstract and poster presented at the 31st annual meeting of the International Academy of Sex Research, Ottawa, Canada.
27. Cantor, J. M., & Blanchard, R. (2003, July). *The reported VIQ–PIQ differences in male sex offenders are artifactual?* Abstract and poster presented at the 29th annual meeting of the International Academy of Sex Research, Bloomington, Indiana.
28. Christensen, B. K., Cantor, J. M., Millikin, C., & Blanchard, R. (2002, February). *Factor analysis of two brief memory tests: Preliminary evidence for modality-specific measurement.* Poster presented at the 30th annual meeting of the International Neuropsychological Society, Toronto, Ontario, Canada.
29. Cantor, J. M., Blanchard, R., Paterson, A., Bogaert, A. (2000, June). *How many gay men owe their sexual orientation to fraternal birth order?* Abstract and poster presented at the International Behavioral Development Symposium, Minot, North Dakota.
30. Cantor, J. M., Binik, Y., & Pfaus, J. G. (1996, November). *Fluoxetine inhibition of male rat sexual behavior: Reversal by oxytocin*. Poster presented at the 26th annual meeting of the Society for Neurosciences, Washington, DC.
31. Cantor, J. M., Binik, Y., & Pfaus, J. G. (1996, June). *An animal model of fluoxetine-induced sexual dysfunction: Dose dependence and time course*. Poster presented at the 28th annual Conference on Reproductive Behavior, Montréal, Canada.
32. Cantor, J. M., O'Connor, M. G., Kaplan, B., & Cermak, L. S. (1993, June). *Transient events test of retrograde memory: Performance of amnestic and unimpaired populations*. Poster presented at the 2nd annual science symposium of the Massachusetts Neuropsychological Society, Cambridge, MA.

EDITORIAL AND PEER-REVIEWING ACTIVITIES

Editor-in-Chief

Sexual Abuse: A Journal of Research and Treatment Jan., 2010–Dec., 2014

Editorial Board Memberships

Journal of Sexual Aggression Jan., 2010–Dec., 2021
Journal of Sex Research, The Jan., 2008–Aug., 2020
Sexual Abuse: A Journal of Research and Treatment Jan., 2006–Dec., 2019
Archives of Sexual Behavior Jan., 2004–Present
The Clinical Psychologist Jan., 2004–Dec., 2005

Ad hoc Journal Reviewer Activity

American Journal of Psychiatry
Annual Review of Sex Research
Archives of General Psychiatry
Assessment
Biological Psychiatry
BMC Psychiatry
Brain Structure and Function
British Journal of Psychiatry
British Medical Journal
Canadian Journal of Behavioural Science
Canadian Journal of Psychiatry
Cerebral Cortex
Clinical Case Studies
Comprehensive Psychiatry
Developmental Psychology
European Psychologist
Frontiers in Human Neuroscience
Human Brain Mapping
International Journal of Epidemiology
International Journal of Impotence Research
International Journal of Sexual Health
International Journal of Transgenderism
Journal of Abnormal Psychology
Journal of Clinical Psychology
Journal of Consulting and Clinical Psychology
Journal of Forensic Psychology Practice
Journal for the Scientific Study of Religion
Journal of Sexual Aggression
Journal of Sexual Medicine
Journal of Psychiatric Research
Nature Neuroscience
Neurobiology Reviews
Neuroscience & Biobehavioral Reviews
Neuroscience Letters
Proceedings of the Royal Society B (Biological Sciences)
Psychological Assessment
Psychological Medicine
Psychological Science
Psychology of Men & Masculinity
Sex Roles
Sexual and Marital Therapy
Sexual and Relationship Therapy
Sexuality & Culture
Sexuality Research and Social Policy
The Clinical Psychologist
Traumatology
World Journal of Biological Psychiatry

GRANT REVIEW PANELS

2017–2021 Member, College of Reviewers, *Canadian Institutes of Health Research,* Canada.

2017 Committee Member, Peer Review Committee—Doctoral Research Awards A. *Canadian Institutes of Health Research*, Canada.

2017 Member, International Review Board, Research collaborations on behavioural disorders related to violence, neglect, maltreatment and abuse in childhood and adolescence. *Bundesministerium für Bildung und Forschung [Ministry of Education and Research],* Germany.

2016 Reviewer. National Science Center [*Narodowe Centrum Nauki*], Poland.

2016 Committee Member, Peer Review Committee—Doctoral Research Awards A. *Canadian Institutes of Health Research*, Canada.

2015 Assessor (Peer Reviewer). Discovery Grants Program. *Australian Research Council,* Australia.

2015 Reviewer. *Czech Science Foundation,* Czech Republic.

2015 Reviewer, "Off the beaten track" grant scheme. *Volkswagen Foundation,* Germany.

2015 External Reviewer, Discovery Grants program—Biological Systems and Functions. *National Sciences and Engineering Research Council of Canada*, Canada

2015 Committee Member, Peer Review Committee—Doctoral Research Awards A. *Canadian Institutes of Health Research*, Canada.

2014 Assessor (Peer Reviewer). Discovery Grants Program. *Australian Research Council,* Australia.

2014 External Reviewer, Discovery Grants program—Biological Systems and Functions. *National Sciences and Engineering Research Council of Canada*, Canada.

2014 Panel Member, Dean's Fund—Clinical Science Panel. *University of Toronto Faculty of Medicine*, Canada.

2014 Committee Member, Peer Review Committee—Doctoral Research Awards A. *Canadian Institutes of Health Research*, Canada.

2013 Panel Member, Grant Miller Cancer Research Grant Panel. *University of Toronto Faculty of Medicine*, Canada.

2013 Panel Member, Dean of Medicine Fund New Faculty Grant Clinical Science Panel. *University of Toronto Faculty of Medicine,* Canada.

2012 Board Member, International Review Board, Research collaborations on behavioural disorders related to violence, neglect, maltreatment and abuse in childhood and adolescence (2nd round). *Bundesministerium für Bildung und Forschung [Ministry of Education and Research],* Germany.

2012 External Reviewer, University of Ottawa Medical Research Fund. *University of Ottawa Department of Psychiatry*, Canada.

2012 External Reviewer, Behavioural Sciences—B. *Canadian Institutes of Health Research*, Canada.

2011 Board Member, International Review Board, Research collaborations on behavioural disorders related to violence, neglect, maltreatment and abuse in childhood and adolescence. *Bundesministerium für Bildung und Forschung [Ministry of Education and Research],* Germany.

TEACHING AND TRAINING

PostDoctoral Research Supervision
Law & Mental Health Program, Centre for Addiction and Mental Health, Toronto, Canada

Dr. Katherine S. Sutton	Sept., 2012–Dec., 2013
Dr. Rachel Fazio	Sept., 2012–Aug., 2013
Dr. Amy Lykins	Sept., 2008–Nov., 2009

Doctoral Research Supervision
Centre for Addiction and Mental Health, Toronto, Canada

Michael Walton • University of New England, Australia	Sept., 2017–Aug., 2018
Debra Soh • York University	May, 2013–Aug, 2017
Skye Stephens • Ryerson University	April, 2012–June, 2016

Masters Research Supervision
Centre for Addiction and Mental Health, Toronto, Canada

Nicole Cormier • Ryerson University	June, 2012–present
Debra Soh • Ryerson University	May, 2009–April, 2010

Undergraduate Research Supervision
Centre for Addiction and Mental Health, Toronto, Canada

Kylie Reale • Ryerson University	Spring, 2014
Jarrett Hannah • University of Rochester	Summer, 2013
Michael Humeniuk • University of Toronto	Summer, 2012

Clinical Supervision (Doctoral Internship)
Clinical Internship Program, Centre for Addiction and Mental Health, Toronto, Canada

Katherine S. Sutton • Queen's University	2011–2012
David Sylva • Northwestern University	2011–2012
Jordan Rullo • University of Utah	2010–2011
Lea Thaler • University of Nevada, Las Vegas	2010–2011
Carolin Klein • University of British Columbia	2009–2010
Bobby R. Walling • University of Manitoba	2009–2010

TEACHING AND TRAINING

Clinical Supervision (Doctoral- and Masters- level practica)
Centre for Addiction and Mental Health, Toronto, Canada

Tyler Tulloch • Ryerson University	2013–2014
Natalie Stratton • Ryerson University	Summer, 2013
Fiona Dyshniku • University of Windsor	Summer, 2013
Mackenzie Becker • McMaster University	Summer, 2013
Skye Stephens • Ryerson University	2012–2013
Vivian Nyantakyi • Capella University	2010–2011
Cailey Hartwick • University of Guelph	Fall, 2010
Tricia Teeft • Humber College	Summer, 2010
Allison Reeves • Ontario Institute for Studies in Education/Univ. of Toronto	2009–2010
Helen Bailey • Ryerson University	Summer, 2009
Edna Aryee • Ontario Institute for Studies in Education/Univ. of Toronto	2008–2009
Iryna Ivanova • Ontario Institute for Studies in Education/Univ. of Toronto	2008–2009
Jennifer Robinson • Ontario Institute for Studies in Education/Univ. of Toronto	2008–2009
Zoë Laksman • Adler School of Professional Psychology	2005–2006
Diana Mandelew • Adler School of Professional Psychology	2005–2006
Susan Wnuk • York University	2004–2005
Hiten Lad • Adler School of Professional Psychology	2004–2005
Natasha Williams • Adler School of Professional Psychology	2003–2004
Lisa Couperthwaite • Ontario Institute for Studies in Education/Univ. of Toronto	2003–2004
Lori Gray, née Robichaud • University of Windsor	Summer, 2003
Sandra Belfry • Ontario Institute for Studies in Education/Univ. of Toronto	2002–2003
Althea Monteiro • York University	Summer, 2002
Samantha Dworsky • York University	2001–2002
Kerry Collins • University of Windsor	Summer, 2001
Jennifer Fogarty • Waterloo University	2000–2001
Emily Cripps • Waterloo University	Summer, 2000
Lee Beckstead • University of Utah	2000

PROFESSIONAL SOCIETY ACTIVITIES

OFFICES HELD

2018–2019	Local Host. Society for Sex Therapy and Research.
2015	Member, International Scientific Committee, World Association for Sexual Health.
2015	Member, Program Planning and Conference Committee, Association for the Treatment of Sexual Abusers
2012–2013	Chair, Student Research Awards Committee, Society for Sex Therapy & Research
2012–2013	Member, Program Planning and Conference Committee, Association for the Treatment of Sexual Abusers
2011–2012	Chair, Student Research Awards Committee, Society for Sex Therapy & Research
2010–2011	Scientific Program Committee, International Academy of Sex Research
2002–2004	Membership Committee • APA Division 12 (Clinical Psychology)
2002–2003	Chair, Committee on Science Issues, APA Division 44
2002	Observer, Grant Review Committee • Canadian Institutes of Health Research Behavioural Sciences (B)
2001–2009	Reviewer • APA Division 44 Convention Program Committee
2001, 2002	Reviewer • APA Malyon-Smith Scholarship Committee
2000–2005	Task Force on Transgender Issues, APA Division 44
1998–1999	Consultant, APA Board of Directors Working Group on Psychology Marketplace
1997	Student Representative • APA Board of Professional Affairs' Institute on TeleHealth
1997–1998	Founder and Chair • APA/APAGS Task Force on New Psychologists' Concerns
1997–1999	Student Representative • APA/CAPP Sub-Committee for a National Strategy for Prescription Privileges
1997–1999	Liaison • APA Committee for the Advancement of Professional Practice
1997–1998	Liaison • APA Board of Professional Affairs
1993–1997	Founder and Chair • APA/APAGS Committee on LGB Concerns

PROFESSIONAL SOCIETY ACTIVITIES

MEMBERSHIPS

2017–2021 Member • *Canadian Sex Research Forum*

2009–Present Member • *Society for Sex Therapy and Research*

2006–Present Member (elected) • *International Academy of Sex Research*

2006–Present Research and Clinical Member • *Association for the Treatment of Sex Abusers*

2003–2006 Associate Member (elected) • *International Academy of Sex Research*

2002 Founding Member • CPA Section on Sexual Orientation and Gender Identity

2001–2013 Member • *Canadian Psychological Association* (CPA)

2000–2015 Member • *American Association for the Advancement of Science*

2000–2015 Member • *American Psychological Association* (APA)

APA Division 12 (Clinical Psychology)

APA Division 44 (Society for the Psychological Study of LGB Issues)

2000–2020 Member • *Society for the Scientific Study of Sexuality*

1995–2000 Student Member • *Society for the Scientific Study of Sexuality*

1993–2000 Student Affiliate • *American Psychological Association*

1990–1999 Member, American Psychological Association of Graduate Students (APAGS)

CLINICAL LICENSURE/REGISTRATION

Certificate of Registration, Number 3793
College of Psychologists of Ontario, Ontario, Canada

AWARDS AND HONORS

2017 Elected Fellow, Association for the Treatment of Sexual Abusers

2011 Howard E. Barbaree Award for Excellence in Research
Centre for Addiction and Mental Health, Law and Mental Health Program

2004 fMRI Visiting Fellowship Program at Massachusetts General Hospital
American Psychological Association Advanced Training Institute and NIH

1999–2001 CAMH Post-Doctoral Research Fellowship
Centre for Addiction and Mental Health Foundation and Ontario Ministry of Health

1998 Award for Distinguished Contribution by a Student
American Psychological Association, Division 44

1995 Dissertation Research Grant
Society for the Scientific Study of Sexuality

1994–1996 McGill University Doctoral Scholarship

1994 Award for Outstanding Contribution to Undergraduate Teaching
"TA of the Year Award," from the McGill Psychology Undergraduate Student Association

MAJOR MEDIA

(Complete list available upon request.)

Feature-length Documentaries

Vice Canada Reports. *Age of Consent.* 14 Jan 2017.
Canadian Broadcasting Company. *I, Pedophile.* Firsthand documentaries. 10 Mar 2016.

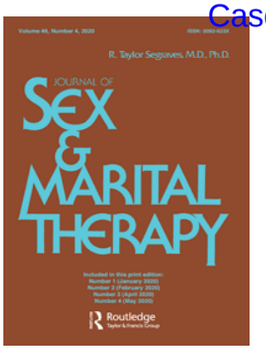
Appearances and Interviews

11 Mar 2020. Ibbitson, John. It is crucial that Parliament gets the conversion-therapy ban right. *The Globe & Mail.*
25 Jan 2020. Ook de hulpvaardige buurman kan verzamelaar van kinderporno zin. *De Morgen.*
3 Nov 2019. Village of the damned. *60 Minutes Australia.*
1 Nov 2019. HÅKON F. HØYDAL. Norsk nettovergriper: – Jeg hater meg selv: Nordmannen laster ned overgrepsmateriale fra nettet – og oppfordrer politiet til å gi amnesti for slike som ham.
10 Oct 2019. Smith, T. Growing efforts are looking at how—or if—#MeToo offenders can be reformed. *National Public Radio.*
29 Sep 2019. Carey, B. Preying on Children: The Emerging Psychology of Pedophiles. *New York Times.*
29 Apr 2019. Mathieu, Isabelle. La poupée qui a troublé les Terre-Neuviens. *La Tribune.*
21 Mar 2019. Pope Francis wants psychological testing to prevent problem priests. But can it really do that? *The Washington Post.*
12 Dec 2018. Child sex dolls: Illegal in Canada, and dozens seized at the border. Ontario Today with Rita Celli. *CBC.*
12 Dec 2018. Celli, R. & Harris, K. Dozens of child sex dolls seized by Canadian border agents. *CBC News.*
27 Apr 2018. Rogers, Brook A. The online 'incel' culture is real–and dangerous. *New York Post.*
25 Apr 2018. Yang, J. Number cited in cryptic Facebook post matches Alek Minassian's military ID: Source. *Toronto Star.*
24 Ap 2018 Understanding 'incel'. *CTV News.*
27 Nov 2017. Carey, B. Therapy for Sexual Misconduct? It's Mostly Unproven. *New York Times.*
14 Nov 2017. Tremonti, A. M. The Current. *CBC.*
9 Nov2017. Christensen, J. Why men use masturbation to harass women. *CNN.* http://www.cnn.com/2017/11/09/health/masturbation-sexual-harassment/index.html
7 Nov 2017. Nazaryan, A. Why is the alt-right obsessed with pedophilia? *Newsweek.*
15 Oct 2017. Ouatik, B. Déscouvre. Pédophilie et science. *CBC Radio Canada.*
12 Oct 2017. Ouatik, B. Peut-on guérir la pédophilie? *CBC Radio Canada.*
11 Sep 2017. Burns, C. The young paedophiles who say they don't abuse children. *BBC News.*
18 Aug 2017. Interview. *National Post Radio.* Sirius XM Canada.
16 Aug 2017. Blackwell, Tom. Man says he was cured of pedophilia at Ottawa clinic: 'It's like a weight that's been lifted': But skeptics worry about the impact of sending pedophiles into the world convinced their curse has been vanquished. *National Post.*
26 Apr 2017. Zalkind, S. Prep schools hid sex abuse just like the catholic church. *VICE.*
24 Apr 2017. Sastre, P. Pédophilie: une panique morale jamais n'abolira un crime. *Slate France.*
12 Feb 2017. Payette, G. Child sex doll trial opens Pandora's box of questions. *CBC News.*
26 Nov 2016. Det morke uvettet ["The unknown darkness]". *Fedrelandsvennen.*
13 July 2016. Paedophilia: Shedding light on the dark field. *The Economist.*

1 Jul 2016. Debusschere, B. Niet iedereen die kinderporno kijkt, is een pedofiel: De mythes rond pedofilie ontkracht. *De Morgen.*
12 Apr 2016. O'Connor, R. Terence Martin: The Tasmanian MP whose medication 'turned him into a paedophile'. *The Independent.*
8 Mar 2016. Bielski, Z. 'The most viscerally hated group on earth': Documentary explores how intervention can stop pedophiles. *The Globe and Mail.*
1 Mar 2016. Elmhirst, S. What should we do about paedophiles? *The Guardian.*
24 Feb 2016. The man whose brain tumour 'turned him into a paedophile'. *The Independent.*
24 Nov 2015. Byron, T. The truth about child sex abuse. *BBC Two.*
20 Aug 2015. The Jared Fogle case: Why we understand so little about abuse. *Washington Post.*
19 Aug 2015. Blackwell, T. Treat sex offenders for impotence—to keep them out of trouble, Canadian psychiatrist says. *National Post.*
2 Aug 2015. Menendez, J. BBC News Hour. *BBC World Service.*
13 Jul 2015. The nature of pedophilia. *BBC Radio 4.*
9 Jul 2015. The sex-offender test: How a computerized assessment can help determine the fate of men who've been accused of sexually abusing children. *The Atlantic.*
10 Apr 2015. NWT failed to prevent sex offender from abusing stepdaughter again. *CBC News.*
10 Feb 2015. Savage, D. "The ethical sadist." In Savage Love. *The Stranger.*
31 Jan 2015. Begrip voor/van pedofilie [Understanding pedophilia]. *de Volkskrant.*
9 Dec 2014. Carey, B. When a rapist's weapon is a pill. *New York Times*.
1 Dec 2014. Singal, J. Can virtual reality help pedophiles? *New York Magazine.*
17 Nov2014. Say pedófile, busco aydua. *El Pais.*
4 Sep 2014. Born that way? *Ideas, with Paul Kennedy.* CBC Radio One.
27 Aug 2014. Interrogating the statistics for the prevalence of paedophilia. BBC.
25 Jul 2014. Stephenson, W. The prevalence of paedophilia. *BBC World Service.*
21 Jul 2014. Hildebrandt, A. Virtuous Pedophiles group gives support therapy cannot. *CBC.*
26 Jan 2014. Paedophilia a result of faulty wiring, scientists suggest. *Daily Mail.*
22 Dec 2013. Kane, L. Is pedophilia a sexual orientation? *Toronto Star.*
21 Jul 2013. Miller, L. The turn-on switch: Fetish theory, post-Freud. *New York Magazine.*
1 Jul 2013. Morin, H. Pédophilie: la difficile quête d'une origine biologique. *Le Monde.*
2 Jun 2013. Malcolm, L. The psychology of paedophilia. *Australian National Radio.*
1 Mar 2013. Kay, J. The mobbing of Tom Flanagan is unwarranted and cruel. *National Post.*
6 Feb 2013. Boy Scouts board delays vote on lifting ban on gays. *L.A. Times.*
31 Aug 2012. CNN Newsroom interview with Ashleigh Banfield. *CNN.*
24 Jun 2012. CNN Newsroom interview with Don Lemon. *CNN.*

LEGAL TESTIMONY, PAST 5 YEARS

2022	Hersom & Doe v WVa Health & Human Services	Southern District, West Virginia
2022	BPJ v WVa Board of Education	Southern District, West Virginia
2021	Cross et al. v Loudoun School Board	Loudoun, Virginia
2021	Allan M. Josephson v Neeli Bendapudi	Western District of Kentucky
2021	Re Commitment of Michael Hughes (Frye Hearing)	Cook County, Illinois
2019	US vs Peter Bright	Southern Dist. of New York, NY
2019	Probate and Family Court (Custody Hearing)	Boston, Massachusetts
2019	Re Commitment of Steven Casper (Frye Hearing)	Kendall County, Illinois
2019	Re Commitment of Inger (Frye Hearing)	Poughkeepsie, New York
2018	Re Commitment of Fernando Little (Frye Hearing)	Utica, New York
2018	Canada vs John Fitzpatrick (Sentencing Hearing)	Toronto, Ontario, Canada



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Taylor & Francis Group

Journal of Sex & Marital Therapy

ISSN: 0092-623X (Print) 1521-0715 (Online) Journal homepage: https://www.tandfonline.com/loi/usmt20

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James M. Cantor

To cite this article: James M. Cantor (2020) Transgender and Gender Diverse Children and Adolescents: Fact-Checking of AAP Policy, Journal of Sex & Marital Therapy, 46:4, 307-313, DOI: 10.1080/0092623X.2019.1698481

To link to this article: https://doi.org/10.1080/0092623X.2019.1698481

Published online: 14 Dec 2019.

JOURNAL OF SEX & MARITAL THERAPY
2020, VOL. 46, NO. 4, 307–313
https://doi.org/10.1080/0092623X.2019.1698481

Transgender and Gender Diverse Children and Adolescents: Fact-Checking of AAP Policy

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ABSTRACT

The American Academy of Pediatrics (AAP) recently published a policy statement: *Ensuring comprehensive care and support for transgender and gender-diverse children and adolescents*. Although almost all clinics and professional associations in the world use what's called the *watchful waiting* approach to helping gender diverse (GD) children, the AAP statement instead rejected that consensus, endorsing *gender affirmation* as the only acceptable approach. Remarkably, not only did the AAP statement fail to include any of the actual outcomes literature on such cases, but it also misrepresented the contents of its citations, which repeatedly said the very opposite of what AAP attributed to them.

The American Academy of Pediatrics (AAP) recently published a policy statement entitled, *Ensuring comprehensive care and support for transgender and gender-diverse children and adolescents* (Rafferty, AAP Committee on Psychosocial Aspects of Child and Family Health, AAP Committee on Adolescence, AAP Section on Lesbian, Gay, Bisexual, and Transgender Health and Wellness, 2018). These are children who manifest discontent with the sex they were born as and desire to live as the other sex (or as some alternative gender role). The policy was quite a remarkable document: Although almost all clinics and professional associations in the world use what's called the *watchful waiting* approach to helping transgender and gender diverse (GD) children, the AAP statement rejected that consensus, endorsing only *gender affirmation.* That is, where the consensus is to delay any transitions after the onset of puberty, AAP instead rejected waiting before transition. With AAP taking such a dramatic departure from other professional associations, I was immediately curious about what evidence led them to that conclusion. As I read the works on which they based their policy, however, I was pretty surprised—rather alarmed, actually: These documents simply did not say what AAP claimed they did. In fact, the references that AAP cited as the basis of their policy instead outright contradicted that policy, repeatedly endorsing *watchful waiting*.

The AAP statement was also remarkable in what it left out—namely, the actual outcomes research on GD children. In total, there have been 11 follow-up studies of GD children, of which AAP cited one (Wallien & Cohen-Kettenis, 2008), doing so without actually mentioning the outcome data it contained. The literature on outcomes was neither reviewed, summarized, nor subjected to meta-analysis to be considered in the aggregate—It was merely disappeared. (The list of all existing studies appears in the appendix.) As they make clear, *every* follow-up study of GD children, without exception, found the same thing: Over puberty, the majority of GD children cease to want to transition. AAP is, of course, free to establish whatever policy it likes on

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whatever basis it likes. But any assertion that their policy is based on evidence is demonstrably false, as detailed below.

AAP divided clinical approaches into three types—conversion therapy, watchful waiting, and gender affirmation. It rejected the first two and endorsed *gender affirmation* as the only acceptable alternative. Most readers will likely be familiar already with attempts to use conversion therapy to change sexual orientation. With regard to gender identity, AAP wrote:

> "[C]onversion" or "reparative" treatment models are used to prevent children and adolescents from identifying as transgender or to dissuade them from exhibiting gender-diverse expressions. … Reparative approaches have been proven to be not only unsuccessful[38] but also deleterious and are considered outside the mainstream of traditional medical practice.[29,39–42]

The citations were:

38. Haldeman DC. The practice and ethics of sexual orientation conversion therapy. *J Consult Clin Psychol.* 1994;62(2):221–227.

29. Adelson SL; American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI). Practice parameter on gay, lesbian, or bisexual sexual orientation, gender nonconformity, and gender discordance in children and adolescents. *J Am Acad Child Adolesc Psychiatry.* 2012;51(9):957–974.

39. Byne W. Regulations restrict practice of conversion therapy. *LGBT Health.* 2016;3(2):97–99.

40. Cohen-Kettenis PT, Delemarrevan de Waal HA, Gooren LJ. The treatment of adolescent transsexuals: changing insights. *J Sex Med.* 2008;5(8):1892–1897.

41. Bryant K. Making gender identity disorder of childhood: historical lessons for contemporary debates. *Sex Res Soc Policy.* 2006;3(3):23–39.

42. World Professional Association for Transgender Health. *WPATH De-Psychopathologisation Statement.* Minneapolis, MN: World Professional Association for Transgender Health; 2010.

AAP's claims struck me as odd because *there are no studies of conversion therapy for gender identity.* Studies of conversion therapy have been limited to *sexual orientation,* and, moreover, to the sexual orientation *of adults,* not to gender identity and not of children in any case. The article AAP cited to support their claim (reference number 38) is indeed a classic and well-known review, but it is a review of sexual orientation research *only.* Neither gender identity, nor even children, received a single mention in it. Indeed, the narrower scope of that article should be clear to anyone reading even just its title: "The practice and ethics of *sexual orientation* conversion therapy" [italics added].

AAP continued, saying that conversion approaches for GD children have already been rejected by medical consensus, citing five sources. This claim struck me as just as odd, however—I recalled associations banning conversion therapy for sexual orientation, but not for gender identity, exactly because there is no evidence for generalizing from adult sexual orientation to childhood gender identity. So, I started checking AAP's citations for that, and these sources too pertained only to sexual orientation, not gender identity (specifics below). What AAP's sources *did* repeatedly emphasize was that:

A. Sexual orientation of adults is unaffected by conversion therapy and any other [known] intervention;
B. Gender dysphoria in childhood before puberty desists in the majority of cases, becoming (cis-gendered) homosexuality in adulthood, again regardless of any [known] intervention; and
C. Gender dysphoria in childhood persisting after puberty tends to persist entirely.

That is, in the context of GD children, it simply makes no sense to refer to externally induced "conversion": The majority of children "convert" to cisgender or "desist" from transgender

regardless of any attempt to change them. "Conversion" only makes sense with regard to adult sexual orientation because (unlike childhood gender identity), adult homosexuality never or nearly never spontaneously changes to heterosexuality. Although gender identity and sexual orientation may often be analogous and discussed together with regard to social or political values and to civil rights, they are nonetheless distinct—with distinct origins, needs, and responses to medical and mental health care choices. Although AAP emphasized to the reader that "gender identity is not synonymous with 'sexual orientation'" (Rafferty et al., 2018, p. 3), they went ahead to treat them as such nonetheless.

To return to checking AAP's fidelity to its sources: Reference 29 was a practice guideline from the Committee on Quality Issues of the American Academy of Child and Adolescent Psychiatry (AACAP). Despite AAP applying this source to *gender identity,* AACAP was quite unambiguous regarding their intent to speak to sexual orientation and *only* to sexual orientation: "Principle 6. Clinicians should be aware that there is no evidence that *sexual orientation* can be altered through therapy, and that attempts to do so may be harmful. There is no established evidence that change in a predominant, enduring *homosexual* pattern of development is possible. Although sexual fantasies can, to some degree, be suppressed or repressed by those who are ashamed of or in conflict about them, sexual desire is not a choice. However, behavior, social role, and—to a degree—identity and self-acceptance are. Although operant conditioning modifies sexual fetishes, it does not alter *homosexuality*. Psychiatric efforts to alter *sexual orientation* through 'reparative therapy' *in adults* have found little or no change in *sexual orientation,* while causing significant risk of harm to self-esteem" (AACAP, 2012, p. 967, italics added).

Whereas AAP cites AACAP to support gender affirmation as the only alternative for treating GD children, AACAP's actual view was decidedly neutral, noting the lack of evidence: "Given the lack of empirical evidence from randomized, controlled trials of the efficacy of treatment aimed at eliminating gender discordance, the potential risks of treatment, and longitudinal evidence that gender discordance persists in only a small minority of untreated cases arising in childhood, further research is needed on predictors of persistence and desistence of childhood gender discordance as well as the long-term risks and benefits of intervention before any treatment to eliminate gender discordance can be endorsed" (AACAP, 2012, p. 969). Moreover, whereas AAP rejected watchful waiting, what AACAP recommended was: "In general, it is desirable to help adolescents who may be experiencing gender distress and dysphoria to defer sex reassignment until adulthood" (AACAP, 2012, p. 969). So, not only did AAP attribute to AACAP something AACAP never said, but also AAP withheld from readers AACAP's actual view.

Next, in reference 39, Byne (2016) also addressed only sexual orientation, doing so very clearly: "Reparative therapy is a subset of conversion therapies based on the premise that *same-sex attraction* are reparations for childhood trauma. Thus, practitioners of reparative therapy believe that exploring, isolating, and repairing these childhood emotional wounds will often result in reducing *same-sex attractions*" (Byne, 2016, p. 97). Byne does not say this of gender identity, as the AAP statement misrepresents.

In AAP reference 40, Cohen-Kettenis et al. (2008) did finally pertain to gender identity; however, this article never mentions conversion therapy. (!) Rather, in this study, the authors presented that clinic's lowering of their minimum age for cross-sex hormone treatment from age 18 to 16, which they did on the basis of a series of studies showing the high rates of success with this age group. Although it did strike me as odd that AAP picked as support against conversion therapy an article that did not mention conversion therapy, I could imagine AAP cited the article as an example of what the "mainstream of traditional medical practice" consists of (the logic being that conversion therapy falls outside what an 'ideal' clinic like this one provides). However, what this clinic provides is the very *watchful waiting* approach that AAP rejected. The approach

espoused by Cohen-Kettenis (and the other clinics mentioned in the source—Gent, Boston, Oslo, and now formerly, Toronto) is to make puberty-halting interventions available at age 12 because: "[P]ubertal suppression may give adolescents, together with the attending health professional, more time to explore their gender identity, without the distress of the developing secondary sex characteristics. The precision of the diagnosis may thus be improved" (Cohen-Kettenis et al., 2008, p. 1894).

Reference 41 presented a very interesting history spanning the 1960s–1990s about how feminine boys and tomboyish girls came to be recognized as mostly pre-homosexual, and how that status came to be entered into the DSM at the same time as homosexuality was being *removed* from the DSM. Conversion therapy is never mentioned. Indeed, to the extent that Bryant mentions treatment at all, it is to say that treatment is entirely irrelevant to his analysis: "An important omission from the *DSM* is a discussion of the kinds of treatment that GIDC children should receive. (This omission is a general orientation of the DSM and not unique to GIDC)" (Bryant, 2006, p. 35). How this article supports AAP's claim is a mystery. Moreover, how AAP could cite a 2006 history discussing events of the 1990s and earlier to support a claim about the *current* consensus in this quickly evolving discussion remains all the more unfathomable.

Cited last in this section was a one-paragraph press release from the World Professional Association for Transgender Health. Written during the early stages of the American Psychiatric Association's (APA's) update of the DSM, the statement asserted simply that "The WPATH Board of Directors strongly urges the de-psychopathologisation of gender variance worldwide." Very reasonable debate can (and should) be had regarding whether gender dysphoria should be removed from the DSM as homosexuality was, and WPATH was well within its purview to assert that it should. Now that the DSM revision process is years completed however, history has seen that APA ultimately retained the diagnostic categories, rejecting WPATH's urging. This makes AAP's logic entirely backwards: That WPATH's request to depathologize gender dysphoria was *rejected* suggests that it is *WPATH's* view—and therefore the AAP policy—which fall "outside the mainstream of traditional medical practice." (!)

AAP based this entire line of reasoning on their belief that conversion therapy is being used "to prevent children and adolescents from identifying as transgender" (Rafferty et al., 2018, p. 4). That claim is left without citation or support. In contrast, what is said by AAP's sources is "delaying affirmation should *not* be construed as conversion therapy or an attempt to change gender identity" in the first place (Byne, 2016, p. 2). Nonetheless, AAP seems to be doing exactly that: simply relabeling any alternative approach as equivalent to conversion therapy.

Although AAP (and anyone else) may reject (what they label to be) conversion therapy purely on the basis of political or personal values, there is no evidence to back the AAP's stated claim about the existing science on gender identity at all, never mind gender identity of children.

AAP also dismissed the watchful waiting approach out of hand, not citing any evidence, but repeatedly calling it "outdated." The criticisms AAP provided, however, again defied the existing evidence, with even its own sources repeatedly calling watchful waiting the current standard. According to AAP:

> [G]ender affirmation is in contrast to the outdated approach in which a child's gender-diverse assertions are held as "possibly true" until an arbitrary age (often after pubertal onset) when they can be considered valid, an approach that authors of the literature have termed "watchful waiting." This outdated approach does not serve the child because critical support is withheld. Watchful waiting is based on binary notions of gender in which gender diversity and fluidity is pathologized; in watchful waiting, it is also assumed that notions of gender identity become fixed at a certain age. The approach is also influenced by a group of early studies with validity concerns, methodologic flaws, and limited follow-up on children who identified as TGD and, by adolescence, did not seek further treatment ("desisters").[45,47]

The citations from AAP's reference list are:

45. Ehrensaft D, Giammattei SV, Storck K, Tishelman AC, Keo-Meier C. Prepubertal social gender transitions: what we know; what we can learn—a view from a gender affirmative lens. *Int J Transgend.* 2018;19(2):251–268

47. Olson KR. Prepubescent transgender children: what we do and do not know. *J Am Acad Child Adolesc Psychiatry.* 2016;55(3):155–156.e3

I was surprised first by the AAP's claim that watchful waiting's delay to puberty was somehow "arbitrary." The literature, including AAP's sources, repeatedly indicated the pivotal importance of puberty, noting that outcomes strongly diverge at that point. According to AAP reference 29, in "*prepubertal* boys with gender discordance—including many without any mental health treatment—the cross gender wishes usually fade over time and do not persist into adulthood, with only 2.2% to 11.9% continuing to experience gender discordance" (Adelson & AACAP, 2012, p. 963, italics added), whereas "when gender variance with the desire to be the other sex is present *in adolescence,* this desire usually does persist through adulthood" (Adelson & AACAP, 2012, p. 964, italics added). Similarly, according to AAP reference 40, "Symptoms of GID *at prepubertal ages* decrease or even disappear in a considerable percentage of children (estimates range from 80–95%). Therefore, any intervention in childhood would seem premature and inappropriate. However, GID persisting *into early puberty* appears to be highly persistent" (Cohen-Kettenis et al., 2008, p. 1895, italics added). That follow-up studies of prepubertal transition differ from postpubertal transition is the very meaning of non-arbitrary. AAP gave readers exactly the reverse of what was contained in its own sources. If AAP were correct in saying that puberty is an arbitrarily selected age, then AAP will be able to offer another point to wait for with as much empirical backing as puberty has.

Next, it was not clear on what basis AAP could say that watchful waiting withholds support—AAP cited no support for its claim. The people in such programs often receive substantial support during this period. Also unclear is on what basis AAP could already know exactly which treatments are "critical" and which are not—Answering that question is the very purpose of this entire endeavor. Indeed, the logic of AAP's claim appears entirely circular: It is only if one were already pre-convinced that gender affirmation is the only acceptable alternative that would make watchful waiting seem to withhold critical support—What it delays is gender affirmation, the method one has already decided to be critical.

Although AAP's next claim did not have a citation appearing at the end of its sentence, binary notions of gender were mentioned both in references 45 and 47. Specifically, both pointed out that existing outcome studies have been about people transitioning from one sex to the other, rather than from one sex to an in-between status or a combination of masculine/feminine features. Neither reference presented this as a reason to reject the results from the existing studies of complete transition however (which is how AAP cast it). Although it is indeed true that the outcome data have been about complete transition, some future study showing that partial transition shows a different outcome would not invalidate what is known about complete transition. Indeed, data showing that partial transition gives better outcomes than complete transition would, once again, support the watchful waiting approach which AAP rejected.

Next was a vague reference alleging concerns and criticisms about early studies. Had AAP indicated what those alleged concerns and flaws were (or which studies they were), then it would be possible to evaluate or address them. Nonetheless, the argument is a red herring: Because all of the later studies showed the same result as did the early studies, any such allegation is necessarily moot.

Reference 47 was a one-and-a-half page commentary in which the author off-handedly mentions criticisms previously made of three of the eleven outcome studies of GD children, but does not provide any analysis or discussion. The only specific claim was that studies (whether early or late) had limited follow-up periods—the logic being that had outcome researchers lengthened the follow-up period, then people who seemed to have desisted might have returned to the clinic as

cases of "persistence-after-interruption." Although one could debate the merits of that prediction, AAP instead simply withheld from the reader the result from the original researchers having tested that very prediction directly: Steensma and Cohen-Kettenis (2015) conducted another analysis of their cohort, by then ages 19–28 (mean age 25.9 years), and found that 3.3% (5 people of the sample of 150) later returned. That is, in long-term follow-up, the childhood sample showed 66.7% desistence instead of 70.0% desistance.

Reference 45 did not support the claim that watchful-waiting is "outdated" either. Indeed, that source said the very opposite, explicitly referring to watchful waiting as the *current* approach: "Put another way, if clinicians are straying from SOC 7 guidelines for social transitions, not abiding by the watchful waiting model *favored by the standards,* we will have adolescents who have been consistently living in their affirmed gender since age 3, 4, or 5" (Ehrensaft et al., 2018, p. 255). Moreover, Ehrensaft et al. said there are cases in which they too would still use watchful waiting: "When a child's gender identity is unclear, the watchful waiting approach can give the child and their family time to develop a clearer understanding and is not necessarily in contrast to the needs of the child" (p. 259). Ehrensaft et al. are indeed critical of the watchful waiting model (which they feel is applied too conservatively), but they do not come close to the position the AAP policy espouses. Where Ehrensaft summaries the potential benefits and potential risks both to transitioning and not transitioning, the AAP presents an ironically binary narrative.

In its policy statement, AAP told neither the truth nor the whole truth, committing sins both of commission and of omission, asserting claims easily falsified by anyone caring to do any fact-checking at all. AAP claimed, "This policy statement is focused specifically on children and youth that identify as TGD rather than the larger LGBTQ population"; however, much of that evidence was about sexual orientation, not gender identity. AAP claimed, "Current available research and expert opinion from clinical and research leaders … will serve as the basis for recommendations" (pp. 1–2); however, they provided recommendations entirely unsupported and even in direct opposition to that research and opinion.

AAP is advocating for something far in excess of mainstream practice and medical consensus. In the presence of compelling evidence, that is just what is called for. The problems with Rafferty, however, do not constitute merely a misquote, a misinterpretation of an ambiguous statement, or a missing reference or two. Rather, AAP's statement is a systematic exclusion and misrepresentation of entire literatures. Not only did AAP fail to provide compelling evidence, it failed to provide the evidence at all. Indeed, AAP's recommendations are *despite* the existing evidence.

Disclosure statement

No potential conflict of interest was reported by the author.

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Steensma, T. D., & Cohen-Kettenis, P. T. (2015). More than two developmental pathways in children with gender dysphoria? *Journal of the American Academy of Child and Adolescent Psychiatry*, *52*, 147–148. doi:10.1016/j.jaac.2014.10.016

Wallien, M. S. C., & Cohen-Kettenis, P. T. (2008). Psychosexual outcome of gender-dysphoric children. *Journal of the American Academy of Child and Adolescent Psychiatry*, *47*, 1413–1423. doi:10.1097/CHI.0b013e31818956b9

Appendix

Count	Group	Study
2/16 4/16 10/16	gay* trans-/crossdress straight*/uncertain	Lebovitz, P. S. (1972). Feminine behavior in boys: Aspects of its outcome. *American Journal of Psychiatry, 128,* 1283–1289.
2/16 2/16 12/16	trans- uncertain gay	Zuger, B. (1978). Effeminate behavior present in boys from childhood: Ten additional years of follow-up. *Comprehensive Psychiatry, 19,* 363–369.
0/9 9/9	trans- gay	Money, J., & Russo, A. J. (1979). Homosexual outcome of discordant gender identity/role: Longitudinal follow-up. *Journal of Pediatric Psychology, 4,* 29–41.
2/45 10/45 33/45	trans-/crossdress uncertain gay	Zuger, B. (1984). Early effeminate behavior in boys: Outcome and significance for homosexuality. *Journal of Nervous and Mental Disease, 172,* 90–97.
1/10 2/10 3/10 4/10	trans- gay uncertain straight	Davenport, C. W. (1986). A follow-up study of 10 feminine boys. *Archives of Sexual Behavior, 15,* 511–517.
1/44 43/44	trans- cis-	Green, R. (1987). *The "sissy boy syndrome" and the development of homosexuality*. New Haven, CT: Yale University Press.
0/8 8/8	trans- cis-	Kosky, R. J. (1987). Gender-disordered children: Does inpatient treatment help? *Medical Journal of Australia, 146,* 565–569.
21/54 33/54	trans- cis-	Wallien, M. S. C., & Cohen-Kettenis, P. T. (2008). Psychosexual outcome of gender-dysphoric children. *Journal of the American Academy of Child and Adolescent Psychiatry, 47,* 1413–1423.
3/25 6/25 16/25	trans- lesbian/bi- straight	Drummond, K. D., Bradley, S. J., Badali-Peterson, M., & Zucker, K. J. (2008). A follow-up study of girls with gender identity disorder. *Developmental Psychology, 44*, 34–45.
17/139 122/139	trans- cis-	Singh, D. (2012). *A follow-up study of boys with gender identity disorder*. Unpublished doctoral dissertation, University of Toronto.
47/127 80/127	trans- cis-	Steensma, T. D., McGuire, J. K., Kreukels, B. P. C., Beekman, A. J., & Cohen-Kettenis, P. T. (2013). Factors associated with desistence and persistence of childhood gender dysphoria: A quantitative follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry, 52,* 582–590.

*For brevity, the list uses "gay" for "gay and cis-", "straight" for "straight and cis-", etc.

DEFENDANT'S EXHIBIT 3

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER, *et al.*,	)	
Plaintiffs,	)	
v.	)	No. 2:22-cv-00184-LCB-SRW
KAY IVEY, in her official capacity as Governor of the State of Alabama, *et al.*,	)	
Defendants.	)	

DECLARATION OF MICHAEL K. LAIDLAW, M.D.

My name is Michael K. Laidlaw. I am over the age of 19, I am qualified to give this declaration, and, I have personal knowledge of the matters set forth herein.

I am a physician with specialties in endocrinology and internal medicine. I received a Bachelor of Science Degree in Biology with concentration in Molecular Cell Biology in 1997. I received my medical degree from the University of Southern California in 2001. I completed my residency in internal medicine at Los Angeles County/University of Southern California Medical Center in 2004. I also completed a fellowship in endocrinology, diabetes and metabolism at Los Angeles County/University of Southern California Medical Center in 2006.

The information provided regarding my professional background are detailed in my curriculum vitae attached as Exhibit A.

I have been practicing endocrinology in private practice in Rocklin, CA for the past 15 years. In my clinical practice as an endocrinologist, I evaluate patients with hormone excess, hormone deficiency, and other glandular disorders. These conditions result in numerous physical and psychological manifestations which I diagnose and treat.

I first began writing about gender dysphoria and the harms of gender affirmative therapy in a letter I sent to a local school board in Newcastle, California in January of 2018. I

voiced my concerns regarding misinformation and pertinent omissions in a book read in school entitled "I am Jazz" which is a children's book that discusses gender identity. These concerns were later published in The Public Discourse in an essay entitled "Gender Dysphoria and Children: An Endocrinologist's Evaluation of I am Jazz". (Laidlaw, 2018).

In 2019, I coauthored, along with four of my physician colleagues, a letter to the editor published in the Journal of Clinical Endocrinology and Metabolism, "Letter to the Editor: Endocrine Treatment of Gender-Dsyphoria/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline," in which we voiced our serious concerns with gender affirmative therapy (GAT) (Laidlaw, 2019).

In May of 2019 I spoke in the U.K.'s House of Lords at the invitation of Lord Lewis Moonie. The title of my speech was "Medical Harms Associated with the Hormonal and Surgical Therapy of Child and Adolescent Gender Dysphoria".

My recent publications include a letter to the editor of JCEM published in December 2021 "Erythrocytosis in a Large Cohort of Trans Men Using Testosterone: A Long-Term Follow-Up Study on Prevalence, Determinants, and Exposure Years."; "Gender affirmation surgery conclusion lacks evidence (letter)" published in the American Journal of Psychiatry in 2020; and "The Right to Best Care for Children Does Not Include the Right to Medical Transition" published in The American Journal of Bioethics in 2019. Other publications and Amicus Curiae Briefs are listed on my CV.

In the past four years, I have provided expert testimony in the following cases: JULIANA PAOLI v. JOSEPH HUDSON et al. heard in THE SUPERIOR COURT OF THE STATE OF CALIFORNIA, COUNTY OF TULARE. CASE NO. 279126. 2021;
United States District Court for the District of Arizona. DH and John Doe, Plaintiffs, vs. Jami Snyder, Director of the Arizona Health Care Cost Containment System, in her official capacity, Defendant. Case No. 4:20-cv-00335-SHR. 2020;
Supreme Court of British Columbia. File No. S2011599, Vancouver Registry. Between A.M. Plaintiff and Dr. F and Daniel McKee Defendants. 11/23/20 & 11/25/20;
and Court of Appeal File No. CA45940, Vancouver Registry. B.C. Canada. Supreme Court File No. E190334, between A.B. Respondent/Claimant, and C.D. Appellant/Respondent, and E.F. Respondent/Respondent. 24 Jun 2019.

I have been retained by Defendant in the above-captioned lawsuit to provide an expert opinion on the medical soundness of the Alabama Vulnerable Child Compassion and Protection Act. The opinions expressed are based on my experience and education, a

review of the complaint and expert reports submitted by the plaintiffs, and the literature cited below.

I am compensated at the rate of $450 per hour for my analysis, study, consultations, and preparation of expert reports, $650 per hour for testifying in court or deposition, and $250 per hour for travel. My compensation is not dependent upon the substance of my opinions or the outcome of the case.

A. Endocrine Disorders

Before discussing gender dysphoria and gender affirmative therapy from the perspective of an endocrinologist, it is helpful to discuss the background of endocrine diseases. This background demonstrates the difference in gender dysphoria, which is a psychological diagnosis, and other conditions treated by endocrinologists, which are physical diagnoses.

Endocrinology is the study of glands and hormones. Endocrine disorders can be divided into three main types: those that involve hormone excess, those that involve hormone deficiency, and those that involve structural abnormalities of the glands such as cancers.

It is important for the endocrinologist to determine the cause of hormone gland excess or deficiency in order to devise an appropriate treatment plan. The plan will generally be to help bring the hormones back into balance and thus bring the patient back to health.

To give an example of hormone excess, hyperthyroidism is a term which means overactivity of the thyroid gland. In this condition excess thyroid hormone is produced by the thyroid gland. This results in various physical and psychological changes for the afflicted patient. Examples of physical changes can include tachycardia or fast heart rate, hand tremors, and weight loss. Examples of psychological symptoms include anxiety, panic attacks, and sometimes even psychosis.

An endocrinologist can recognize thyroid hormone excess in part by signs and symptoms, but can also confirm the diagnosis with laboratory testing that shows the thyroid hormones to be out of balance. Once this is determined and the degree of excess is known, then treatments can be given to bring these levels back into balance to benefit the patient’s health and to prevent other disease effects caused by excess hormone.

To give another example, consider a deficiency of insulin. Insulin is a hormone which regulates blood glucose levels. If there is damage to the pancreas such that insulin levels are very low, then blood glucose levels will rise. If the glucose levels rise to a certain abnormally high level, then this is considered diabetes. In the case of type 1 diabetes, insulin levels are abnormally low and therefore blood glucose levels are abnormally high leading to a variety of signs and symptoms. For example, the patient may have extreme thirst, frequent urination, muscle wasting, and weight loss. They may often experience lethargy and weakness.

In this case laboratory tests of glucose and insulin levels can confirm the diagnosis. Once diabetes is confirmed, the patient is then treated with insulin to help restore glucose balance in the body and prevent long term complications of diabetes.

To give an example of a structural abnormality, a patient may have a lump on the thyroid gland in the neck. This may be further examined by an imaging test such as an ultrasound. A needle biopsy can be performed so that the cells can be examined under a microscope. A trained medical professional such as a pathologist can then examine the cells to determine if they are benign or cancerous. In the case of a thyroid cancer, a surgical procedure known as a thyroidectomy may be performed to remove the diseased thyroid gland in order to treat the cancer.

Noteworthy in the preceding three examples is that all three disease conditions are diagnosed by physical observations. In other words, a laboratory test of a hormone, an imaging test of an organ, an examination of cells under a microscope, or all three may be employed in the diagnosis of endocrine disease.

B. Gender Dysphoria is a Psychological Diagnosis

Gender dysphoria, on the other hand, is not an endocrine diagnosis, it is in fact a psychological diagnosis. It is diagnosed purely by psychological methods of behavioral observation and questioning.

Likewise what is termed gender identity is a psychological concept. It has no correlate in the human body. In the letter to the editor I wrote with my colleagues, discussed above, we wrote in our critique of the Endocrine Society Guidelines that "There are no laboratory, imaging, or other objective tests to diagnose a 'true transgender' child" (Laidlaw et al., 2019).

For example, one cannot do imaging of the human brain to find the gender identity. Likewise, there is no other imaging, laboratory tests, biopsy of tissue, autopsy of the

brain, or genetic testing that can identify the gender identity. There is no known gene that maps to gender identity or to gender dysphoria. In other words, there is no objective physical measure to identify either gender identity or gender dysphoria.

This is in contrast to all other endocrine disorders which have a measurable physical change in either hormone levels or gland structure which can be confirmed by physical testing. Therefore, gender dysphoria is a purely psychological phenomenon and not an endocrine disorder. But as my colleagues and I wrote in our letter to the editor, it becomes an endocrine condition through gender affirmative therapy: "Childhood gender dysphoria (GD) is not an endocrine condition, but it becomes one through iatrogenic puberty blockade (PB) and high-dose cross-sex (HDCS) hormones. The consequences of this gender-affirmative therapy (GAT) are not trivial and include potential sterility, sexual dysfunction, thromboembolic and cardiovascular disease, and malignancy" (Laidlaw, et al. 2019).

C. Gender Dysphoria and Desistance

Gender dysphoria is a persistent state of distress that stems from the feeling that one's gender identity does not align with their physical sex (American Psychiatric Association, 2013). It has been a relatively rare condition in children and adolescents. However there have been very significant increases in referrals for this condition noted around the globe.

For example, in the UK, "The number of referrals to GIDS [Gender Identity Development Service] has increased very significantly in recent years. In 2009, 97 children and young people were referred. In 2018 that number was 2519" (Bell v Tavistock Judgment, 2020). There has been suggestion from parental reports that this increase may be in part due to social contagion and fueled by social media/internet use (Littman, 2018).[1]

In “a study of the Finnish gender identity service, ‘75% of adolescents [assessed] had been or were currently undergoing child and adolescent psychiatric treatment for reasons other than gender dysphoria’ (Kaltiala-Heino, 2015). In fact, ‘68% had their first contact with psychiatric services due to other reasons than gender identity issues.’ The same study also showed that 26% percent had an autistic spectrum disorder and that a

[1] The French National Academy of Medicine wrote recently: "Parents addressing their children’s questions about transgender identity or associated distress should remain vigilant regarding the addictive role of excessive engagement with social media, which is both harmful to the psychological development of young people and is responsible for a very significant part of the growing sense of gender incongruence" (SEGM, 2022).

disproportionate number of females (87%) were presenting to the gender clinics compared to the past" (Laidlaw in gdworkinggroup.org, 2018).

Desistance is a term indicating that the child, adolescent, or adult who initially presented with gender incongruence has come to experience a realignment of their internal sense of gender and their physical body. "Children with [gender dysphoria] will outgrow this condition in 61% to 98% of cases by adulthood. There is currently no way to predict who will desist and who will remain dysphoric" (Laidlaw et al. 2019).

Because there is no physical marker to diagnose gender identity, and because it is not possible to predict which child or adolescent will desist, it is not possible to know which young person will remain transgender identified as adults. Also, because the rate of desistance is so high, gender affirmative therapy will necessarily cause serious and irreversible harms to many children and adolescents.

D. Biological Sex in Contrast to Gender Identity

Biological sex is the objective physical condition of having organs and body parts which correspond to a binary sex. There are only two physical sexes, male and female. The male is identified as having organs and tissues such as the penis, testicles and scrotum. The female sex is identified by having organs and tissues such as the labia, vagina, uterus, and ovaries. Biological sex is easily identified by physical observation such that adults and even children of say four years old can identify the biological sex of a newborn baby.

This is in contrast to gender identity, which as mentioned does not exist in any physical sense. It is a subjective identification known only once a patient makes it known. It cannot be identified by any physical means, cannot be confirmed by any outside observer, and can change over time.

It is also noteworthy that the physical organs described above as representing biological sex have a physical genetic correlate. In other words, it is a well-established scientific fact that two X chromosomes identify the cells correlating to a female person, and an X and a Y chromosome correlate to a male person.

Sex is clearly identified in 99.98% of cases by chromosomal analysis (Sax, 2002). Sex is also clearly identified at birth in 99.98% of cases (Sax, 2002). Therefore, sex is a clear provable objective reality that can be identified through advanced testing such as karyotyping, or simple genital identification at birth by any layperson. The other 0.02%

of cases have some disorder of sexual development. These do not represent an additional sex or sexes, but simply a disorder on the way to binary sex development. These conditions are not related to the diagnosis of gender dysphoria.

1. Embryologic development

Another confirmation that there are only two biological sexes comes from what is known about embryologic development and fertilization. The biologic development of the human person begins with a gamete from a female termed an ovum or egg and a gamete from a biological male which is termed sperm. The fertilization of the egg by the sperm begins the process of human biological development. The cells of the fertilized ovum then multiply and the person undergoes the incredible changes of embryologic development.

It is noteworthy that the male sperm comes from the biological male and the female egg comes from the biological female. There is no other third or fourth or fifth type of gamete that exists to begin the development of the human person. This is consistent with the binary nature of human sex.

The sex binary of the human embryo is further developed between roughly weeks 8 to 12 of human development. There are two primitive structures present within the developing embryo called the Wolffian duct and Mullerian ducts (Larsen et al., 2003). The Wolffian ducts develop into substructures of the genitalia including the vas deferens and epididymis which belong exclusively to the male sex. For the female, the Mullerian ducts go on to form the uterus, fallopian tubes, cervix and upper one third of the vagina which belong exclusively to the female sex.

Significantly once the male structures are developed from Wolffian ducts, the Mullerian ducts are obliterated. This means that throughout the rest of embryological development the Mullerian ducts will not form into biological female structures. Likewise, in the female, the Wolffian ducts are destroyed by week 12 and will not form male structures at any point in the future.[2]

Thus we can see in very early development that the sex binary is imprinted physically not only in the chromosomes, but also on the very organs that the body produces. Additionally, the potential to develop organs of the opposite sex is eliminated. Thus, in the human being there are only two physical tracts that one may progress along, the one being male and the other being female.

[2] Excepting disorders of sexual development, which are unrelated to the diagnosis of gender dysphoria.

2. Pubertal development

As mentioned previously, at the time of birth an infant's sex is easily identified through observation of the genitalia. Corresponding internal structures could also be confirmed through imaging if needed.

In early childhood, some low level of sex hormones are produced by the sex glands. The male testes produce testosterone. The female ovaries produce primarily the hormone estrogen. These sex glands remain quiescent for the most part, producing low levels of sex hormones until the time of pubertal development.

Puberty is a time of development of the sex organs, body, brain and mind. There are well known changes in physical characteristics of the male such as growth of facial hair, deepening of the voice, and increasing size of the testicles and penis. Importantly the testicles will develop sperm under the influence of testosterone and become capable of ejaculation. Because of these changes, the male will become capable of fertilizing an egg. The inability to produce sperm sufficient to fertilize an egg is termed infertility.

For the female, pubertal development includes changes such as breast development, widening of the pelvis, and menstruation. The female will also begin the process of ovulation which is a part of the menstrual cycle and involves the release of an egg or eggs from the ovary. Once the eggs are released in a manner in which they can become fertilized by human sperm, the female is termed fertile. The inability to release ovum that can be fertilized is infertility. These concepts will become important later on when discussing puberty blockers and opposite sex hormones.

Puberty is also the time of social development when one changes schools appropriate for maturity such as middle school and high school. Groups of kids are placed together in such a way that they will develop with in concert their peers. This timing corresponds to the physical changes of sexual development during puberty.

It is psychologically important for similarly developing kids to be grouped together as they will have similar shared experiences and can continue to grow physically, emotionally, and psychologically through the dramatic changes that occur during puberty.

3. Tanner stages of development

From a medical perspective it is important to know the stage of pubertal development of the developing adolescent. This can be determined through a physical examination of the body. The female will have changes in breast characteristics and pubic hair development. Similarly, the male will have changes in testicular size and pubic hair development. These findings can be compared to the Tanner staging system which will allow the stage of puberty to be known.

Tanner stages are divided into five. Stage 1 is the pre-pubertal state before pubertal development of the child begins. Stage 5 is full adult sexual maturity. Stages 2 through 4 are various phases of pubertal development (Greenspan and Gardner, 2004).

Awareness of the Tanner stage of the developing adolescent is also useful to assess for maturation of sex organ development leading to fertility. For girls, menstruation and ovulation occurs about two years after Tanner stage 2 and will typically be at Tanner stage 4 or possibly 3 (Emmanuel and Boker, 2022). For boys, the first appearance of sperm is typically Tanner Stage 4 (Emmanuel and Bokor, 2022). If puberty is blocked before reaching these critical stages, the sex glands will be locked in a premature state and incapable of fertility.

These concepts will be very important later when discussing puberty blockers and opposite sex hormones.

4. Biological Sex Cannot Be Changed

It is not possible for a person to change from one biological sex to the other, and there is no technology that allows a biological male to become a biological female or vice-versa. It is not technologically possible at this time to change sex chromosomes; these will remain in every cell throughout life. It is not technologically possible to transform sex glands from one to the other. In other words, there are no hormones or other means currently known to change an ovary into a testicle or a testicle into an ovary.

Furthermore, as noted earlier, several of the sex specific structures (such as the epidymis of the male or uterus of the female) are produced early in embryological development from around weeks 8 to 12. The primitive ducts which lead to these organs of the opposite sex are obliterated. There is no known way to resuscitate these ducts and continue development of opposite sex structures.

It is also not possible to produce gametes of the opposite sex. In other words, there is not any known way to induce the testicles to produce eggs. Nor is there any known way to induce the ovaries to produce sperm. Therefore, creating conditions for a biological female to create sperm capable of fertilizing another ovum is impossible. Likewise in the human male testicle cannot be induced to create eggs. The induction of opposite sex fertility is impossible.

In fact, as I will discuss, gender affirming therapy actually leads to infertility and potential sterilization.

E. Iatrogenic Harms

The term iatrogenic is used in medicine to describe harms or newly created medical conditions that are the result of medications, surgeries, or even psychological treatments. In this section I will discuss the iatrogenic harms of “gender affirmative treatment,” which includes treatment addressed by Alabama’s law. Each of the four interventions which I will describe (social transition, puberty blockers, opposite sex hormones, and surgery) lead to iatrogenic harms to the patient. These harms will be described in detail below.

1. Gender Affirmative Therapy

The approaches to gender dysphoria may be divided into three main types. (Zucker, 2020). One is pyschosocial treatment that helps the young person align their internal sense of gender with their physical sex. Another would be to "watch and wait" and allow time and maturity to help the young person to align sex and gender through natural desistance. The third option, which is the focus of that which follows, is referred to as gender affirmative therapy.

Gender affirmative therapy (GAT) consists of psychosocial, medical, and surgical interventions that attempt to psychologically and medically alter the patient so that they come to believe that they may become similar to the physical sex which aligns with their gender identity (but not their biological sex) and thereby reduce gender dysphoria. GAT consists of four main parts: 1) social transition, 2) blocking normal puberty, 3) high dose opposite sex hormones, and 4) surgery of the genitalia and breasts.

The application of this medical therapy to minors is a fairly new intervention and is associated with a number of harms both known and unknown. GAT suffers from a lack

of a quality evidence-base, poorly performed studies, and ongoing unethical human experimentation.

2. Social transition

The first stage of gender affirmative therapy is termed social transition. Social transition is a psychological intervention. The child may be encouraged to adopt the type of clothing and mannerisms or behaviors which are sterotypical of the opposite sex within a culture. For example, in the United States a boy might wear his hair long and wear dresses in order to socially transition. A girl may cut her hair short and wear clothes from the boys' section of a department store.

Social transition has been noted by expert researcher in the field of child gender dysphoria, Ken Zucker, to itself be a form of iatrogenic harm (Zucker, 2020). This insofar as the social transition process may solidify the young person's belief that they are in fact the sex opposite of that which was identified at birth.

It is easy to see why in the child's mind, by having the outward appearance of the opposite sex, that they would believe that they should have been destined to go through puberty of the opposite sex as they have only a poor understanding of the internal structures of the body, the function of the sex glands, the role of the sex glands in fertility and so forth.

Therefore, it would be quite frightening for a boy who believes he is a girl to be turning into a man with all of the adult features that accompany manhood. Vice versa, the girl who has become convinced that she is a boy will be frightened by the physical changes brought on by womanhood.

This is evident in the declaration of Megan Poe where she states: “Seeing Allison’s response to the Alabama legislature’s consideration of the Act and knowing how afraid she is of male puberty” (Megan Poe Declaration, 2022).

In fact it would appear that in the minds of the children and adolescents that they are anticipating a sort of disease state in the future by the hormone changes that will occur as a normal and natural part of human development. Until relatively recently in human history, it has not been possible to block puberty through pharmaceutical means.

3. Puberty blocking medication

The second step of the gender affirmative therapy model involves blocking normal pubertal development.

In order to understand what is occurring in this process, it is helpful to be aware of normal hormone function during pubertal development.

There is a small pea-sized gland in the brain called the pituitary. It is sometimes referred to as the "master gland" as it controls the function of several other glands. One key function for our purposes is the control of the sex glands. There are two specific hormones produced by the pituitary referred to as luteinizing hormone (LH) and follicle stimulating hormone (FSH). These are responsible for sex hormone production and fertility. The LH and FSH act as signals to tell the sex glands begin or continue their function.

In the adult male, the production of LH will cause adult levels of testosterone to be produced by the testicles. In the adult female, the production of LH will cause adult levels of estrogen to be produced by the ovaries.

In early childhood, prior to the beginning of puberty, the pituitary function with respect to the sex glands is quiescent. However, during pubertal development LH will signal the testicle to increase testosterone production and this carries the boy through the stages of pubertal development into manhood. Likewise for the female, the interaction of LH with the ovaries increases estrogen production and carries the girl through the stages of development into womanhood.

There are conditions diagnosed by the endocrinologist which involve a disruption of this normal communication between the pituitary and the sex glands. There is a medical condition called hypogonadotropic hypogonadism. The meaning of this term is that the pituitary is not sending the hormonal signals (LH and FSH) to the sex glands and therefore the sex glands are unable to make their sex hormones. The result is hormonal deficiencies of LH, FSH, and either testosterone or estrogen.

If this condition occurs during puberty, the effect will be to stop pubertal development. This is a disease state which is diagnosed and treated by the endocrinologist.

Medications such as GnRH agonists[3] act on the pituitary gland to lower the pituitary release of LH and FSH levels dramatically. The result is a blockage of the signaling of

[3] Gonadotropin Releasing Hormone agonists

the pituitary to the testicles or ovaries and therefore underproduction of the sex hormones. There are a variety of uses for GnRH agonists. The use and outcome can be very different for different applications.

For example, the initial development of the medication called Lupron was for the treatment of prostate cancer. The idea being that blocking pituitary hormones will block the adult male's release of testosterone from the testicles. Since testosterone will promote the growth of prostate cancer, the idea is to lower testosterone levels to a very low amount and therefore prevent the growth and spread of prostate cancer. This is a labeled use of the medication. In other words, there is FDA approval for this use.

Another labeled use of GnRH agonist medication is for the treatment of central precocious puberty. In the disease state of central precocious puberty, pituitary signaling is activated at an abnormally young age, say age four, to begin pubertal development. In order to halt puberty which has begun at an abnormally early time, a GnRH agonist may be used. Here the action of the medication on the pituitary will disrupt the signaling to the sex glands, stop early sex hormone production, and therefore stop abnormal pubertal development.

Then, at a more normal time of pubertal development, say age 11, the medication is stopped and puberty is allowed to proceed.[4] The end result is to restore normal sex gland function and timing of puberty. This is a labeled use for a GnRH agonist medication.

What about the use of puberty blockers such as Lupron in gender affirmative therapy? In these cases, we have physiologically normal children who are just beginning puberty or are somewhere in the process of pubertal development. They have healthy pituitary glands and sex organs. However, a puberty blocking medication is administered to stop normal pubertal development.

In this case the condition of hypogonadotropic hypogonadism described above is induced medically and is an iatrogenic effect of treating the psychological condition of gender dysphoria. GnRH agonist medications have not been FDA approved for this use.

[4] Once the medication is discontinued, it will take a number of months to a year or longer for the pituitary to regain its usual function.

4. Adverse Health Consequences of Blocking Normal Puberty

There are a number of serious health consequences that occur as the result of blocking normal puberty. The first problem is infertility. The Endocrine Society Guidelines recommend beginning puberty blockers as early as Tanner stage 2. As discussed earlier, this is the very beginning of puberty. Fertility development happens later generally in Tanner stage 4. One can see that if the developing person is blocked at Tanner stage 2 or 3 as advocated by the guidelines, this is prior to becoming fertile. The gonads will remain in an immature, undeveloped state.

This is why the guidelines refer to fertility preservation. However, studies show that less than 5% of adolescents receiving GAT even attempt fertility preservation (Nahata, 2017). Also fertility preservation for persons with immature ovaries and testicles is much more complicated, expensive and in many cases still experimental (Laidlaw, Cretella, et al. 2019).

Naturally, these children are at a developmental age where they are not thinking about adult related concepts such as having children as they are children themselves. This is only natural and to be expected. The medical problem imposed on them is that if they remain blocked in an early pubertal stage then even the addition of opposite sex hormones will not allow for the development of fertility. In fact, high dose opposite sex hormones may permanently damage the immature sex organs leading to sterilization. Certainly the removal of the gonads, which will be discussed later, will ensure sterilization.

Another problem with blocking puberty at an early stage is sexual dysfunction. The child will continue their chronological age progression toward adulthood and yet remain with undeveloped genitalia. This will lead to sexual dysfunction including potential erectile dysfunction and inability to ejaculate and orgasm for of the male. For the female with undeveloped genitalia potential sexual dysfunction may include painful intercourse and impairment of orgasm.

The impairment of sexual function was evident in the TLC reality show "I am Jazz". In the show Jazz who was identified male at birth has been given puberty blockers at an early pubertal stage. In an episode where Jazz visits a surgeon and has a discussion about sexual function, Jazz states: “I haven’t experienced any sexual sensation.” Regarding orgasm, Jazz says: “I don’t know, I haven’t experienced it”[5] (TLC, accessed 2022).

[5] Jazz's age is somewhere in the mid-teens during this episode.

In addition to direct effects on the developing genitalia and fertility there are other important aspects of puberty that are negatively affected. For example, puberty is a time of rapid bone development. This time of development is critical in attaining what we call peak bone density or the maximum bone density that one will acquire in their lifetime (Elhakeem, 2019).

Any abnormal lowering of sex hormones occurring during this critical time will stop the rapid accumulation of bone and therefore lower ultimate adult bone density. If a person does not achieve peak bone density, they would be expected to be at future risk for osteoporosis and the potential for debilitating spine and hip fractures as adults. Hip fractures for the older patient very significantly increase the risk of major morbidity and death (Bentler, 2009). Allowing a "pause" in puberty for any period of time leads to an inability to attain peak bone density.

Another consideration is maturation of the human brain. Much of what happens is actually unknown. However, “sex hormones including estrogen, progesterone, and testosterone can influence the development and maturation of the adolescent brain” (Arain, 2013). Therefore there are unknown, but likely negative consequences to blocking normal puberty with respect to brain development.

A third major problem with blocking normal puberty involves psychosocial development. Adolescence is a critical time of physical, mental, and emotional changes for the adolescent. It is important that they develop socially in conjunction with their peers. This is well recognized in the psychological literature: “For decades, scholars have pointed to peer relationships as one of the most important features of adolescence.” (Brown, 2009). If one is left behind for several years under the impression that they are awaiting opposite sex puberty, they will miss important opportunities for socialization and psychological development. Psychosocial development will be necessarily stunted as they are not developing with their peers. This is a permanent harm as the time cannot be regained.

Aside from the multiple serious problems that are iatrogenically acquired by blocking normal puberty, there appear to be independent risks of the puberty blocking medication themselves. For example, one can read the labeling of a common puberty blocking medication called Lupron Depot-Ped and find under psychiatric disorders: "emotional lability, such as crying, irritability, impatience, anger, and aggression. Depression, including rare reports of suicidal ideation and attempt. Many, but not all, of these patients had a history of psychiatric illness or other comorbidities with an increased risk of depression” (Lupron, 2022). This is particularly concerning given the high rate of psychiatric comorbidity with gender dysphoria discussed previously.

5. The Effect of Puberty Blockers on Desistance

As stated earlier a very high proportion of minors diagnosed with gender dysphoria will eventually desist or come to accept their physical sex. Puberty blockers have been shown to dramatically alter natural desistance.

In a Dutch study that included seventy adolescents who took puberty blockers, all seventy decided to go on to hormones of the opposite sex (de Vries, et al. 2011). In a follow-up study, the majority went on to have sex reassignment surgery by either vaginoplasty for males or hysterectomy with ovariectomy for females (de Vries, et al. 2014). These surgeries resulted in sterilization. This is why puberty blockers, rather than being a “pause” to consider aspects of mental health, are instead a pathway towards future sterilizing surgeries.

6. Opposite Sex Hormones

The third stage of gender affirmative therapy involves using hormones of the opposite sex at high doses to attempt to create secondary sex characteristics in the person's body. Before beginning I will describe FDA approved usages of estrogen and testosterone

a. Testosterone

Testosterone is an anabolic steroid of high potency. It is classified as a Schedule 3 controlled substance by the DEA: "Substances in this schedule have a potential for abuse less than substances in Schedules I or II and abuse may lead to moderate or low physical dependence or high psychological dependence" (DEA, 2022)

I prescribe testosterone to men for testosterone deficiency. The state of testosterone deficiency can cause various problems including problems of mood, sexual function, libido, and bone density. Prescription testosterone is given to correct the abnormally low levels and bring them back into balance.

Estrogen is the primary sex hormone of the female. Prescription estrogen may be used if a woman has low estrogen levels due to premature failure of her ovaries. Estrogen is prescribed to bring these levels back into a normal range for the patient's age. Another labeled use of estrogen is to treat menopausal symptoms.

In GAT, what is termed "cross sex hormones" is the use of hormones of the opposite sex to attempt to create secondary sex characteristics. In order to do so, very high doses of these hormones are administered. When hormone levels climb above normal levels they are termed supraphysiologic.

The female person does produce some smaller amount of testosterone relative to the male. The normal reference range for adult females depending on the lab is about 10 to 50 ng/dL. However, in female disease conditions these levels can be much higher. For example, in polycystic ovarian syndrome levels may range from 50 to 150 ng/dL. PCOS has been associated with insulin resistance (Dunaif, 1989), metabolic syndrome (Apridonidze, 2005) and diabetes (Joham, 2014).

In certain endocrine tumors such as adrenal carcinoma these levels may be substantially higher in the 300 to 1000 ng/dl range. Adrenal carcinoma is a serious medical condition and may be treated by surgery and potent endocrine medications.

b. Opposite Sex Hormones - Supraphysiologic Doses of Testosterone for Females

Recommendations from the Endocrine Society's clinical guidelines are to ultimately raise female levels of testosterone to 320 to 1000 ng/dL[6] which is on the same order as dangerous endocrine tumors for women as described above (Hembree, 2017). A simple calculation shows this level may be anywhere from 6 to 100 times higher than native female testosterone levels. In doing so they are creating a hormone imbalance known as hyperandrogenism. These extraordinarily high levels of testosterone are associated with multiple risks to the physical and mental health of the patient.

"Studies of transgender males taking testosterone have shown up to a nearly 5-fold increased risk of myocardial infarction relative to females not receiving testosterone" (Laidlaw et al.,2021; Alzahrani et al., 2019). A female can also develop unhealthy, high

[6] In the Endocrine Society's Guidelines there is no grading of evidence for the rationale of using such high supraphysiologic doses of opposite sex hormones for the female or male. There seems to be an underlying assumption that because the person believes to be the opposite sex then they acquire the sex specific laboratory ranges of the opposite sex. "The root cause of this flaw in thinking about diagnostic ranges was exemplified in a response letter by Rosenthal et al claiming that gender identity determines the ideal physiologic range of cross-sex hormone levels (5). Thus a psychological construct, the “gender identity,” is imagined to affect physical reality and change a person’s sex-specific laboratory reference ranges. This is clearly not the case, otherwise there would be no serious complications of high-dose androgen treatment in transgender males" (Laidlaw et al., 2021).

levels of red blood cells referred to as erythrocytosis. These high red blood cell counts in young women have been shown to be an independent risk factor for cardiovascular disease, coronary heart disease and death due to both (Gagnon, 1994).

Other permanent effects of testosterone therapy involve irreversible changes to the vocal cords. Abnormal amounts of hair growth which may occur on the face, chest, abdomen, back and other areas is known as hirsutism. Should the female eventually regret her decision to take testosterone, this body hair can be very difficult to remove. Male pattern balding of the scalp may also occur. These changes of voice and hair growth can be very psychologically troubling when attempting to reintegrate into society as a female.

Changes to the genitourinary system include polycystic ovaries and atrophy of the lining of the uterus. The breasts have been shown to have an increase in fibrous breast tissue and a decrease in normal glandular tissue (Grynberg et al., 2010). Potential cancer risks from high dose testosterone include ovarian and breast cancer (Hembree, 2017).

According to research regarding testosterone abuse, high doses of testosterone have been shown to predispose individuals towards mood disorders, psychosis, and psychiatric disorders. The "most prominent psychiatric features associated with AAS [anabolic androgenic steroids, i.e. testosterone] abuse are manic-like presentations defined by irritability, aggressiveness, euphoria, grandiose beliefs, hyperactivity, and reckless or dangerous behavior. Other psychiatric presentations include the development of acute psychoses, exacerbation of tics and depression, and the development of acute confusional/delirious states" (Hall, 2005). Moreover, "[s]tudies... of medium steroid use (between 300 and 1000 mg/week of any AAS) and high use (more than 1000 mg/week of any AAS) have demonstrated that 23% of subjects using these doses of steroids met the DSM-III-R criteria for a major mood syndrome (mania, hypomania, and major depression) and that 3.4% — 12% developed psychotic symptoms" (Hall, 2005).

c. Opposite Sex Hormones - Supraphysiologic Estrogen for Males

For the male, estrogen is being used at supraphysiologic doses. The high doses are used in an attempt to primarily affect an increase of male breast tissue development known as gynecomastia. Gynecomastia is the abnormal growth of breast tissue in the male. The occurrence of gynecomastia in the male is sometimes corrected by medication or more commonly by surgery if needed. Other changes of secondary sex characteristics may develop such as softening of the skin and changes in fat deposition and muscle development.

The doses of estrogen given to males for GAT are high and may vary from two to eight or more times higher than normal adult male levels. This produces the endocrine condition called hyperestrogenemia. Long term consequences include increased risk of myocardial infarction and death due to cardiovascular disease (Irwig, 2018). Also "[t]here is strong evidence that estrogen therapy for trans women increases their risk for venous thromboembolism[7] over 5 fold" (Irwig, 2018).

Breast cancer is a relatively uncommon problem of the male. However the risk of a male developing breast cancer has been shown to be 46 times higher with high dose estrogen (Christel et al., 2019).

It is clear that supraphysiologic doses of either testosterone for the female or estrogen for the male can have detrimental health consequences. This is only now being borne out in the literature for adults. However as more children and adolescents are put on these medications one would expect these consequences to become more frequent and to occur earlier in their lives.

7. Surgeries

The fourth stage of gender affirmative therapy is surgical alterations of the body of various kinds in an attempt to somehow mimic features of the opposite sex.

Individual surgical procedures can be a complex topic. It is helpful to first step back and consider conceptually what any surgery can and cannot accomplish.

In its basic form surgery is subtractive. In other words, a portion of tissue, an organ or organs are removed in order to restore health. For example, a diseased gallbladder may be surgically removed to help the patient get back to wellness. An infected appendix may be surgically removed to prevent worsening infection or even death. In both of these cases an unhealthy body part is surgically removed in order to restore health.

In some cases a diseased tissue or organ is removed so that a foreign replacement part may be substituted for an unhealthy organ or tissue. For example, a diseased heart valve may be replaced with a pig valve or a prosthetic heart valve. Another example is a failed liver may be replaced by liver transplant.

[7] Venous thromboembolism is a blood clot that develops in a deep vein and "can cause serious illness, disability, and in some cases, death" (CDC, 2022).

Though modern surgical techniques and procedures are astounding, there are very noteworthy limitations. Importantly, surgery cannot de novo create new organs. If a person's kidneys fail, the surgeon has no scientific method for creating a new set of kidneys that can be implanted or grown within the patient. This conceptual background is helpful when considering various gender affirming surgeries.

There are a variety of gender affirming surgeries. These may include mastectomies, vaginoplasty, metoidioplasty, and phalloplasty.

a. Mastectomy

Mastectomies are the surgical removal of the breasts. The procedure is used in GAT in an attempt to make the chest appear more masculine. The surgery results in a permanent loss of the ability to breastfeed and significant scarring of 7 to 10 inches. The scars are prone to widening and thickening due to the stresses of breathing and arm movement. Other potential complications include the loss of normal nipple sensation and difficulties with wound healing.

It is important to note that this operation cannot be reversed. The female will never regain healthy breasts capable of producing milk to feed a child. Similar to the problems of receiving opposite sex hormones and puberty blockers at a young age, the adolescent is too young to consent to lifelong changes for which she cannot fully appreciate the ramifications. One would not generally expect a 13-year-old or 16-year-old to have thought deeply or to be concerned about breast-feeding in her 20s or 30s or older.

Another important consideration is that compared to the removal of an unhealthy gallbladder or appendix, in the case of gender dysphoria the breasts are perfectly healthy and there is no organic disease process such as a cancer warranting their removal. The future woman who later desists is left with regret about what happened to her at an age before she could provide true informed consent. Breasts cannot be created by a surgeon and restored to a patient in case of regret. She is left with permanent injury and loss of function with respect to her breasts.

Other types of surgery for females include those of the genitalia and reproductive tract. For example the ovaries, uterus, fallopian tubes, cervix and the vagina may be surgically removed. Removal of the ovaries results in sterilization.

Importantly, removing female body parts does not produce a male. Rather, the female has had sex specific organs permanently destroyed with no hope of replacement, while remaining biologically female.

There have also been attempts to create a pseudo-penis. This procedure is known as phalloplasty. It is not possible to de novo create a new human penis. Instead a roll of skin and subcutaneous tissue is removed from one area of the body, say the thigh or the forearm, and transplanted to the pelvis. An attempt is made to extend the urethra or urinary tract for urination through the structure. This transplanted tissue lacks the structures inherent in the male penis which allow for erection, therefore erectile devices such as rods or inflatable devices are placed within the tube of transplanted tissue in order to simulate erection (Hembree, 2017). The labia may also be expanded to create a simulated scrotum containing prosthetic objects to provide the appearance of testicles.

Complications may include urinary stricture, problems with blood supply to the transplanted roll of tissue, large scarring to the forearm or thigh, infections including peritonitis, and possible injury to the sensory nerve of the clitoris.

b. GAT Surgeries on the Male

GAT surgeries for the male include removal of the testicles alone to permanently lower testosterone levels. This is by nature a sterilizing procedure. Further surgeries may be done in an attempt to create a pseudo-vagina which is called vaginoplasty. In this procedure, the penis is surgically opened and the erectile tissue is removed. The skin is then closed and inverted into a newly created cavity in order to simulate a vagina. A dilator must be placed in the new cavity for some time so that it does not naturally close.

Potential surgical complications may include urethral strictures, infection, prolapse, fistulas and injury to the sensory nerves with partial or complete loss of erotic sensation.

c. The Effect of Puberty Blockers on the Vaginoplasty Procedure

It is important to understand that the use of puberty blockers for the male makes the vaginoplasty procedure even more complicated. Puberty blockers prevent the growth and elongation of the penis that naturally occurs during puberty. Therefore the surgeon has a limited length of penile skin to work with. In these cases a technique is employed whereby a segment of the large bowel (colon) is surgically excised while leaving its blood supply intact. The segment of colon is then connected to the short, inverted penile skin in attempt to extend the length of the pseudo-vagina. Obviously the risk and types

of complications increase further and multiple surgeries and revisions may need to be employed.

F. Life Threatening Physical Medical Conditions Versus Suicidal Ideation

Any child or adolescent who has suicidal ideation or has attempted suicide should receive immediate, appropriate psychiatric care. Psychologists and psychiatrists are trained in the recognition and treatment of suicidal ideation and prevention of suicide. A child or adolescent with gender dysphoria who also has suicidal ideation should not be treated any differently. They require compassionate care and a full psychological evaluation of comorbidities such as depression, anxiety, and self-harming behaviors.

However, suicidal ideation or attempts are categorically different than other life-threatening situations, such as a rapidly expanding brain tumor or a severe infection. In these situations, a medication or a surgery is used to stop the progression of an organic physical condition. In contrast, the danger to the self with suicidal ideation relates to a condition of the mind.

Gender affirmative therapy does not treat any life-threatening physical condition. In fact it creates a number of new medical conditions as described above. It is also not an appropriate treatment for suicidal ideation. Neither puberty blocking medications, nor testosterone, nor estrogen have been FDA approved for suicide prevention. In my opinion, it is possible that the hormone imbalances generated by the medications used in GAT may increase the risk of suicidal ideation and completed suicide.

G. Informed Consent

Any person who is to take a medication, undergo a surgical procedure, or have a psychological intervention should understand the risks and benefits before proceeding. A discussion of these risks and benefits should be provided by medical professionals and then the person of sufficient intellectual capacity and maturity can consent to the treatment.

Naturally difficulties arise when a minor is involved in the process of medical decision-making. Their intellect, emotions, and judgement are not fully developed and they are not capable of fully appreciating permanent, life altering changes such as described above. Therefore, they cannot provide informed consent. They may sometimes "assent" to a procedure or medication with a parent or guardian making the final decision.

With respect to GAT, I believe that it is not possible for the parent or guardian to make a true informed consent decision for the child because of the poor quality of evidence of benefit, the known risks of harm, and the many unknown long-term risks of harm which could only truly be known after years and decades of gender affirmative therapy. A parent or guardian cannot consent to dubious treatments which result in irreversible changes to their child's body, infertility, sexual dysfunction, and in many cases eventual sterilization.

Because this age group is still undergoing brain development and they are immature with respect to intellect, emotion, judgment, and self-control, in my professional opinion there is a significant chance a young person may later regret the irreversible bodily changes that result from hormones or from removing an organ or organs that will no longer function and cannot be replaced.

I would also note that adolescents are more prone to high-risk behavior and less likely to fathom the risks and consequences of these decisions (Steinberg, 2008).

H. The WPATH and The Endocrine Society

The declarations of Dr. Linda Hawkins, Dr. Stephen Rosenthal, and Dr. Jane Moe cite the World Professional Association for Transgender Health's ("WPATH") "Standards of Care for the Health of Transsexual, Transgender, and Gender Non-Conforming People." According to their declarations, Dr. Hawkins is a longstanding member of WPATH, and Dr. Rosenthal is on the Board of Directors of WPATH.

WPATH's "Standards of Care" were prepared within their advocacy organization and are purported to be a "professional consensus about the psychiatric, psychological, medical, and surgical management of gender dysphoria" (WPATH, 2022). However, the "professional consensus" exists only within the confines of its organization. Furthermore, their "Standards of Care," unlike the Endocrine Society's guidelines, do not have a grading system for either the strength of their recommendations or the quality of the evidence presented.

While the Endocrine Society has issued "Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline," these are only "guidelines." The Endocrine Society's guidelines specifically state that their "guidelines cannot guarantee any specific outcome, nor do they establish a standard of care" (Hembree at al, 2017, p. 3895). This contradicts Dr. Rosenthal's claim about the guidelines calling it "a guide detailing the standard of medical care for gender dysphoria".

In the Endocrine Society's guidelines, the quality of evidence for the treatment of adolescents is rated "very low-quality evidence" and "low quality evidence". "The quality of evidence for [puberty blocking agents] is noted to be low. In fact, all of the evidence in the guidelines with regard to treating children/adolescents by [gender affirmative therapy] is low to very low because of the absence of proper studies" (Laidlaw et al., 2019).

Unlike some other recommendations for adolescent GAT, the Endocrine Society's guidelines do not include any grading of the quality of evidence specifically for their justification of laboratory ranges of testosterone or estrogen or for adolescent mastectomy or other surgeries.

I. The Lack of Evidence of Effectiveness of GAT

There is also evidence that questions the long-term effectiveness of opposite sex hormones and gender reassignment surgery. A Swedish study in 2011 examined data over a 30-year period (Dehejne, 2011). The Dhejne team made extensive use of numerous Swedish registries and examined data from 324 patients in Sweden over 30 years who had taken opposite sex hormones and had undergone sex reassignment surgery. They used population controls matched by birth year, birth sex, and reassigned sex. When followed out beyond ten years, the sex-reassigned group had nineteen times the rate of completed suicides and nearly three times the rate of all-cause mortality and inpatient psychiatric care compared to the general population of Sweden.

Other published studies of GAT have been shown to have serious errors. For example a major correction was issued by the American Journal of Psychiatry. The editors of an October 2019 study, titled "Reduction in mental health treatment utilization among transgender individuals after gender-affirming surgeries: a total population study" (Bränström study) retracted their original primary conclusion. Letters to the editor by twelve authors including myself led to a reanalysis of the data and a corrected conclusion stating that in fact the data showed no improvement in mental health for transgender identified individuals after surgical treatment ("Correction", 2020; Van Mol et al., 2020). [8]

The Centers for Medicare and Medicaid Services ("CMS") has found "inconclusive" clinical evidence regarding gender reassignment surgery. Specifically, the CMS Decision Memo for Gender Dysphoria and Gender Reassignment Surgery (CAG-

[8] The study also did not show an improvement in mental health with opposite sex hormones.

00446N) (June 19, 2019) states: “The Centers for Medicare & Medicaid Services (CMS) is not issuing a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria because the clinical evidence is inconclusive for the Medicare population.”

Also noteworthy is that other nations are questioning gender affirmative therapy. For example in the Bell vs Tavistock Judgment in the UK, regarding puberty blockers in GAT, they concluded that "there is real uncertainty over the short and long-term consequences of the treatment with very limited evidence as to its efficacy, or indeed quite what it is seeking to achieve. This means it is, in our view, properly described as experimental treatment" (Bell v Tavistock Judgment, 2020).

Finland in 2020 recognized that “[r]esearch data on the treatment of dysphoria due to gender identity conflicts in minors is limited,” and recommended prioritizing psychotherapy for gender dysphoria and mental health comorbidities over medical gender affirmation (Council for Choices in Healthcare in Finland, 2020).

In 2021, Sweden’s largest adolescent gender clinic announced that it would no longer prescribe puberty blockers or cross-sex hormones to youth under 18 years outside clinical trials (SEGM, 2021).

Dr Hilary Cass "was appointed by NHS England and NHS Improvement to chair the Independent Review of Gender Identity Services for children and young people in late 2020” (The Cass Review website, 2022).

In her interim report dated February 2022, it states that “[e]vidence on the appropriate management of children and young people with gender incongruence and dysphoria is inconclusive both nationally and internationally” (Cass, 2022).

Conclusion

The gender affirmative therapy model suffers from serious deficiencies in logic and lacks scientific foundation. The deep error hidden in this model is that one cannot in fact change sex. One cannot acquire the deep characteristics of biological sex in order to gain the complete sexual and reproductive functions of the opposite sex. This is not technologically possible.

Children and adolescents are of such immature minds that they are likely to believe that it is possible. In fact they may come to believe that their inherent, biologically necessary puberty is "terrifying". This fear begins as the result of social transition. Puberty blockers

sustain this state of mind by retaining a childlike state with respect to the genitalia and body habitus. High dose opposite sex hormones then cause medical conditions such as gynecomastia and hirsuitism. These conditions serve to convince the young person that they are going through puberty of the opposite sex when in fact they are not developing sexually and are infertile.

There are known risks, some of which I have described above, including cardiovascular disease, cancer, deficiencies in ultimate bone density, harms to sexual function, infertility, and for some permanent sterility. The child or adolescent cannot consent to these harms when they are not mature enough to fully comprehend what they mean.

For the reasons set forth above, in my professional opinion as an endocrinologist, no child or adolescent should receive puberty blockers to block normal puberty, nor should they receive supraphysiologic doses of opposite sex hormones to attempt to alter secondary sex characteristics, nor should they have surgeries to remove or alter the breasts, genitalia or reproductive tracts as part of GAT. The child cannot consent or assent to these procedures. The parent or guardian also cannot consent to the life altering changes resulting from GAT. Therefore I believe that the Alabama Vulnerable Child Compassion and Protection Act is based on sound medical principles for the protection of minors.

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct. Executed on May 1, 2022.

Michael K Laidlaw M.D.

Michael K. Laidlaw

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EMPLOYMENT

2006-Present	Michael K Laidlaw, MD Inc. Private Practice – Endocrinology, Diabetes, and Metabolism. Rocklin, CA

EDUCATION

2004-2006	Endocrinology and Metabolism Fellowship - Los Angeles County/University of Southern California Keck School of Medicine
2001-2004	Internal Medicine Residency - Los Angeles County/University of Southern California Keck School of Medicine
1997-2001	University of Southern California Keck School of Medicine Doctor of Medicine Degree May 2001
1990-1997	San Jose State University Bachelor of Science Degree in Biology with a concentration in Molecular Biology, Cum Laude

LICENSURE

California Medical License – Physician and Surgeon: # A81060: Nov 6, 2002. Exp 5/31/2024.

PROFESSIONAL AFFILIATIONS

Endocrine Society 2006-2022
National Board of Physicians and Surgeons - Endocrinology, Diabetes, & Metabolism 2018-2024
National Board of Physicians and Surgeons - Internal Medicine 2018-2024
American Board of Internal Medicine - Endocrinology, Diabetes, and Metabolism – 2006-2016
American Board of Internal Medicine - Internal Medicine - 2005-2015

HONORS AND RECOGNITION

2010	Endocrine Society Harold Vigersky Practicing Physician Travel Award
2004-2005	Vice President - Joint Council of Interns and Residents
2002-2004	Council Member – Joint Council of Interns and Residents
1996, 1997	Dean's Scholar, San Jose State University
1995	Golden Key National Honor Society

RESEARCH, PUBLICATIONS, AND EXPERT REPORTS

2021 Publication – Michael K Laidlaw, Andre Van Mol, Quentin Van Meter, Jeffrey E Hansen. Letter to the Editor from M Laidlaw et al.: "Erythrocytosis in a Large Cohort of Trans Men Using Testosterone: A Long-Term Follow-Up Study on Prevalence, Determinants, and Exposure Years." The Journal of Clinical Endocrinology & Metabolism, Volume 106, Issue 12, December 2021, Pages e5275–e5276, https://doi.org/10.1210/clinem/dgab514

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2011 Abstract – Poster presentation Nov 2011. Journal of Diabetes Science and Technology. A Video Game Teaching Tool for the Prevention of Type 2 Diabetes and Obesity in Children and Young Adults.

2011 Abstract – Journal of Diabetes Science and Technology. A Web-Based Clinical Software Tool to Assist in Meeting Diabetes Guidelines and Documenting Patient Encounters.

2008 Abstract - Accepted to Endocrine Society Annual Meeting 2008. Hypercalcemia with an elevated 1,25 dihydroxy-Vitamin D level and low PTH due to granulomatous disease.

2005-2006 Clinical Research - University of Southern California – Utility of Thyroid Ultrasound in the Detection of Thyroid Cancer. Study involving the use of color flow/power doppler ultrasound and ultrasound guided biopsy to detect the recurrence of thyroid cancer in patients with total thyroidectomies.

2005 Certification - Certification in Diagnostic Thyroid Ultrasound and Biopsy – AACE 2005

2003 Certification - Understanding the Fundamentals: Responsibilities and Requirements for the Protection of Human Subjects in Research. University of Southern California. 29 Sep 2003 - 29 Sep 2006

2002-2005 Clinical Research - University of Southern California - Determining the Role of Magnesium in Osteoporosis. Study involved collecting and analyzing patient data related to patient characteristics, laboratory results, bone mineral density exams, nutrition analysis, and genetic analysis in order to determine a link between magnesium deficiency and osteoporosis.

1996 Research Assistant - San Jose State University - Role of the suprachiasmatic nucleus pacemaker in antelope ground squirrels.

1995-1996 Research Assistant - San Jose State University/NASA. Acoustic tolerance test and paste diet study for space shuttle rats.

PERSONAL

Languages: Conversational Spanish, French
Tutor: Biochemistry, computer science, High School mentor
Computers: Ruby, Rails, Javascript, C++, C, Java, and HTML programming

DEFENDANT'S EXHIBIT 4

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER, *et al.*,	)	
Plaintiffs,	)	
v.	)	No. 2:22-cv-00184-LCB-SRW
KAY IVEY, in her official capacity as Governor of the State of Alabama, *et al.*,	)	
Defendants.	)	

DECLARATION OF QUENTIN L. VAN METER, M.D.

My name is Quentin L. Van Meter. I am over the age of 19, I am qualified to give this declaration, and I have personal knowledge of the matters set forth herein.

My CV is attached to this declaration. My recent publications in the *Journal of Clinical Endocrinology and Metabolism* are listed on my CV.

In the past four years, I have provided expert testimony in state legislative committee hearings in Alabama, Pennsylvania, Missouri, Iowa, and California, and I have been deposed as an expert witness in Virginia, Ohio, Missouri, and Georgia:

- 2018: Court of the Queens Bench Ontario, court file 1808-00144, deposed
- 2018: Sieffert v Hamilton Co Ohio, court testimony
- 2019: Gavin Grimm v Gloucester Co Virginia School Board, deposed
- 2019: Multiple Plaintiffs v State of Ohio Bureau of Records, deposed
- 2020: Loughman v Loughman, Harris County, Texas, deposed
- 2021: Spahr v Spahr, St Louis County, MO, court testimony
- 2021: Laura Cauthen v James Cauthen, Cobb County GA, court testimony

I am compensated at the rate of $350.00 per hour for record review and document preparation and $450.00 per hour for deposition or court testimony on this matter. My compensation is not dependent upon the substance of my opinions or the outcome of the case.

Qualifications

I have been retained by counsel for Defendants as an expert in connection with the above-captioned litigation. I have actual knowledge of the matters stated in this declaration. My professional background, experience, and publications are detailed in my curriculum vitae. A true and accurate copy is attached as Exhibit A to this declaration. I received my B.A. in Science at the College of William and Mary and my M.D. from the Medical College of Virginia, Virginia Commonwealth University. I am currently a pediatric endocrinologist in private practice in Atlanta, Georgia. I am the President of Van Meter Pediatric Endocrinology, P.C. I am on the clinical faculties of Emory University School of Medicine and Morehouse College of Medicine, in the role of adjunct Associate Professor of Pediatrics. I am board certified in Pediatrics and Pediatric Endocrinology. I have been licensed to practice medicine in Georgia since 1991. I have been previously licensed to practice medicine in California, Louisiana, and Maryland.

I did my Pediatric Endocrine fellowship at Johns Hopkins Hospital from 1978-1980. The faculty present at that time had carried on the tradition of excellence established by Lawson Wilkins, M.D. Because of the reputation of the endocrine program as a center for exceptional care for children with disorders of sexual differentiation, I had well-above average exposure to such patients. As a Pediatric Fellow, I was also exposed to adults with Gender Identity Disorder, then called Trans-Sexuality, and received training from John Money, Ph.D., in his Psychohormonal Division.

Differentiation in the Fetus

From the moment of conception, a fetus is determined to be either a male (XY), female (XX), or in rare cases, to have a combination of sex-determining chromosomes, many of which are not compatible with life, and some of which are the cause of identifiable clinical syndromes.

The presence of a Y chromosome in the developing fetus directs the developing gonadal tissue to develop as a testicle. The absence of a functional Y chromosome allows the gonadal tissue to develop as an ovary. Under the influence of the mother's placental hormones, the testicle will produce testosterone which directs the genital tissue to form a penis and a scrotum. Simultaneously, the testicle produces anti-Müllerian Hormone (AMH) which regresses development of the tissue that would otherwise develop into the uterus, fallopian tubes, and upper third of the vagina. This combination of actions in early fetal development is responsible for what we subsequently see on fetal sonograms, and what we observe at birth as male or female genitalia. It is only when the genital structures are ambiguous in appearance that sex assignment is withheld until a thorough expert team evaluation has occurred.

For reasons most often occurring as random events, there are malfunctions of the normal differentiation. These aberrations of normal development are responsible for what we classify as Disorders of Sexual Differentiation (DSD), and they represent a very small fraction of the human population. The incidence of such circumstances occurs in 1:4500 to 1:5500 births.[1] Sex is binary, male or female, and is determined by chromosomal complement and corresponding reproductive role. The exceedingly rare DSDs are all medically identifiable deviations from this sexual binary norm. The 2006 consensus statement of the Intersex Society of North America and the 2015 revision of the Statement do not endorse DSD as a third sex.[2] DSD outcomes range from appearance of female external genitalia in an XY male (complete androgen insensitivity syndrome) to appearance of male external genitalia in an XX female (severe congenital adrenal hyperplasia).

As one would expect, there are variations of the degree of hormonally driven changes that create ambiguous genital development that prevent assigning of a specific classification as

either male or female at birth. DSD patients are not "transgender"; they have an objective, physical, medically verifiable, physiologic condition. Transgender people generally do not have intersex conditions or any other verifiable physical anomaly. People who identify as "feeling like the opposite sex" or "somewhere in between" do not comprise a third sex. They remain biological men or biological women.

In some DSDs there exist more than one set of chromosomes. When there is a divergence of the appearance of the external genitalia from the chromosomally determined sex due to the presence of both an ovarian and testicular cell lines in a patient simultaneously, the patient is classified as having ovo-testicular DSD (formerly termed a true hermaphrodite). When there is a disruption in the development of genital structures but there is solely testicular tissue present in the chromosomal male or solely ovarian tissue in the chromosomal female, the term 46 XY DSD or 46 XX DSD is used instead respectively (formerly termed male pseudohermaphrodite or female pseudohermaphrodite).

The decision to assign a sex of rearing is complex and is specific to the diagnosis. Patients with complete androgen insensitivity (CAIS) are XY DSD but are never reared as a male. Because testosterone never influences development, they become happy, functional female adults with infertility. Females with severe congenital adrenal hyperplasia (CAH) are XX DSD but are not reared as males despite the male appearance of the genitalia at birth. Although these girls may show a tendency for male play behaviors as children, they generally assume a female sexual identity. Therapeutic interventions in the DSD individuals from infancy onward are aimed at what function can be expected from their disordered sexual anatomy in terms of function and fertility. Most often, the chromosomal sex aligns with the sex of rearing.

Gender Identity

"Gender" is a term that refers to the psychological and cultural characteristics associated with biological sex. It is a psychological concept and sociological term, not a biological one. The term gender possessed solely a linguistic meaning prior to the 1950s. This changed when sexologists of the 1950s and 1960s co-opted the term to conceptualize cross-dressing and transsexualism in their psychological practice. "Gender identity" is a term coined by my former endocrine faculty member John Money in the 1970s and has come to refer to an individual's mental and emotional sense of being male or female. The norm is for individuals to have a gender identity that aligns with one's biological sex.

Gender discordance (formerly Gender Identity Disorder) is used to describe a psychological condition in which a person experiences marked incongruence between his experienced gender and the gender associated with his biological sex. He will often express the belief that he is the opposite sex. Gender discordance occurs in 0.001% of biological females and in 0.0033% of biological males.[3] Exact numbers are hard to document since reporting is often anecdotal. Gender discordance is not considered a normal developmental variation.

"Gender Dysphoria" is a diagnostic term to describe the emotional distress caused by gender incongruity.[4] John Money played a prominent role in the early development of gender theory and transgenderism. He understood gender to be "the social performance indicative of an internal sexed identity."[5] He joined the Johns Hopkins faculty in 1951 specifically to have access to children diagnosed with DSD, hoping to prove his theory that gender was arbitrary and fluid. Money experimented with DSD infants by assigning them to the opposite biological sex through surgical revision, counseling, and hormonal manipulation during puberty. His mode of operation was to have a theory and then experiment with patients to see how his theory worked. This kind

of endeavor does not anticipate or prevent adverse outcomes and is the antithesis of ethical science. Money never submitted his research proposals for review; today, Institutional Review Boards (IRBs) serve to rigorously review proposed clinical research protocols to prevent all potential and real harm to patients.

Because of his experience with infants, Money initially garnered support from endocrine colleagues and surgical colleagues, and Johns Hopkins became a renowned center for care of patients with DSD in the 1970s, garnering referrals from around the world. Follow-up studies on these infants later showed, however, that altering their natal sexual identity via social intervention could lead to severe psychological harm. Clinical case reports of children with DSD have revealed that gender identity is indeed not immune to environmental input.[6]

Meanwhile, Money had expanded into the field of adult patients with persistent gender identity disorder. This very small group of patients chose voluntarily, as adults, to enter a very precise protocol which began with living socially as the opposite sex for a year, eventually receiving hormonal therapy to change their physical appearance to some extent. The final step was surgical revision of the body structures that would otherwise be at odds with their desired gender. This small group of patients was followed for a number of years past their final surgical procedures and required continuous counseling. These patients expressed some degree of subjective satisfaction but showed no objective improvement in overall wellbeing.[7] The legacy of John Money fell into disrepute and the transsexual treatment program at Johns Hopkin was closed in the 1980s based on the lack of evidence that this protocol produced an effective cure.

Etiology of Gender Disorders

Transgender affirming professionals claim transgender individuals have a "feminized brain" trapped in a male body at birth and vice versa based upon various brain studies. Diffusion-

weighted MRI scans have demonstrated that the pubertal testosterone surge in boys increases white matter volume. A study by Rametti and colleagues found that the white matter microstructure of the brains of female-to-male (FtM) transsexual adults, who had not begun testosterone treatment, more closely resembled that of men than that of women.[8] Other diffusion-weighted MRI studies have concluded that the white matter microstructure in both FtM and male-to-female (MtF) transsexuals falls halfway between that of genetic females and males.[9] These studies, however, are of limited clinical significance due to the small number of subjects and failure to account for neuroplasticity.

Neuroplasticity is the well-established phenomenon in which long-term behavior alters brain microstructure. For example, the MRI scans of experienced cab drivers in London are distinctly different from those of non-cab drivers, and the changes noted are dependent on the years of experience.[10] There is no evidence that people are born with brain microstructures that are forever unalterable, but there is significant evidence that experience changes brain microstructure.[11,12] Therefore, any transgender brain differences would more likely be the result of transgender behavior than its cause.

Furthermore, infants' brains are imprinted prenatally by their own endogenous sex hormones, which are secreted from their gonads beginning at approximately eight weeks' gestation.[13,14,15] There are no published studies documenting MRI-verified differences in the brains of gender-disordered children or adolescents. The DSD guidelines also specifically state that current MRI technology cannot be used to identify those patients who should be raised as males or raised as females.[16] Behavior geneticists have known for decades that while genes and hormones influence behavior, they do not hard-wire a person to think, feel, or behave in a particular way. The science of epigenetics has established that genes are not analogous to rigid

"blueprints" for behavior. Rather, humans "develop traits through the dynamic process of gene-environment interaction. ... [genes alone] don't determine who we are." [17]

Regarding transgenderism, twin studies of adults prove definitively that prenatal genetic and hormone influence is minimal. The largest twin study of transgender adults found that only 20 percent of identical twins were both transgender-identified.[18] Since identical twins contain 100 percent of the same DNA from conception and develop in exactly the same prenatal environment exposed to the same prenatal hormones, if genes and/or prenatal hormones contributed to a significant degree to transgenderism, the concordance rates would be close to 100 percent. Instead, 80 percent of identical twin pairs were discordant. This difference would indicate that at least 80 percent of what contributes to transgenderism as an adult in one co-twin consists of one or more non-shared post-natal experiences including but not limited to non-shared family experiences. These findings also mean that persistent GD is due predominately to the impact of nonshared environmental influences. These studies provide compelling evidence that discordant gender is not hard-wired genetically.

Gender Dysphoria vs. Gender Identity Disorder

Up until the recent revision of the DMS-IV criteria, the American Psychological Association (APA) held that Gender Identity Disorder (GID) was the mental disorder described as a discordance between the natal sex and the gender identity of the patient. Dr. Kenneth Zucker, who is a highly respected clinician and researcher from Toronto, carried on evaluation and treatment of GID patients for forty years. His works, widely published, found that the vast majority of boys and girls with GID identify with their biological sex by the time they emerge from puberty to adulthood, through either watchful waiting or family and individual counseling.[19] His results were mirrored in studies from Europe.[20,21]

When the DMS-V revision of the diagnosis of GID was proposed by the APA committee responsible for revision, Dr. Zucker strongly opposed the change to the term Gender Dysphoria, which purposefully removed gender discordance as a mental disorder apart from the presence of significant emotional distress. With this revision, Gender Dysphoria describes the mental anguish which is experienced by the gender discordant patient. The theory that societal rejection is the root cause of Gender Dysphoria was validly questioned by a study from Sweden which showed that the dysphoria was not eliminated by hormones and sex reassignment surgery even with widespread societal acceptance.[22]

Treatment of Gender Dysphoria

The treatment of children and adolescents with gender discordance and accompanying gender dysphoria should include an in-depth evaluation of the child and family dynamics. This evaluation provides a basis on which to proceed with psychologic therapy. The entire biologic and social family should be involved in psychological therapy designed to assist the patient, if at all possible, to align gender identity with natal sex. Psychological support by competent counselors with an intent of resolving the gender conflict should be provided as long as the patient continues to suffer emotionally. Given the high degree of eventual desistance of gender discordance/dysphoria by the end of puberty, it would be ethical and logical to counsel the patient and family to rear the child in conformity with natal sex.

There should be no interruption of natural puberty. Natural pubertal maturation in accordance with one's natal sex is not a disease. It is designed to carry malleable, immature children forward to be healthy adults capable of conceiving their own progeny. Puberty affects physical changes, some of them painful, unique to the natal sex to reflect the laws of nature. Interruption of puberty has been reserved for children who begin puberty at an age much

younger than normal in an effort to preserve final height potential and avoid the social consequences of precocious maturation.

There are a number of physical changes that are a consequence of normally timed puberty that could be classified as disadvantageous: changes in body proportions can alter success with dance and gymnastics; acne can be severe and disfiguring; a boy soprano can suddenly hardly carry a tune. It has not been the ethical standard of care to stop puberty so that these changes can be circumvented. Erikson described the stage of adolescence as "Identity versus Role Confusion" during which the teen works at developing a sense of self by testing roles then integrating them into a single identity.[23] This process is often unpleasant regardless of the presence or absence of gender identity conflicts. The major benefit of enduring puberty in a GD patient is that it provides a strong likelihood of alignment of his gender identity with his natal sex. There is no doubt that these patients need compassionate care to get them through their innate pubertal changes.

The light at the end of the tunnel is the proven scientific evidence that 80%- 95% of pre-pubertal children with GD will come to identify with their biological sex by late adolescence. Some will require lifelong supportive counseling while others will not.[24] Intervention at a young age with gonadotropin releasing hormone analogs (often referred to as puberty blockers) to either stop puberty early on or prevent it from starting before it naturally occurs is suggested by guidelines developed by WPATH without scientific basis. There is evidence that bone mineral density is irreversibly decreased if puberty blockers are used during the years of adolescence.[25] To treat puberty as a pathologic state of health that should be avoided by using puberty blockers (GnRH analogs) is to interrupt a major necessary physiologic transformation at a critical age when such changes can effectively happen. We have definite evidence of the need for estrogen in

females to store calcium in their skeleton in their teen years. That physiologic event can't be put off successfully to a later date. It is very difficult to imagine ethical controlled clinical trials that could elucidate the effects of delaying puberty until the age of consent.

The use of cross-sex hormones during this same time frame has no basis of safety and efficacy. The use of such treatment in adults raises scientifically valid concerns that were amply expressed in the 2009 Endocrine Society Guidelines on Transgender treatment. The next step in WPATH-recommended intervention is to use cross-sex hormone therapy during the time when the patient would naturally be experiencing endogenous pubertal changes. This too is not based on scientifically proven theories. The use of cross-sex hormones can cause permanent infertility.[26]

The final recommended step is so-called "sex reassignment surgery," which can include surgical removal of the breasts in natal females, or removal of the penis and scrotum in natal males. Each of these steps has adverse outcomes, some reversible and others not. Mastectomies leave scars, and there is great difficulty in creating a functional vaginal-like orifice, and certainly no success in creating an innervated erectile penis where none existed previously. Sex reassignment surgery is, by nature, permanent.

Recurrent Themes in the Plaintiff Declarations

Puberty blockers are stated to be completely reversible in their effects on the adolescent who has entered puberty based on clinical studies in young children with precocious puberty who have been treated with these drugs. This is comparing apples to oranges. Precocious puberty, by definition, is defined as puberty which starts before the 8th birthday for a female child or the before the 9th birthday in a male child. The end of treatment is carefully timed so that resumption of puberty occurs at the average age for females (10.5 years) and males (11.5 years). This allows

the necessary functions of puberty to prepare the body for reproduction and affects the bones, gonads, and brain, among other body systems. On the other hand, blocking puberty at the age of normal puberty prevents the needed accretion of calcium into the skeleton and prevents the maturation of the gonads. There is no long-term data that compares bone, gonad, and brain health in pubertal-aged patients who have had puberty interrupted and those who have not, as was noted as a concern in the Endocrine Society Guidelines. There are no such ongoing studies completed that guarantee the full reversibility of blocking puberty in this age group, but there is evidence that normal bone density can't be fully reestablished. Without any verifiable safety data, using the puberty blockers for interrupting normal puberty is not a sanctionable off-label use of these drugs and is therefore to be considered uncontrolled, non-consentable experimentation on children.

It has been stated that the plaintiffs are only asking that established standards of care be followed. There are no standards of care for transgender health. Standards of care established by broad consensus are reached by inclusion of the whole spectrum of opinions, clinical experience and published science in the formation thereof. The guidelines published by WPATH,[27] the Endocrine Society,[26,28] the American Academy of Pediatrics,[29] and the Pediatric Endocrine Society[30] are solely the opinions of like-minded practitioners who excluded any contrary opinion. The Endocrine Society Guidelines, as mentioned before, clearly stated that they are not to be considered standards of care. Before true consensus-driven standards of care are established for the treatment of transgender patients of all ages, following the current guidelines is risky experimentation.

The plaintiff declarations repeatedly refer to the established increased risk of suicide if any of the affirmation strategies are not followed to completion. There are only two total

population studies in the peer-reviewed medical literature.[22,31,32] They show that when every recorded case in the population of Sweden was analyzed, neither medical affirmation or medical affirmation followed by surgical affirmation improved the mental health of the patients in the long run.

Finally, I am curious about the clear lack of documentation of references in the plaintiffs' declarations. They are merely stating their personal opinions without supporting evidence and relying on anecdotal case reports.

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct. Executed on 1 May, 2022.

Quentin L. Van Meter, M.D.

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PERSONAL

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EDUCATION:

Undergraduate:	College of William & Mary, 1969 B.S. – 1969
Medical School:	Medical College of Virginia, 1973 M.D. – 1973

CLINICAL TRAINING:

Institution:	The University of California, San Francisco
Hospital:	Naval Regional Medical Center, Oakland
Position:	Pediatric Intern – 1973 – 1974 Pediatric Resident – 1974 – 1976
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PROFESSIONAL CERTIFICATION & SOCIETIES:

Diplomate, National Board of Medical Examiners, 1974

American Board of Pediatrics, certified in general pediatrics, 1978, sub-board certified in Pediatric Endocrinology, 1983

Fellow:	American Academy of Pediatrics, Georgia Chapter 1975 -present President, Uniformed Services West Chapter, 1987 – 1990 District VIII member, AAP Committee on Awards for Excellence in Research, 1990-1994 Editor, The Georgia Pediatrician, 1994 – 1998
	Chairman, Georgia Chapter Legislative Committee, 1996 – 2006
Fellow:	The American College of Pediatricians, 2007 – present Member of the Board of Directors, 2008- present President, 2018-present
Member:	Pediatric Endocrine Society, 1989 – present
Member:	American Diabetes Association Professional Section, 1988 – present
Member:	Endocrine Society, 1994-present
Member:	Southern Pediatric Endocrine Society, 1992 – Present
Member:	American Association of Clinical Endocrinologists, 2005 – present
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FACULTY POSITIONS:

Institution:	Morehouse School of Medicine
Position:	Associate Clinical Professor, Pediatrics, 2004 – present
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Position:	Adjunct Associate Professor, Pediatrics, 1991 – present
Institution:	University of California, San Francisco
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Institution:	University of California, San Diego, School of Medicine
Position:	Assistant Clinical Professor, Pediatrics, 1980 – 1986
Institution:	LSU School of Medicine, Clinical Instructor, Pediatrics, 1977 – 1978

MILITARY SERVICE:

Commission:	Medical Corps, United States Navy, August 1971
Rank:	Captain, retired
Duty Stations:	Health Professional Scholarship Student, 1971 – 1974
	Intern and Resident, Pediatrics, Naval Regional Medical Center, Oakland, 1973 – 1976
	Staff Pediatrician, Naval Regional Medical Center, Oakland, 1976

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Full time out-service fellow in Pediatric Endocrinology,
Johns Hopkins Hospital, 1978 – 1980

Staff Pediatric Endocrinologist, Naval Hospital San Diego,
1980 – 1986

Chairman and Director, Residency Training, Department of Pediatrics
Naval Hospital Oakland, 1986 – 1991

OTHER PROFESSIONAL ACTIVITIES:

Consultant, Pediatric Endocrinology,
Nellis Air Force Base Hospital, Las Vegas, Nevada
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Consultant, Pediatric Endocrinology,
Naval Hospital Lemoore, CA
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Consultant, Pediatric Endocrinology,
Letterman Army Medical Center, Presidio of San Francisco, CA
1990 – 1991

Consulting Endocrinologist,
Columbus Regional Medical Center, Columbus, GA
1991 – 1994

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Pediatric Endocrinologist Peer Reviewer 2006 – present
MCMC, LLC, Boston, MA
IMEDECS, Lansdale PA

Speaker's Bureau
Novo Nordisk
AAP Eqipp course on Growth- development committee- 2012

PUBLICATIONS: (Articles in Peer Reviewed Journals)

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Bradley S. Miller[1], Wayne V. Moore[2], Patricia Y. Fechner[3], Huong Jil Nguyen[4], Quentin L. Van Meter[5], John S. Fuqua[6], David Ng[7], Eric Humphriss[8], R. W. Charlton[8], George M. Bright[8], 3-Year Update of the Phase 2a and Long-term Safety Studies (VERTICAL and VISTA) of Somavaratan (VRS-317), a Long-acting rhGH for the Treatment of Pediatric Growth Hormone Deficiency, presented at the 2017 IMPE meeting in Washington D.C.

ADDITIONAL PRESENTATIONS/LECTURES:

Pediatrics Update, CME Associates, San Diego – Orlando Annual Conferences: Lectures on Pediatric Endocrine Subjects – 1986 – 2001. Course Moderator, 1997, 1998, 1999, 2000, 2001

Endocrine and Gastroenterology Update, CME Associates, Maui HI Nov 2001, Lecturer and Course Moderator

Lecture on Panhypopitutarism, Pharmacia Conference, Nashville TN April 2002.

Family Medicine Review Course, Orlando, FL, 1992 – 2001

Pediatric Grand Rounds, Tanner Medical Center, October 1997

Pediatric Grand Rounds, Hughes Spaulding Children's Hospital, September, 2003

Pediatrics in the Park, Fall CME meeting for the Georgia Chapter of the American Academy of Pediatrics, November 2003

Pediatric Grand Rounds, Columbus Regional Medical Center, January 2004

Frontiers in Pediatrics CME Course, sponsored by the Atlanta Children's Health Network, Atlanta, March 2004.

Pediatric Grand Rounds, Eggleston Children's Hospital, May 2004.

Sue Schley Matthews Pediatric Conference, Columbus Regional Medical Center, September 2004

56th Annual Scientific Assembly and Exhibition of the Georgia Academy of Family Physicians, Nov 2004

Program Co-Chairman: Southern Pediatric Endocrine Society Annual meeting, Nov 2004, November 2014

Presentations on Diabetes, Growth Failure, and Thyroid Disease to the Postgraduate Pediatric Nurse Practitioner Program, Georgia State University, Nov 2005, June 2006, May 2007

Issues in Medicine, US Medical Congress Conference and Exhibition, Las Vegas, meeting planner and speaker, June, 2006

CME Presentations for the Georgia Chapter of the American Academy of Pediatrics Spring and Fall Meetings 2004-present

Pediatric Grand Rounds, Columbus Regional Medical Center, Columbus, GA, 2011-present

Human Growth Foundation Regional CME Conference, Atlanta GA March 2013, February 2014 Columbus Georgia

International Federation of Therapeutic Counseling Choice: Transgender Medicine, IFTCC Launch, October 15, 2018 London, Third International Congress, October 25 2018 Budapest.

Southern Pediatric Endocrine Society, Orlando FL, Feb 2019

Matthew Bulfin Conference, Indianapolis IN April 2019

CMDA annual conference, Ridgecrest NC, May 2019

Support 4 Family conference, London, UK June 2019

Audio Digest Pediatrics - ① v. 41, no. 4; ② v. 41, no. 20; ③ v. 43, no. 17

Audio Digest Family Practice - ① v. 42, no. 5; ② v. 44, no. 11; ③ v. 44, no. 44; ④ v. 45, no 15

Audio Digest Otolaryngology - ① v. 32, no. 14

CURRENT HOSPITAL APPOINTMENTS:

Eggleston/Scottish Rite Children's Hospitals, active staff, Pediatric Endocrinology

PAST AND CURRENT CLINICAL RESEARCH:

2006	Sanofi-Aventis HMR1964D/3001	study completed 2007
2006	Tercica MS301-	study completed 2008
2007	Tercica MS310-	study completed 2008
2007	Tercica MS306-	study completed 2010
2007	Tercica MS316-	study completed 2012
2008	EMD Serono 28358	study completed 2009
2012	Versartis 12VR2	study completed 2014
2012	Debiopharm 8206-CPP-301	study started July 2012
2013	Versartis 13 VR3	study started Dec 2013
2014	Novo-Nordisk Elipse	study started 2014
2015	Versartis 14 VR4	study completed 2017
2017	Mannkind MKC-TI-155	study completed 2019
2018	Abbvie M16-904	study started 2018
2019	Novo-Nordisk Real-4	study started 2019
2019	Lilly 18B-MC-ITSB	study started 2019
2021	Pfizer PROGRES	study started 2021

2021	Lumos OragrowtH210	study started July 2021
2022	Novo-Nordisk Real-8	study starts July 2022

LEGAL EXPERT WITNESS:

2017	North Carolina Legislature- transgender bathroom bill
2018	Jessica Siefert transgender case, Cincinnati, OH
2018	Alberta, Canada school system transgender case
2018	Decatur GA School Board transgender case
2019	British Columbia transgender case
2019	Gavin Grimm transgender case, Gloucester County, VA
2019	Rowe vs Isle of Wight School Board, UK
2019	Younger transgender case, Dallas, TX
2020	Alabama State House and Senate committee hearings
2020	Pennsylvania State House Health Subcommittee hearings
2020	Iowa State House committee hearing
2020	California State House committee hearing
2020	Harris Count TX custody case
2021	Missouri State House committee hearing
2021	NAACP *v* State of Arkansas

DEFENDANT'S EXHIBIT 5

UNITED STATES DISTRICTCOURT
FOR THE MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER; BRIANNA BOE, individually and on behalf of her minor son, MICHAEL BOE; JAMES ZOE, individually and on behalf of his minor son, ZACHARY ZOE; MEGAN POE, individually and on behalf of her minor daughter, ALLISON POE; KATHY NOE, individually and on behalf of her minor son, CHRISTOPHER NOE; JANE MOE, Ph.D; and RACHEL KOE, M.D.

Plaintiffs,

v.

KAY IVEY, in her official capacity As Governor of the State of Alabama; STEVE MARSHALL, in his official capacity as Attorney General of the State of Alabama; DARYL D. BAILEY, in his official capacity as District Attorney for Montgomery County; C. WILSON BAYLOCK, in his official capacity as District Attorney for Cullman County; JESSICA VENTIERE, in her official capacity as District Attorney for Lee County; TOM ANDERSON in his official capacity as District Attorney for the 12th Judicial Circuit; and DANNY CARR, in his official Capacity as District Attorney for Jefferson County.

Defendants

CIVIL ACTION # 2:22-cv-00184-LCB-SRW

Expert Report of Paul W. Hruz, M.D., Ph.D.

Pursuant to 28 U.S.C. 1746, I declare:

1. RETAINED AS EXPERT WITNESS - VITAE: I have been retained by counsel for Defendants as an expert witness in connection with the above-captioned litigation. I have actual knowledge of the matters stated in this declaration. My professional background, experience, and publications are detailed in my curriculum vitae. A true and accurate copy of my CV is attached as Exhibit A to this declaration.

2. EDUCATION - ACADEMIC APPOINTMENTS: I received my Doctor of Philosophy degree from the Medical College of Wisconsin in 1993. I received my Medical Degree from the Medical College of Wisconsin in 1994. I am an Associate Professor of Pediatrics in the Division of Pediatric Endocrinology and Diabetes at Washington University School of Medicine. I also have a secondary appointment as Associate Professor of Cellular Biology and Physiology in the Division of Biology and Biological Sciences at Washington University School of Medicine. I served as Chief of the Division of Pediatric Endocrinology and Diabetes at Washington University from 2012-2017. I served as the Director of the Pediatric Endocrinology Fellowship Program at Washington University from 2008-2016. I am currently serving as Associate Fellowship Program Director at Washington University in St. Louis.

3. HISTORY OF BOARD CERTIFICATIONS: I am board certified in Pediatrics and Pediatric Endocrinology. I have been licensed to practice medicine in Missouri since 2000. I also have a temporary license to practice telemedicine in Illinois during the COVID-19 pandemic. My professional memberships include the American Diabetes Association, the Pediatric Endocrine Society, and the Endocrine Society.

4. SCIENTIFIC PUBLICATIONS IN PEER REVIEWED JOURNALS: I have published 60 scholarly articles over my academic career spanning over two decades. This includes

peer-reviewed publications in the leading journals in the fields of metabolism, cardiology, HIV, and ethics including the Gastroenterology, Circulation, Diabetes, Science Signaling, the Journal of Biological Chemistry and FASEB Journal. See my current Curriculum Vitae attached as Exhibit A.

5. EDITORIAL DUTIES - RESEARCH GRANTS: I have served as a Reviewer for a number of leading science journals in relevant fields including the Journal of Clinical Endocrinology and Metabolism, the Journal of Biological Chemistry, Diabetes, Scientific Reports and PlosOne. I have received over 4.6 million dollars in governmental and non-governmental funding for scientific research including grants from the National Institutes of Health, the American Diabetes Association, The American Heart Association, the March of Dimes, and the Harrington Discovery Institute. I am a member of the Alpha Omega Alpha Medical Honor Society and have received the Armond J. Quick Award for Excellence in Biochemistry, the Eli Lilly Award for Outstanding Contribution to Drug Discovery, and the Julio V. Santiago Distinguished Scholar in Pediatrics Award.

6. CLINICAL EXPERIENCE: During the more than 20 years that I have been in clinical practice, I have participated in the care of hundreds of infants and children, including adolescents, with disorders of sexual development. I was a founding member of the multidisciplinary Disorders of Sexual Development (DSD) program at Washington University. I continue to contribute to the discussion of complex cases and the advancement of research priorities in this field. In the care of these patients, I have acquired expertise in the understanding and management of associated difficulties in gender identification and gender transitioning treatment issues. I have trained and/or supervised hundreds of medical students, residents and clinical fellows in the practice of medicine.

7. PREVIOUS LEGAL CASES AS AN EXPERT WITNESS: Related to the litigation of issues of sex and gender, I have been designated as an expert witness in Joaquín Carcaño et al vs. Patrick McCrory (United States District Court, M.D. North Carolina), Jane Doe vs Board of Education of the Highland School District (United States District Court For the Southern District of Ohio Eastern Division, Case No. 2:16-CV-524), Ashton Whitaker vs. Kenosha Unified School District (United States District Court Eastern District of Wisconsin, Civ. Action No. 2:16-cv-00943), Adams vs. the School Board of St. John's County (United States District Court Middle District Of Florida Jacksonville Division, Case No. 3:17-cv-739-J-32JBT), Terri Bruce vs State of South Dakota (The United States District Court District of South Dakota Western Division, Case No. 17-5080), Kadel vs. Falwell (The United States District Court For The Middle District Of North Carolina, Case No.: 1:19-cv-272-LCB-LPA), Brandt v Rutledge (The United States District Court Eastern District of Arkansas Central Division, Case No. 4:21-CV-00450-JM), and Cause DF-15-09887-SD of the 255th Judicial Circuit of Dallas County, TX regarding the dispute between J.A. D.Y. and J.U. D.Y., Children. Only in the last case did I testify at trial. I have also served as a science consultant or subjected written testimony for court cases in Canada (B.C. Supreme Court File No. E190334) and Great Britain (Bell v Tavistock).

8. COMPENSATION: I am being compensated at an hourly rate for actual time devoted, at the rate of $400 per hour including report drafting, travel, testimony, and consultation. My compensation does not depend on the outcome of this litigation, the opinions I express, or the testimony I provide.

9. CONSULTS-DISCUSSIONS REGARDING THE RELEVANT SCIENCE and CLINICAL ISSUES: In my role as a scientist and as the Director of the Division of Pediatric Endocrinology at Washington University, I extensively studied the existing scientific research

literature related to the incidence, potential etiology, and treatment of gender dysphoria as efforts were made to develop a Transgender Medicine Clinic at Saint Louis Children's Hospital. I have participated in local and national meetings where the endocrine care of children with gender dysphoria has been discussed in detail and debated in depth. I have met individually and consulted with several pediatric endocrinologists (including Dr. Norman Spack) and other professionals specializing in sexual health (including Eli Coleman) who have developed and led transgender programs in the United States. I have also consulted with, met with, and had detailed discussions with dozens of parents of children with gender dysphoria to understand the unique difficulties experienced by this patient population. I continue to evaluate the ongoing experimental investigation of this condition. I am frequently consulted by other medical professionals to help them understand the complex medical and ethical issues related to this emerging field of medicine.

10. In my opinion, there is a serious lack of quality scientific evidence regarding the safety and efficacy of gender affirming medical interventions for individuals who exercise sex discordant gender identity. Use of such medical interventions remains a highly controversial and largely experimental approach.

Pediatric patients referred to our practice for the evaluation and treatment of gender dysphoria are cared for by an interdisciplinary team of providers that includes a psychologist and pediatric endocrinologist who have been specifically chosen for this role based upon a special interest and professional knowledge and training in this rare patient population. Due to the documented, important, ethical concerns regarding the safety, efficacy, and scientific validity of controversial, unproven, and experimental treatment paradigms, I have not personally engaged in the delivery of gender affirming medical interventions to children with gender dysphoria. Given the

unproven long-term benefits and the well-documented risks and harms of "transitioning" children, I decline to participate in such experimental treatments until the science has proven that the relative risks and benefits of this approach warrant such procedures.

My decision is strengthened by the knowledge that the vast majority of children who report gender dysphoria will, if left untreated, grow out of the problem — a natural coping-developmental process — and willingly accept their biological sex. Despite differences in country, culture, decade, follow-up length and method, multiple studies have come to a remarkably similar conclusion: Very few gender dysphoric children still want to transition by the time they reach adulthood. Many turn out to have been struggling with sexual orientation issues rather than Gender Discordant "transgender" identity. The exact number of children who experience realignment of gender identity with biological sex by early adult life varies by study. Estimates within the peer reviewed published literature range from 50-98%, with most reporting desistance in approximately 85% of children prior to the widespread adoption of the "gender affirmation only" approach. Thus, desistance (i.e., the child accepting their natal, biological sex identity and declining "transitioning" treatments) is the outcome for the vast majority of affected children who are not actively encouraged to proceed with sex-discordant gender affirmation. Since there are no reliable assessment methods for identifying the small percentage of children with persisting sex-gender identity discordance from the vast majority who will accept their biological sex, and since puberty blocking treatments, hormone transition treatments, and surgical transition treatments are all known to have potentially life-long devastating, negative effects on patients, I and many colleagues view it as unethical to treat children with an unknown future by using experimental, aggressive, and intrusive gender affirming medical interventions. See J. Cantor,

Ph.D. summary of multiple research studies at http://www.sexologytoday.org/2016/01/do-trans-kids-stay-trans-when-they-grow_99.html, and other publications reviewed in detail below).

11. PEER-REVIEWED, PUBLISHED RESEARCH IN CREDIBLE SCIENCE-MEDICAL JOURNALS: My opinions as detailed in this declaration are based upon my knowledge and direct professional experience in the subject matters discussed. The materials that I have relied upon are the same types of materials that other experts in my field of clinical practice rely upon when forming opinions on the subject including hundreds of published, peer reviewed scientific research (and professional) articles. As discussed in detail in this declaration, the extant published literature on the use of puberty blockers, cross-sex hormones and gender affirming surgeries are based, almost entirely, upon studies with major methodological limitations (see Hruz, P. W. Deficiencies in Scientific Evidence for Medical Management of Gender Dysphoria. *Linacre Q* 87, 34-42, doi:10.1177/0024363919873762 (2020). This includes:

- Significant recruitment biases including internet based convenience sampling
- Relatively small sample sizes for addressing a condition that is likely to be multi-factorial
- Short term follow up
- Lack of randomization to different treatment arms
- Failure to even consider alternate hypotheses
- Failure to include proper control groups and, in many studies NO control group at all
- Reliance on cross sectional sampling that may identify associations, but cannot establish causal relationships between intervention and outcome.

- A high rate of patients lost to follow up in longitudinal analyses which is relevant to questions of regret, desistance and completed suicide.
- Biased interpretation of study findings with a goal of validating *a priori* conclusions rather than seeking evidence to disprove the null hypothesis
- Ignoring starkly contradictory research documenting the lack of effectiveness of "transitioning" procedures, the low quality of research in this area, and the ongoing contentions and disagreements over this highly controversial, experimental medical field

12. PUBLIC DISCLOSURES OF THE METHODOLOGICAL FAILURES OF GENDER TRANSITIONING MEDICAL INTERVENTIONS: In addition to peer reviewed published research articles related to gender affirming medical interventions (see specific citations below), I also cite a wide variety of evidence documenting the recent, very public, disclosures of the multiple and serious methodological errors, failures, and defects of "transitioning treatment" research. Specific examples include:

THE BRANSTROM LONG-TERM TREATMENT OUTCOME STUDY: The historic Branstrom report is a peer reviewed, published, scientific journal article that documents a long-term treatment (10+ years) outcome research investigation testing the effects of hormonal and surgical "transitioning" treatments on patients. This historic research found *no reliable benefits from these disfiguring-sterilizing "treatments"* as well as evidence suggesting *increased* suicide attempts and anxiety disorders following the "gender transitioning" treatments. In addition, detailed methodological critiques discovered significant research errors by the authors that appear to support the investigative theory that the authors had initially attempted to manipulate

and misreport the findings of the study. (See, very detailed notes and review below with multiple citations). The authors ultimately recanted their initial misreporting and agreed that their study produced *no reliable evidence of benefits* for gender reassignment hormone and surgical treatments. The Branstrom study is truly a devastating and historic blow to the WORLD PROFESSIONAL ASSOCIATION FOR TRANSGENDER HEALTH's (WPATH) "treatment guidelines" and to the financially lucrative transgender "transitioning" treatment industry. Together with other evidence, this historic investigation has helped to generate a profound collapse of support for these experimental procedures across Europe. See *Correction of a Key Study: No Evidence of "Gender-Affirming" Surgeries Improving Mental Health.* https://segm.org/ajp_correction_2020. Accessed 29 June 2021. , Van Mol, A., Laidlaw, M., Grossman, M., & McHugh, P. (2020). *Gender-Affirmation Surgery Conclusion Lacks Evidence.* Am. J. Of Psych., 177(8), 765-766. (see detailed review below).

NATIONAL FINLAND REVIEW RECOMMENDS SUSPENDING TRANSITIONING TREATMENTS FOR CHILDREN AS EXPERIMENTAL and of UNCERTAIN BENEFIT: A National Science Review in FINLAND carefully examined all relevant science and suspended transition treatments for minors under age 16. See One Year Since Finland Broke with WPATH "Standards of Care." https://segm.org/Finland_devites_from_WPATH_prioritizing_psychotherapy_no_surgery_for_minors. The official review recommends that psychotherapy should be the first line of treatment for gender dysphoric youth. See 2020 Recommendation of the Council for Choices in Health Care in Finland (PALKO / COHERE Finland) Medical Treatment Methods for Dysphoria Related to Gender Variance In Minors, "Cross-sex identification in childhood, even in extreme cases, generally disappears during puberty…. The first-line treatment for gender dysphoria is psychosocial support and, as necessary, psychotherapy and

treatment of possible comorbid psychiatric disorders. … No gender confirmation surgeries are performed on minors." … "Potential risks of GnRH therapy include disruption in bone mineralization and the as yet unknown effects on the central nervous system"… "there are no medical treatments (for transitioning) that can be considered evidence-based… In cases of children and adolescents, ethical issues are concerned with the natural process of adolescent identity development, and the possibility that medical interventions may interfere with this process. It has been suggested that hormone therapy (e.g., pubertal suppression) alters the course of gender identity development; i.e., it may consolidate a gender identity that would have otherwise changed in some of the treated adolescents. The reliability of the existing studies with no control groups is highly uncertain, and because of this uncertainty, no decisions should be made that can permanently alter a still-maturing minor's mental and physical development…. A lack of recognition of comorbid psychiatric disorders common among gender-dysphoric adolescents can also be detrimental. Since reduction of psychiatric symptoms cannot be achieved with hormonal and surgical interventions, it is not a valid justification for gender reassignment. A young person's identity and personality development must be stable so that they can genuinely face and discuss their gender dysphoria, the significance of their own feelings, and the need for various treatment options. For children and adolescents, these factors are key reasons for postponing any interventions until adulthood…. In light of available evidence, gender reassignment of minors is an experimental practice." See One Year Since Finland Broke with WPATH "Standards of Care." https://segm.org/Finland_devites_from_WPATH_prioritizing_psychotherapy_no_surgery_for_minors.

SWEDEN'S FLAGSHIP KAROLINSKA HOSPTIAL SUSPENDS TRANSITIONING TREATMENTS FOR CHILDREN UNDER 16 AND REQUIRES RESEARCH OVERSIGHT FOR PATIENTS UNDER 18: In Sweden, the world-renowned Karolinska Hospital reviewed the current research and suspended pediatric gender transitions for patients under 16 outside of experimental, monitored clinical trials settings as of May 2021. Treatment will focus on psychotherapy and assessment. See Sweden's Karolinska Ends All Use of Puberty Blockers and Cross-Sex Hormones for Minors Outside of Clinical Studies. https://segm.org/Sweden_ends_use_of_Dutch_protocol. See also, Karolinska Policy Change K2021-3343 March 2021 (in English).pdf; Karolinska Hospital Ends the Use of Puberty Blockers for patients under 16: New policy statement from the Karolinska Hospital. The "Dutch protocol" for treating gender dysphoric minors has been discontinued over concerns of medical harm and uncertain benefits. This new Swedish policy is consistent with Finland's recently revised guidelines and changes in England's policies as well as the Arkansas legislation in the U.S. All have been changed to prioritize psychological interventions and social support in contrast to medical interventions, particularly for youth with no young childhood history of gender dysphoria (presently the most common patient presentation)" See Society for Evidence Based Gender Medicine Press Release at https://segm.org/Sweden_ends_use_of_Dutch_protocol and Karolinska Policy Change K2021-3343 March 2021 (English, unofficial translation).pdf Karolinska Guideline K2021-4144 April 2021 (English, unofficial translation).pdf

SWEDEN National review documents the lack of quality research in this controversial field. See Sweden Policy Review, Gender dysphoria in children and adolescents: an inventory of the literature, SBU Policy Support no 307, 2019 (https://www.sbu.se/307e) "This report

was commissioned by the Swedish government and is a scoping review of the literature on gender dysphoria in children and adolescents. The report can be a basis for further evaluation of risk of bias and evidence."…" The Swedish national review reported: "No relevant randomized controlled (treatment outcome) trials in children and adolescents were found." The review also reported … "Conclusions: — We have not found any scientific studies which explains the increase in incidence in children and adolescents who seek the heath care because of gender dysphoria — We have not found any studies on changes in prevalence of gender dysphoria over calendar time, nor any studies on factors that can affect the societal acceptance of seeking for gender dysphoria. — There are few studies on gender affirming surgery in general in children and adolescents and only single studies on gender affirming genital surgery. — Studies on long-term effects of gender affirming treatment in children and adolescents are few, especially for the groups that have appeared during the recent decennium….— Almost all identified studies are observational, some with controls and some with evaluation before and after gender affirming treatment. No relevant randomized controlled trials in children and adolescents were found. … We have not found any composed national information from Sweden on: — the proportion of those who seek health care for gender dysphoria that get a formal diagnosis nor — the proportion starting endocrine treatment to delay puberty nor — the proportion starting gender affirming hormonal treatment nor — the proportion subjected to different gender affirming surgery."

UK RESEARCHERS, COURTS, and OTHER REVIEWERS HIGHLIGHTED THE PAUCITY OF RESEARCH, LIMITATIONS, DEFECTS, and RISKS IN THE STILL EXPERIMENTAL "GENDER TRANSITIONING" TREATMENT FIELD:

The British official medical review office (NICE) published reports on transitioning science. See Cohen, D. and Barnes, H., BBC, "Evidence for puberty blockers use very low, says

NICE" … "The evidence for using puberty blocking drugs to treat young people struggling with their gender identity is "very low", an official review has found. The National Institute of Health and Care Excellence (NICE) said existing studies of the drugs were small and "subject to bias and confounding." The assessment of the evidence into the drugs was commissioned by NHS England. It is part of a review into gender identity services for children and young people. See https://arms.nice.org.uk/resources/hub/1070905/attachment. The NICE review noted it was difficult to draw conclusions from existing studies because of the way they had been designed. They were "all small" and did not have control groups, which are used to directly compare the effect of different treatments. There were other issues with the studies too, such as not describing what other physical and mental health problems a young person may have alongside gender dysphoria.

NICE also reviewed the evidence base for cross-sex hormones. See https://arms.nice.org.uk/resources/hub/1070871/attachment. The review found the evidence of clinical effectiveness and safety of cross-sex hormones was also of "very low" quality. "Any potential benefits of gender-affirming hormones must be weighed against the largely unknown long-term safety profile of these treatments in children and adolescents with gender dysphoria," NICE said. Both documents were prepared by NICE in October 2020 and will now help inform Dr. Hilary Cass's independent review into NHS gender identity services for children and young people. See also Carmichael P, Butler G, Masic U, et al. Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK. medRxiv 2020.12.01.20241653; doi:https://doi.org/10.1101/2020.12.01.20241653. This British study conclusion noted: "We found no evidence of change (no improvement) in psychological function with GnRHa treatment as indicated by parent report (CBCL) or self-re-

port (YSR) of overall problems, internalizing or externalizing problems or self-harm…." Puberty blockers used to treat children aged 12 to 15 who have severe and persistent gender dysphoria had no significant effect on their psychological function, thoughts of self-harm, or body image, a study has found. However, as expected, the children experienced reduced growth in height and bone strength by the time they finished their treatment at age 16. See, also Dyer, C. Puberty blockers: children under 16 should not be referred without court order, says NHS England. BMJ2020;371:m4717.doi:10.1136/bmj.m4717 pmid:33268453. See, Dyer, C., Puberty blockers do not alleviate negative thoughts in children with gender dysphoria, finds study, BMJ 2021;372:n356 doi: https://doi.org/10.1136/bmj.n356 (Published 08 February 2021); see also Dyer, C. Puberty blockers do not alleviate [suicidal] negative thoughts in children with gender dysphoria, finds study. BMJ 372, n356, doi:10.1136/bmj.n356 (2021). https://www.medrxiv.org/content/10.1101/2020.12.01.20241653v1 BBC summary: https://www.bbc.com/news/uk-55282113journal.pone.0243894. pmid:33529227. See also, "Tavistock's Experimentation with Puberty Blockers: Scrutinizing the Evidence," TransgenderTrend.com, March 5, 2019. Regarding the UK's Tavistock and Portman NHS Trust's Gender Identity Development Service's experimental trial of puberty blockers for early teenagers with gender dysphoria. Oxford's Professor Michael Biggs wrote, "To summarize, GIDS launched a study to administer experimental drugs to children suffering from gender dysphoria."… "After a year on GnRHa [puberty blockers] children reported greater self-harm, and girls experienced more behavioral and emotional problems and expressed greater dissatisfaction with their body—so puberty blockers actually exacerbated gender dysphoria."

See also Griffin, L., Clyde, K., Byng, R., Bewley, S., Sex, gender and gender identity: a re-evaluation of the evidence. BJPsych Bulletin (2020) doi:10.1192/bjb.2020.73, Cambridge University Press, 21 July 2020, As Griffin, et al discussed, "As there is evidence that many psychiatric disorders persist despite positive affirmation and medical transition, it is puzzling why transition would come to be seen as a key goal rather than other outcomes, such as improved quality of life and reduced morbidity. When the phenomena related to identity disorders and the evidence base are uncertain, it might be wiser for the profession to admit the uncertainties". … "In addition, Griffin et al wrote: "Transgender support groups have emphasized the risk of suicide. After controlling for coexisting mental health problems, studies show an increased risk of suicidal behaviour and self-harm in the transgender population, although underlying causality has not been convincingly demonstrated. (See Marshall E, Claes L, Bouman WP, Witcomb GL, Arcelus J. Non-suicidal self-injury and suicidality in trans people: a systematic review of the literature. Int Rev Psychiatry 2016; 28: 58–69.). In sum, political activists and too many providers have used a fear of suicide to push experimental unproven, hazardous treatments.

REVIEW OF WPATH: A 2021 review found WPATH standards "incoherent." See Dahlen, Sara, et al. "International Clinical Practice Guidelines for Gender Minority/Trans People: Systematic Review and Quality Assessment." BMJ Open, vol. 11, no. 4, Apr. 2021, p. e048943. Both WPATH and Endocrine Society guidelines have recently been assessed for quality by a systematic review, which found them to be of low quality. Specific to WPATH, the reviewers noted the difficulty of even extracting clear recommendations, describing the WPATH guidelines as "incoherent." Standards of care should provide practitioners with evidence-based standards by which they may reliably inform the patient of projected outcomes, and do so with a

known error rate. Such data is the starting point for obtaining informed consent, which is not provided by either of these guidelines.

THE INDEPENDENT REVIEW OF GENDER IDENTITY SERVICES FOR CHILDREN AND YOUNG PEOPLE: INTERIM REPORT by Dr. Cass in the UK published in February 2022 concluded that "Evidence on the appropriate management of children and young people with gender incongruence and dysphoria is *inconclusive* both nationally and internationally." Dr. Cass notes that "There is lack of consensus and open discussion about the nature of gender dysphoria and therefore about the appropriate clinical response." (see https://cass.independent-review.uk/publications/interim-report/)

THE SOCIETY FOR EVIDENCE BASED GENDER MEDICINE (SEGM) REVIEW SUMMARIZES THE HEALTH RISKS of TRANSITIONING: Consistent with changes in Sweden, Finland, England, and Arkansas, SEGM published a research summary documenting the serious health risks of "transitioning treatments" compared to the well-known lack of evidence of reliable benefits for such treatments. See Science Studies – Health Risks of Medical and Surgical Gender Reassignment." SEGM at. https://www.segm.org/studies.

EXPERTS ARE CONCERNED WITH UNEXPLAINED DEMOGRAPHIC SHIFTS IN PATIENTS FOR WHOM PREVIOUS RESEARCH IS OF UNKNOWN USEFULNESS — For decades transgender patients were mostly older adults or very young boys. Over the last few years a tsunami of teenaged girls has flipped the demographics of transgender patients—now up to 7 to 1 teen girls. Many experts have noted that the previous research on trans patients cannot be relied upon when the patient group has so rapidly and mysteriously been transformed. In sum, the newly presenting cases are vastly overrepresented by adolescent females, the majority of whom also have significant mental health problems and neurocognitive comorbidities such as

autism-spectrum disorder or ADHD. See de Graaf, Nastasja M., and Polly Carmichael. "Reflections on Emerging Trends in Clinical Work with Gender Diverse Children and Adolescents." Clinical Child Psychology and Psychiatry, vol. 24, no. 2, Apr. 2019, pp. 353–64. The most recent evidence supports the emerging theory of social contagion as estimates of gender dysphoria-transgenderism are rocketing upwards from 1 in 10,000 to "the number of U.S. transgender-identified youth may be as high as 9%." See Kidd, Kacie M., et al. "Prevalence of Gender-Diverse Youth in an Urban School District." Pediatrics, vol. 147, no. 6, June 2021, p. e2020049823. This unexplained, radical transformations of demographics does not happen in actual illnesses (cancer, heart disease, anxiety disorders, etc), but is tragically consistent with previous mental health system disasters such as the once very rare "multiple personality disorder" and "recovered repressed memory" patients that radically increased in the 1990s. Dr. Thomas Steensma, a prominent investigator of the Dutch protocol—the original model for transitioning treatments—has recently noted that "[w]e don't know whether studies we have done in the past can still be applied to this time," specifically because of the unexplained surge in female adolescents reporting gender dysphoria. "Many more children are registering, but also of a different type… Suddenly there are many more girls applying who feel like a boy... now there are three times as many females as males." He concluded with the warning that "[w]e conduct structural research in the Netherlands. But the rest of the world is blindly adopting our research." See https://www.voorzij.nl/more-research-is-urgently-needed-into-transgender-care-for-young-people-where-does-the-large-increase-of-children-come-from/

A MARCH 2021 STUDY—WITH THE LARGEST SAMPLE YET—IS CONSISTENT WITH THE NEW DIRECTION OF FINLAND, SWEDEN, THE UK, and FRANCE—SHOWS THAT MOST YOUNG GENDER DYSPHORIA CHILDREN GROW

OUT OF THE PROBLEM WITH NO MEDICAL INTERVENTION. See Devita Singh1, Susan J. Bradley 2 and Kenneth J. Zucker, Frontiers in Psychiatry, March 2021, Volume 12, Article 632784, www.frontiersin.org. "Watchful Waiting" is the recommended treatment: In the past, 67% of children meeting the diagnostic criteria for gender dysphoria no longer had the diagnosis as adults, with an even higher, 93% rate of natural resolution of gender-related distress for the less significantly impacted cases. See also, e.g. Zucker, K. J. (2018). The myth of persistence: Response to "A critical commentary on follow-up studies and 'desistance' theories about transgender and gender non-conforming children" by Temple Newhook et al. (2018). International Journal of Transgenderism, 19(2), 231–245.

THE COCHRANE REVIEW FOUND INSUFFICIENT EVIDENCE OF BENEFITS: The widely respected Cochrane Review examined hormonal treatment outcomes for male-to-female transitioners over 16 years. They found "insufficient evidence to determine the efficacy or safety of hormonal treatment approaches for transgender women in transition." It is remarkable that decades after the first transitioned male-to-female patient, quality evidence for the benefit of transitioning is still lacking. See Haupt, C., Henke, M. et. al., Cochrane Database of Systematic Reviews Review - Intervention, Antiandrogen or estradiol treatment or both during hormone therapy in transitioning transgender women, 28 November 2020 and https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013138.pub2/full.

13. A reasonable understanding of relative risk versus benefit for medical products or procedures is a fundamental obligation in providing appropriate clinical care. This is the bedrock standard of "evidence based medical practice." As detailed throughout this declaration, this foundational standard has never been met by the gender transition industry. As noted by Levine et al. "The risks of gender-affirmative care are ethically managed through a properly conducted

informed consent process. Its elements-deliberate sharing of the hoped-for benefits, known risks and long-term outcomes, and alternative treatments-must be delivered in a manner that promotes comprehension. The process is limited by: erroneous professional assumptions; poor quality of the initial evaluations; and inaccurate and incomplete information shared with patients and their parents" (Levine, S. B., Abbruzzese, E., & Mason, J. W. (2022). Reconsidering Informed Consent for Trans-Identified Children, Adolescents, and Young Adults. *Journal of sex & marital therapy*, 1–22. Advance online publication. https://doi.org/10.1080/0092623X.2022.2046221).

Differences between the gender transition industry's approach to gender dysphoria and the treatment of other medical conditions include not only the poor quality of evidence regarding safety and efficacy, but also attempts to silence standard scientific discussion and consideration of alternative hypotheses, failures to acknowledge existing data showing persistence of suicidality after intervening, the intentional impairment and destruction of normally formed and functioning male and female sexual organs to address psychological-psychiatric distress, the manipulation of language from standard medical definitions to accommodate novel ideology, and widespread failures in properly reporting research data related to gender transitioning. Each of these differences are discussed in detail in my declaration with appropriate examples and relevant scientific and professional citations.

When considering clinical practice guidelines, it is essential that physicians recognize the relative risks and benefits of such documents. If done properly, they can distill large data sets into actionable clinical recommendations. However, there is a long history of clinical practice guidelines that have later been found to be deficient, resulting in wasted medical resources, failure to achieve desired benefits, or to have caused substantial harm to patients. (See, e.g., Woolf, S. H., Grol, R., Hutchinson, A., Eccles, M., & Grimshaw, J. (1999). Clinical guidelines:

potential benefits, limitations, and harms of clinical guidelines. *BMJ (Clinical research ed.)*, 318(7182), 527–530. https://doi.org/10.1136/bmj.318.7182.527)

14. It is highly misleading to imply that the current Endocrine Society guidelines, first published in 2009 and revised in 2017 represent the opinions of the Societies 18,000 members. (Hembree, W. C., Cohen-Kettenis, P., Delemarre-van de Waal, H. A., Gooren, L. J., Meyer, W. J., 3rd, Spack, N. P., Tangpricha, V., Montori, V. M., & Endocrine Society (2009). Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *The Journal of clinical endocrinology and metabolism*, *94*(9), 3132–3154. https://doi.org/10.1210/jc.2009-0345; Hembree, W. C., Cohen-Kettenis, P. T., Gooren, L., Hannema, S. E., Meyer, W. J., Murad, M. H., Rosenthal, S. M., Safer, J. D., Tangpricha, V., & T'Sjoen, G. G. (2017). Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. *The Journal of clinical endocrinology and metabolism*, *102*(11), 3869–3903. https://doi.org/10.1210/jc.2017-01658). The committee that drafted these guidelines was composed of *less than a dozen* self-selected members. The guidelines were never submitted to the entire membership for comment and approval prior to publication. They also did not undergo external review. Such political methodologies are common in association "statements" and "endorsement" and not at all scientific nor reliable nor valid.

15. The hazard of making treatment recommendations based on studies with major methodological weaknesses can be readily seen by considering representative studies used by advocates of medical gender affirmation to justify this approach.

15A. For example, the study by De Vries and colleagues (de Vries AL, Steensma TD, Doreleijers TA, Cohen-Kettenis PT. Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. *J Sex Med*. 2011;8(8):2276-2283) is often cited to support

longitudinal evidence of benefit from pubertal blockade. Although improvements in mood improved and the risk of behavioral disorders with pubertal blockade were found over baseline, in this study there was no control group. Thus, the authors were unable to determine the basis of this improvement. The authors acknowledge that psychological support or other reasons may have contributed to (or wholly caused) this observation. It is also important to note that gender dysphoria itself *did not diminish* in study subjects, and there were *no changes* in body image-related distress.

15B. The study by Turban and colleagues (Turban, J. L., King, D., Carswell, J. M., & Keuroghlian, A. S. (2020). Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation. *Pediatrics*, *145*(2), e20191725) is often cited as proof that pubertal blockade prevents suicide in transgender youth. However, this study used an unreliable, biased sampling methodology. As stated in the paper, the authors considered "a cross-sectional online survey of 20,619 transgender adults aged 18 to 36 years" from the 2015 U.S Transgender Survey. This was an online survey of transgender and "genderqueer" adults recruited from trans-friendly websites. Among the many problems with this sampling methodology, there is NO evidence of study subject identities, NO way to assess for potential false subjects, and NO medical diagnosis for entry. No causation can be determined from this retrospective, cross-sectional design. Furthermore, the study failed to even assess Desisters and Regretters. Turban claimed that desisters and regretters would "not be likely" in this study group, which also only included adults. Thus, the study "does not include outcomes for people who may have initiated pubertal suppression and subsequently no longer identify as transgender." Turban's misleading claim of lower suicidal ideation for treated patients excluded the most seriously mentally ill patients that would have been DENIED affirmation treatment. Those who received treatment with pubertal suppression, when compared

with those who wanted pubertal suppression but did not receive it, had lower odds of lifetime suicidal ideation (adjusted odds ratio = 0.3; 95% confidence interval = 0.2– 0.6). In Table 3 of the paper, under "Suicidality (past 12 months)" reductions for suppressed group v non-suppressed were seen for ideation (50.6% v 64.8%) and "ideation with plan" (55.6% v 58.2%). However, it is important to note that suicidal "ideation with plan and suicide attempt" for the suppressed group INCREASED after treatment to 24.4% v 21.5% for the "non-treatment group." The most clinically significant result in this study — that "Affirmation Treatments INCREASED SERIOUS SUICIDE ATTEMPTS — was IGNORED BY THE AUTHORS (i.e., not statistically significant but clinically significant) = "Suicide attempts resulting in inpatient care" = 45.5% for suppression groups vs 22.8% for those who did not receive pubertal suppression. It would be most reasonable to conclude from an observation of 45% attempted suicide in the treated arm that the intervention was unsuccessful in improving health. Turban et al. ignored their own finding that a history of puberty suppression was associated with an INCREASE in recent serious suicide attempts. In sum, the Turban 2020 Pediatrics study, based on an unverified US Transgender Online Survey, tells us little about the effects of puberty suppression on children with gender dysphoria. (See, Michael Biggs, Puberty Blockers and Suicidality in Adolescents Suffering from Gender Dysphoria. Archives of Sexual Behavior, accepted 14 May 2020, DOI: 10.1007/s10508-020-01743-6 and the multiple Letters to the Editor that criticized the multiple methodological errors in this study, https://pediatrics.aappublications.org/content/145/2/e20191725/tab-e-letters#re-pubertal-suppression-for-transgender-youth-and-risk-of-suicidal-ideation)

15C. The 2021 study of Bustos, et al., (Bustos, V. P., Bustos, S. S., Mascaro, A., Del Corral, G., Forte, A. J., Ciudad, P., Kim, E. A., Langstein, H. N., & Manrique, O. J. (2021). Regret

after Gender-affirmation Surgery: A Systematic Review and Meta-analysis of Prevalence. *Plastic and reconstructive surgery. Global open*, *9*(3), e3477) attempts to provide a systematic review of 27 observational or interventional studies that report on regret or detransition following gender-transition surgeries. A total of 7928 subjects were included in their meta analysis. The authors concluded that only 1% or less of those who had gender-transition surgeries expressed regret. It is important to understand the serious methodological limitations and high risk of bias contained within the analysis in the 2021 Bustos et al. study (see Expósito-Campos, P., & D'Angelo, R. (2021). Letter to the Editor: Regret after Gender-affirmation Surgery: A Systematic Review and Meta-analysis of Prevalence. *Plastic and reconstructive surgery. Global open*, *9*(11), e3951). This includes failure to include major relevant studies addressing this question (e.g. Dhejne, C., Öberg, K., Arver, S., & Landén, M. (2014). An analysis of all applications for sex reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets. *Archives of sexual behavior*, *43*(8), 1535–1545), inaccurate analysis within one of the studies considered **(**Wiepjes CM, Nota NM, de Blok CJM, et al. The Amsterdam Cohort of Gender Dysphoria Study (1972–2015): Trends in Prevalence, Treatment, and Regrets. J Sex Med 2018; 15: 582–590) and the general lack of controlled studies, incomplete and generally short-term follow-up, large numbers of lost subjects, and lack of valid assessment measures in the published literature addressing this question. As noted by Expósito-Campos and D'Angelo (2021), moderate to high risk of bias was present in 23 of the 27 studies included in the analysis. Furthermore, 97% of subjects analyzed were found within studies deemed to be of fair to poor scientific quality. Thus, this study cannot be used as strong support for the contention that regret is rare.

15D. The 2018 paper by Wiepjies, et al. (Wiepjes, C. M., Nota, N. M., de Blok, C., Klaver, M., de Vries, A., Wensing-Kruger, S. A., de Jongh, R. T., Bouman, M. B., Steensma, T.

D., Cohen-Kettenis, P., Gooren, L., Kreukels, B., & den Heijer, M. (2018). The Amsterdam Cohort of Gender Dysphoria Study (1972-2015): Trends in Prevalence, Treatment, and Regrets. *The journal of sexual medicine*, *15*(4), 582–590) is a retrospective review of records from all patients of the Center of Expertise on Gender Dysphoria gender clinic in Amsterdam from 1972-2015. While the study appears to report on the regret rates among a large cohort of adolescents (812) and children (548), regret is only reported for children and adolescents who had undergone gonadectomy once over 18 years of age. Of the adolescents, 41% started puberty suppression. Of those who started GnRH agonists, only 2% stopped this intervention (meaning that 98% of those who started puberty suppression progressed to cross-sex hormone therapy). An additional 32%, having already completed puberty, started cross-sex hormone therapy without use of a GnRH agonist. Classification of regret was very stringent, requiring physician documentation of patient verbalized regret after gonadectomy and start of sex-concordant hormones to treat the iatrogenic hypogonadism. This means there are significant limitations to the conclusions that can be drawn from 2018 paper by Wiepjies, et al. There is no discussion in this paper regarding adolescent regret of use of puberty blockers, cross-sex hormones or mastectomies. Importantly 36% of patients were lost to follow up. This is notable given that gonadectomy iatrogenically induces the pathologic state of primary hypogonadism. Affected patients have a lifelong dependency for exogenously administered sex-steroid hormones, and thus an acute need for ongoing follow-up. The number of lost subjects who experienced regret or completed suicides is unknown. It is also significant that the average time to regret was 130 months. The authors themselves acknowledge that it may be too early to predict regret in patients who started hormone therapy in the past 10 years.

15E. The 2021 study by Narayan et al (Narayan, S. K., Hontscharuk, R., Danker, S., Guerriero, J., Carter, A., Blasdel, G., Bluebond-Langner, R., Ettner, R., Radix, A., Schechter, L., & Berli, J. U. (2021). Guiding the conversation-types of regret after gender-affirming surgery and their associated etiologies. *Annals of translational medicine*, *9*(7), 605) examines anonymous survey results from 154 surgeons affiliated with WPATH. The response rate for this survey was 30%. Of the respondents, 57% had encountered patients with surgical regret. It is important to recognize that this study was specifically directed toward patients who had undergone surgical transition. Acknowledged biases of this study include selection bias, recall bias, and response bias. This type of study cannot accurately identify the prevalence in the transgender population as a whole, and is particularly limited in the ability to assess potential for regret in the pediatric population.

15F. The 2018 Olson-Kennedy paper (Olson-Kennedy J, Warus J, Okonta V, Belzer M, Clark LF. Chest Reconstruction and Chest Dysphoria in Transmasculine Minors and Young Adults: Comparisons of Nonsurgical and Postsurgical Cohorts. *JAMA Pediatr.* 2018;172(5):431–436) presents the results of a survey of biologically female patients with male gender identity at the lead author's institution using a novel rating system for "chest dysphoria" created by the study authors. There were an equal number (68) of nonsurgical and post-surgical subjects surveyed. Those who had undergone bilateral mastectomies were reported to have less chest dysphoria than those who did not receive this intervention. Limitations of this study include convenience sampling of nonsurgical study subjects with high potential for selection bias, cross-sectional design, and lack of validation of the primary outcome measure. Test validation is particularly relevant in assessing adolescent questionnaires due to a variety of cognitive and situational

factors in this population (see Brener, N.D., J. Billy, and W.R. Grady. 2003. "Assessment of Factors Affecting the Validity of Self-Reported Health-Risk Behavior among Adolescents: Evidence from the Scientific Literature." *Journal of Adolescent Health* 33 (6): 436–57). Rigorous validation methods have been previously used in several other established questionnaires addressing adolescent self-perception (see Palenzuela-Luis, N., Duarte-Clíments, G., Gómez-Salgado, J., Rodríguez-Gómez, J. Á., & Sánchez-Gómez, M. B. (2022). Questionnaires Assessing Adolescents' Self-Concept, Self-Perception, Physical Activity and Lifestyle: A Systematic Review. *Children (Basel, Switzerland)*, *9*(1), 91). As previously noted, this study cannot provide information about a causal relationship between the intervention and outcome observed.

15G. The 2021 Almazan study (Almazan, A.N. & A.S. Keuroghlian. (2021). Association Between Gender-Affirming Surgeries and Mental Health Outcomes. *JAMA Surgery, 156*(7): 611–618) attempts to address mental health outcomes in relation to gender-transition surgery. As previously noted, this study relies upon data from the 2015 US Transgender Survey. Limitations and weaknesses of this survey tool includes convenience sampling, recruitment of patients through transgender advocacy organizations, demand bias (a.k.a. the good subject effect), a high number of respondents who reported having not transitioned medically or surgically (and reported no desire to do so in the future), and several data irregularities. One notable data irregularity was that a high number of respondents reported that their age was exactly 18 years. As noted by D'Angelo and colleagues, these irregularities raise serious questions about the reliability of the USTS data (D'Angelo, R., et al. (2021). One Size Does Not Fit All: In Support of Psychotherapy for Gender Dysphoria. *Archives of sexual behavior*, *50*(1): 7–16. https://doi.org/10.1007/s10508-020-01844-2), and therefore, the reliability of conclusions based on that data.

15H. In his declaration, Dr. Rosenthal cites the 2021 paper by Green et al (Association of Gender-Affirming Hormone Therapy With Depression, Thoughts of Suicide, and Attempted Suicide Among Transgender and Nonbinary Youth. *J Adolescent Health* 1-7 (2021) to support his assertion that gender affirming therapy lowers depression and suicide. Similar to the major methodological weaknesses noted above, this study relied upon a non-probability convenience sample of youth who identified as LGBTQ. Recruitment was made by targeted ads on Facebook, Twitter and Snapchat. In addition to the inherent bias of such study methodology, the data obtained by cross-sectional analysis cannot determine whether there is a causal relationship between access to gender affirming medical interventions and changes in depression or suicide.

15I. Rosenthal's citation of the paper by Turban et al (Access to gender-affirming hormones during adolescence and mental health outcomes among transgender adults. PLoS ONE 17(1) 2021; https://doi.org/10.1371/journal. pone.0261039) is similarly misleading as this study relied upon data from the same 2015 US transgender survey for which the major methodological weaknesses were discussed in detail above (¶15B)

16. There are major and highly significant differences between male and female responses to many drugs including sex hormones. (See, e.g., Madla, C. M., Gavins, F., Merchant, H. A., Orlu, M., Murdan, S., & Basit, A. W. (2021). Let's talk about sex: Differences in drug therapy in males and females. *Advanced drug delivery reviews*, 113804. Advance online publication. https://doi.org/10.1016/j.addr.2021.05.014). Giving estrogen to a biological male is not equivalent to giving the same hormone to a biological female. Likewise, giving testosterone to a biological female is not equivalent to giving the same hormone to a biological male. (See for example Soldin, O. P., & Mattison, D. R. (2009). Sex differences in pharmacokinetics and pharmacodynamics. Clinical pharmacokinetics, 48(3), 143–157 and Pogun S., Yararbas G. (2010) Sex

Differences in Drug Effects. In: Stolerman I.P. (eds) Encyclopedia of Psychopharmacology. Springer, Berlin, Heidelberg.). Differences are not limited to pharacokinetic effects but are present even at the cellular level. (See, e.g., Walker, C. J., Schroeder, M. E., Aguado, B. A., Anseth, K. S., & Leinwand, L. A. (2021). Matters of the heart: Cellular sex differences. *Journal of molecular and cellular cardiology*, S0022-2828(21)00087-0. Advance online publication. https://doi.org/10.1016/j.yjmcc.2021.04.010). Failure to acknowledge these differences can have tragic consequences. For example, in addition to the inherent sterilizing effect of cross-sex hormone administration, non-physiological levels of estrogen in males has been shown to increase the risk of thromboembolic stroke above the incidence observed in females (e.g. Getahun, D., Nash, R., Flanders, W. D., Baird, T. C., Becerra-Culqui, T. A., Cromwell, L., Hunkeler, E., Lash, T. L., Millman, A., Quinn, V. P., Robinson, B., Roblin, D., Silverberg, M. J., Safer, J., Slovis, J., Tangpricha, V., & Goodman, M. (2018). Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons: A Cohort Study. *Annals of internal medicine*, *169*(4), 205–213. https://doi.org/10.7326/M17-2785).

17. The claim that adolescents with persistent gender dysphoria after reaching Tanner Stage 2 *almost always* persist in their gender identity in the long-term whether or not they were provided gender affirming care is not supported by high quality scientific evidence. Frequent citation of a book chapter by Turban, De Vries and Zucker does not provide evidence in support of this claim. Within the chapter cited it states, "The natural history of gender identity for children who express gender nonconforming or transgender identities is an *area of active research.*" Only a single reference is found, and this is itself another book (Cohen-Kettenis PT, Pfäfflin F: Transgenderism and Intersexuality in Childhood and Adolescence: Making Choices.

London, Sage, 2003). Within the text of the Cohen-Kettenis book, *there is no experimental evidence to support the assertion that nearly all Tanner stage adolescents have persistent transgendered identity*. In fact, *in Chapter 4 of this text, evidence is presented that the majority of evaluated subjects did not have persistence* but rather eventually presented as homosexual adults. Cited references for this outcome include: Green, R. (1987). The "sissy boy syndrome" and the development of homosexuality. New Haven, CT: Yale University Press.; Money, J., & Russo, A. J. (1979). Homosexual outcome of discordant gender identity/role: Longitudinal follow-up. Journal of Pediatric Psychology,4, 29-41.; Zucker, K. J., & Bradley, S. J. (1995). Gender identity disorder and psychosexual problems in children and adolescents. New York/London: Guilford Press.; Zuger, B. (1984). Early effeminate behavior in boys: Outcome and significance for homosexuality. Journal of Nervous and Mental Disease, 172, 90-97.

18. Serious Methodological Limitations, Flaws, and Defects in the Gender Transition Industry's Methods for the Diagnostic-Labelling of "Gender Dysphoria": The DSM (Diagnostic and Statistical Manual of the American Psychiatric Association) involves an often controversial consensus seeking, (not scientific evidence seeking), political-voting process that began historically as an attempt to construct a reliable dictionary for psychiatry. The DSM has historically included unreliable, since debunked, diagnoses such as "multiple personality disorder" that fueled a harmful "craze" damaging vulnerable patients until scientists, legal professionals, juries, and licensing boards put a stop to it. (See the detailed discussion below). It is important for legal professionals to understand that the DSM was created using a consensual, political process of committees and voting and does not depend upon an evidence-based, uniformly valid and reliable scientific process. Small groups of professionals, often with ideological agendas, can form

committees and create "diagnoses" to be "voted" into the DSM. Much of DSM content is decided by the "voting" of small committees of advocates and activist practitioners whose judgment may suffer from significant financial conflicts of interest — as appears to be the case with all three of the plaintiffs' experts in this case.

19. Well-Documented Methodological Limitations, Flaws, and Defects in Gender Identity ("Transgender") Subjective Clinical Assessments: The clinical assessment methodology in sex discordant gender medicine is currently limited to self-report information from patients without objective scientific markers, medical tests, or scientific assessment tools. There are no reliable radiological, genetic, physical, hormonal, or biomarker tests that can establish gender identity or reliably predict treatment outcomes. A few hours of conversation with often poorly trained social workers often provides the only gatekeeping process to severe and irreversible iatrogenic surgical and hormonal injuries. Most importantly, *the long-term effects of "transitioning" have never been scientifically validated*. No valid-reliable methodology for such assessments has been accepted by the relevant scientific community and it appears that no known error rates for such assessments have ever been published. A more detailed discussion of the foundational science documenting the limitations and methodological defects in this field is offered below.

20. Essential Methodological Problems in the Gender Transition Industry: The research is characterized by sampling errors, the misreporting of findings, the misreporting of relevant history, misquoting of research studies, low quality research designs, failures to complete randomized clinical trials, and widespread confirmation bias, including the failure to properly explore alternative hypotheses (e.g., social contagion, mental illness, complex developmental processes, family dynamics, etc.), and other failures of basic scientific methodology. It is essential to properly consider alternative theories/hypotheses for the rapid and nearly exponential increase

of transgender cases—such as social contagion, mental illness, and/or complex developmental processes—especially as reportedly driven by news media, social media "YouTube "influencers" (who reportedly sell "transitioning" to vulnerable youth on social media), educational systems (that reportedly pressure 1st graders to "identify as non-binary"), as well as political-activist "pro-transition" health care workers (too few of whom seem to have carefully reviewed and understood the relevant scientific history and ongoing controversies in this field).

21. TERMINOLOGY - BIOLOGICAL SEX: Biological sex is a term that specifically refers to a member of a species in relation to the member's capacity to either donate (male) or receive (female) genetic material for the purpose of reproduction. Sex thus cannot be "assigned at birth" because it is permanently determined by biology at conception. This remains the standard definition that has been accepted by the relevant scientific community and used worldwide by scientists, medical personnel, and society in general for decades. The scientific and clinical measurement of sex is done with highly reliable and valid objective methodologies. Visual medical examination of the appearance of the external genitalia is the primary methodology used by clinicians to recognize sex. In cases where genital ambiguity is present, additional testing modalities including chromosomal analysis, measurement of hormone levels, radiographic imaging of internal sexual anatomy and biological response to provocative testing are utilized. The measurement and assessment of biological sex has been documented by valid-reliable research published in credible journals, and is accepted by the relevant scientific community. The error rate for the measurement and assessment of biological sex is very low, below 1%.

22. TERMINOLOGY - GENDER: Gender, a term that had traditionally been reserved for grammatical purposes, is currently used to describe the psychological and cultural characteristics of a person in relation to biological sex. Gender in such new definitions would therefore

exist only in reference to subjective personal perceptions and feelings and societal expectations, but not biology. The term "gender" is currently used in a variety of ways and has thus become a controversial and unreliable term that means different things to different observers often varying according to political and ideological positions. The only definition of gender accepted by the worldwide, relevant scientific (biology, genetics, neonatology, zoology, medicine, etc.) community retains the historic biological connection to reproductive purpose with other definitions mired in controversy. The reliability and validity of various usages of the term "gender" is currently quite controversial and the relevant scientific community has accepted no use other than in relation to biological sex, which includes participate in activities related to reproduction. The serious dangers of incorrectly using the term "gender" is acknowledged by the Endocrine Society (Bhargava, A., Arnold, A. P., Bangasser, D. A., Denton, K. M., Gupta, A., Hilliard Krause, L. M., Mayer, E. A., McCarthy, M., Miller, W. L., Raznahan, A., & Verma, R. (2021) Considering Sex as a Biological Variable in Basic and Clinical Studies: An Endocrine Society Scientific Statement. *Endocrine reviews*, bnaa034. Advance online publication. https://doi.org/10.1210/endrev/bnaa034). In addition, the error rate for multiple uses of the term "gender" outside of the accepted biologically related use is unknown, untested, and unpublished. The measurement and assessment of biological sex and gender has been documented by valid-reliable research published in credible journals, and is accepted by the relevant scientific community. The error rate for the measurement and assessment of biological sex and gender is very low, below 1%.

23. TERMINOLOGY - GENDER IDENTITY: Gender identity refers to a person's individual experience and perception and unverified verbal patient reports of how they experience being male or female or a combination of these or other categories. The term "gender identity" is

currently controversial. It is a term that means very different things to different observers often varying according to political, ideological, religious, and other factors. There is no current worldwide definition of "gender identity" accepted by the relevant scientific (cf. clinical) community. The reliability and validity of the term "gender identity" is controversial and not accepted by the relevant scientific community. The measurement error rate for non-biological "gender identity" is unknown, untested, and unpublished and could be very high.

24. TERMINOLOGY - SEXUAL ORIENTATION: Sexual orientation refers to a person's enduring pattern of arousal and desire for intimacy with males, females, or both.

25. TERMINOLOGY - DNA and CHROMOSOMES: Sex is genetically encoded at the moment of conception due to the presence of specific DNA sequences (i.e. genes) that direct the production of signals that influence the formation of the bipotential gonad to develop into either a testis or ovary. This genetic information is normally present on X and Y chromosomes. Chromosomal sex refers to the normal complement of X and Y chromosomes (i.e. normal human males have one X and one Y chromosome whereas normal human females have two X chromosomes). Genetic signals are mediated through the activation or deactivation of other genes and through programmed signaling of hormones and cellular transcription factors. The default pattern of development in the absence of external signaling is female. The development of the male appearance (phenotype) depends upon active signaling processes.

26. BIOLOGICAL SEX IS BINARY—NOT A CONTINUUM—FOR 99%+ of MAMMALS INCLUDING HUMANS: For members of the human species (and virtually all mammals), sex is normatively aligned in a binary fashion (i.e., either male or female) in relation to biologic purpose. The presence of individuals with disorders of sexual development (along the

range of the established Prader scale) does not alter this fundamental reality. Medical recognition of an individual as male or female is correctly made at birth in nearly 99.98% of cases according to external phenotypic expression of primary sexual traits (i.e., the presence of a penis for males and presence of labia and vagina for females). The recognition of an individual as male or female made at birth according to biological features has been documented by valid-reliable research published in credible journals, and is generally accepted by the relevant scientific community. The error rate for the measurement and assessment of an individual as male or female made at birth according to biological features is very low indeed, certainly below 1%.

27. THE GENITAL-BIOLOGICAL FUNCTION OF REPRODUCTION: Due to genetic and hormonal variation in the developing fetus, normative development of the external genitalia in any individual differs with respect to size and appearance while maintaining an ability to function with respect to biologic purpose (i.e. reproduction). Internal structures (e.g. gonad, uterus, vas deferens) normatively align in more than 99.9%+ of mammals with external genitalia, including humans. In my opinion, this view is generally accepted by the relevant scientific communities in endocrinology, neonatology, developmental biology, genetics, and other relevant fields. In my opinion, all relevant sciences agree that the development of genital structures is intrinsically oriented to biological reproduction.

28. BIOLOGICAL ASSESSMENT OF SEX: Reliance upon external phenotypic expression of primary sexual traits is a highly accurate, reliable and valid means to assign biologic sex. In over 99.9% of cases, this designation will correlate with internal sexual traits and capacity for normal biologic sexual function. Sex is therefore not "assigned at birth" but is rather recognized at birth. In my opinion, this view is generally accepted by the relevant scientific communities in endocrinology, psychiatry, neonatology, biology, genetics, gynecology, and other fields.

29. DISORDERS OF SEXUAL DEVELOPMENT ARE VERY RARE: Due to the complexity of the biological processes that are involved in normal sexual development, it is not surprising that a very small number of individuals are born with defects in this process (1 in 5,000 births). Defects can occur through either inherited or de *novo* mutations in genes that are involved in sexual determination or through environmental insults during critical states of sexual development. Persons who are born with such abnormalities are considered to have a disorder of sexual development (DSD). Most often, this is first detected as ambiguity in the appearance of the external genitalia. Such detection measurements are reliable and valid and accepted by the relevant scientific community. In my opinion, this view is generally accepted by the relevant scientific communities in endocrinology, neonatology, gynecology, psychiatry, biology, genetics, and other fields. See Leonard Sax (2002) How common is lntersex? A response to Anne Fausto-Sterling, The Journal of Sex Research, 39:3, 174-178, DOI: 10.1080/00224490209552139

DISORDERS OF SEXUAL DEVELOPMENT ARE NOT A THIRD SEX: Normal variation in external genital appearance (e.g. phallic size) does not alter the basic biologic nature of sex as a binary trait. "Intersex" conditions represent disorders of normal development, not a third sex. In my opinion, this view is generally accepted by the relevant scientific communities in endocrinology, urology, surgery, neonatology, gynecology, psychiatry, biology, genetics, and other fields.

30. DISORDERS OF SEXUAL DEVELOPMENT REQUIRE ASSESSMENTS OF OBJECTIVE EVIDENCE: The medical care of persons with disorders of sexual development (DSDs) is primarily directed toward identification of the etiology of the defect and treatment of any associated complications. Similar to other diseases, diagnostic tools such as the Prader scale are used to assess, measure, and assign a "stage" to the severity of the deviation from normal

(e.g. assessments of objective, reliable evidence). In children with DSDs, characterization based upon phenotype alone does not reliably predict chromosomal sex nor does it necessarily correlate with potential for biological sexual function. Decisions on initial sex assignment in these very rare cases require detailed assessment of objective, reliable medical evidence by a team of expert medical providers. In my opinion, this view is generally accepted by the relevant scientific communities in endocrinology, urology, surgery, neonatology, gynecology, psychiatry, biology, genetics, and other fields.

31. INTERSEX CONDITIONS REQUIRE PROPER CONSIDERATION OF ALTERNATIVE HYPOTHESES AND TREATMENT PLANS: Standard medical practice in the treatment of persons with DSDs has evolved with growing understanding of the physical, psychological, and psychiatric needs and outcomes for affected individuals. Previously, it was felt that a definitive sex assignment was necessary shortly after birth with the belief that this would allow patients with a disorder of sexual development to best conform to the assigned sex and so parents-caregivers could help socialize the child to the assigned sex. Current practice is to defer sex assignment until the etiology of the disorder is determined and, if possible, a reliable prediction can be made on likely biologic and psychologic outcomes. When this cannot be done with confidence, a presumptive sex assignment is made. Factors used in making such decisions include chromosomal sex, phenotypic appearance of the external genitalia, and parental desires. The availability of new information can, in rare circumstances, lead to sex reassignment. Decisions on whether to surgically alter the external genitalia to align with sex are generally deferred until the patient is able to provide consent. See Lee, P. A. et al. Global Disorders of Sex Development Update since 2006: Perceptions, Approach and Care. Horm Res Paediatr 85, 158-180, doi:10.1159/000442975 (2016)). In my opinion, this view is generally accepted by the relevant

scientific communities in endocrinology, urology, surgery, neonatology, gynecology, psychiatry, biology, genetics, and other fields.

32. METHODOLOGICAL DEFECTS of the GENDER TRANSTION INDUSTRY - WHY IS THE TRANSGENDER MEDICINE FIELD STILL SO CONTROVERSIAL AFTER DECADES OF RESEARCH?:

- Despite several highly defective research efforts, the gender transition industry has failed to prove long term benefits that outweigh the reported harms, dangers, and serious injuries of "gender affirmation" interventions—including inability to reach orgasm, vaginal atrophy, compromised cognitive function, lifelong reliance on medication and repeated surgical intervention to deal with the cumulative effects of these iatrogenic harms, stunted growth, damage to social support systems, and increased risk of serious suicide attempts.
- The gender transition industry has repeatedly presented false, deceptive, and misleading information to the public and to patients regarding the known risks, dangers, injuries and benefits of "affirmation treatments." (E.g. the Bränström, Turban, and related research errors of omission and misreporting.)
- The Gender Transition Industry has failed to generate reliable and valid treatment outcome research sufficient to support this risky medical experiment. (E.g., the national reviews of England (NICE), Sweden, Finland, Cochrane review, etc).
- Because of the lack of competent, valid, peer reviewed published research support, the gender transition industry relies upon support from "professional associations." Yet such associations are engaged in consensus-seeking-political voting methodologies and not evidence-based, peer reviewed science. Such political-

professional associations have made similar, disastrous mistakes in the past. For example, the American Medical Association supported racist, "junk" science eugenics "treatments" in the 1930s and the American Psychiatric Association did not act to prevent or halt the harms of the repressed-memory/multiple personality industry of the 1990s.

33. METHODOLOGICAL DEFECTS of the GENDER TRANSITION INDUSTRY INCLUDE LIMITATIONS and HAZARDS OF RELYING ON UNVERIFIED PATIENT SELF-REPORT DATA WITH NO OBJECTIVE EVIDENCE: In contrast to disorders of sexual development, gender dysphoria cannot be reliably, objectively assessed, as it is based on patient self-reports. (There are no blood tests, no x-rays, no lab results, and no objective data.) Individuals who verbally report experiencing significant distress due to perceived discordance between gender identity and sex cannot currently be reliably, validly, and objectively assessed as experiencing "gender dysphoria." (See American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th edn, (2013).) Although gender perceptions, feelings, and "identity" usually align with biological sex, some individuals report experiencing discordance in these distinct traits. Specifically, for example, biologic females may report experiencing that they identify as males and biologic males may report experiencing that they identify as females. As gender by definition is distinct from biological sex, one's gender identity does not change a person's biological sex. There is currently no known reliable and valid methodology for assessing the accuracy or nature of unverified, verbal reports of discordant "identity." There is thus no known "error rate" for relying upon such reports to engage in hormonal and surgical treatments that might result in lasting, irreversible damages to normal, healthy organs and the destruction of normal biological functions (e.g. sterility), as the current research documents. In my opinion, this

view is generally accepted by the relevant scientific communities in endocrinology, urology, surgery, neonatology, gynecology, psychiatry, biology, genetics, and other fields.

34. METHODOLOGICAL DEFECTS of the GENDER TRANSITION INDUSTRY include the KNOWN LIMITATIONS OF RELYING ON UNVERIFIED, PATIENT SELF-REPORT DATA UNRELIABLY ASSESSED BY HEALTH CARE PROFESSIONALS. The relevant science documents that mental health care professionals are unreliable human "lie detectors" ("often no better than flipping a coin"). Currently, there is no known methodology for reliably discerning true from false patient reports without corroborating evidence such as radiology, lab tests, or other objective evidence. The gender transition industry's sole reliance upon patient self-report data carries unknown risks of errors, misinformation, deception and lasting harm to patients from treatments that deliberately damage healthy organs and destroy essential normal bodily processes (e.g. often causing sterility). Assessment of gender dysphoria currently depends almost entirely upon unverified, self-reported evidence provided by patients. A patient's spoken or written reports of alleged "memories" of symptoms and behaviors are the only source of evidence for the diagnosis in many cases. This is a source of potentially profound unreliability in patient care as the relevant science documents that physicians are poor "lie detectors"—often no more reliable in discerning false reports than flipping a coin—and sometimes much worse. The relevant research also documents that even though humans (including therapists) are poor "lie detectors," many poorly trained physicians and mental health professionals personally—and falsely—believe they are "experts" at this complex and difficult task. See, e.g., Vrij, Aldert, Granhag, P. and Porter, S. (2010) Pitfalls and opportunities in nonverbal and verbal lie detection. Psychological Science In The Public Interest, 11 (3). pp. 89-121. ISSN 1529-1006 10.1177/1529100610390861. The final error that I will highlight is that professional lie catchers

tend to overestimate their ability to detect deceit. Research has consistently shown that when professional lie catchers and laypersons are compared, "professionals are more confident in their veracity judgments but are NO more accurate" (emphasis added). See also Rosen, G. M. and Phillips, W.R., A Cautionary Lesson from Simulated Patients, *Journal of the American Academy of Psychiatry and Law*, 32, 132-133, (2004).

35. METHODOLOGICAL DEFECTS of the GENDER TRANSITION INDUSTRY include the reliance upon (often poorly trained) mental health professionals to assess unverified patient reports. Although much of medicine became science-based in the 20th century, the mental health field reportedly continues to lag behind.

The gender transition industry often involves social workers or other mental health professionals "assessing" patients reporting gender dysphoria to determine if they will "benefit" from "affirmation" medical interventions. Given the extraordinary lack of competent, methodologically sound research justifying the use of gender affirmation "treatments" (as demonstrated in independent reviews by England, Sweden, Finland, the Cochrane review, and others, see below), there is no method for mental health professionals to reliably determine who might "benefit" from experimental interventions. Such unreliable assessment protocols risk harm to patients as they depend upon the widespread, unreliable method of having psychotherapists depend upon "clinical judgment" methodologies to make life-changing decisions and offer "professional" opinions with little or no scientific validity. See, e.g., Mischel, W. Connecting Clinical Practice to Scientific Progress, Psychological Science in the Public Interest, November 2008, vol 9, no 2 i-ii. The past President of the Association for Psychological Science, Prof. Walter Mischel,

stated "the current disconnect between psychological science and clinical practice is an unconscionable embarrassment." See Mischel, W. Connecting Clinical Practice to Scientific Progress, Psychological Science in the Public Interest, Vol 9, No 2, 2009.

Over the past century many components of the health care system—surgery, radiology, laboratory testing, internal medicine, pharmacological systems, etc.—became science-driven and far more effective and reliable. Courts are often unaware that this transformation—moving from widespread use of unreliable methodologies to the widespread use of reliable science-based methodologies—has, in many ways, not yet occurred in the mental health system. See, e.g., West, Catherine, 'An Unconscionable Embarrassment,' Association for Psychological Science, Observer, October 2009, see http://www.psychologicalscience.org/index.php/publications/observer/2009/october-09/an-unconscionable-embarrassment.html; See, also Baker, T., McFall, R. & Shoham, V., Current Status and Future Prospects of Clinical Psychology: Toward a Scientifically Principled Approach to Mental and Behavioral Health Care, Psychological Science in the Public Interest, Vol. 9, No. 2 (2009); see also Harrington, A., Mind Fixers: Psychiatry's Troubled Search for the Biology of Mental Illness, W. W. Norton & Company; 1st edition, April 16, 2019; see also Dawes, R.M., House of cards: Psychology and psychotherapy built on myth, New York: Free Press (1997); see also Garb, H. N., & Boyle, P. A (2003). Understanding why some (mental health) clinicians use pseudoscientific methods: Findings from research on clinical judgment. In S. O. Lilienfeld, S. J. Lynn, &. J. M. Lohr (Eds.), Science and pseudo-science in clinical psychology (pp. 17–38). New. York, NY: Guilford Press.

36. DYSPHORIC REPORTS ARE COMMON FROM CHILDREN WITH A RANGE OF ILLNESSES: Reports of feelings of anxiety, depression, isolation, frustration, and embarrassment are not unique to children with gender dysphoria, but rather are common to children

who differ physically or psychologically from their peers. Difficulties are accentuated as children progress through the normal stages of neuro-cognitive and social development. In my clinical practice of pediatric endocrinology, this is most commonly seen in children with diabetes. Attempts to deny or conceal the presence of disease rather than openly acknowledge and address specific needs can have devastating consequences including death. With proper acknowledgment of the similarity and differences between children with gender dysphoria and other developmental challenges, prior medical experience in treating a range of reported troubles can guide the development of effective approaches to both alleviate suffering and minimize harm to school aged and adolescent children experiencing gender dysphoria.

37. COURTS SHOULD BE AWARE THAT CLINICAL EXPERIENCE IN THE MENTAL HEALTH FIELDS—WHERE CLINICIANS OFTEN LACK ACCURATE FEEDBACK—IS OFTEN OF LIMITED VALUE: As the gender transition industry routinely permits poorly qualified social workers or other mental health professionals to subjectively make life changing decisions in gender dysphoria cases—such mental health professionals often unreliably overestimate their ability to offer such "crystal ball" assessments and predictions. Few of these professionals seem aware of the research showing the grave limitations on the experience, judgment, and methodologies of mental health professionals. See, e.g., Tracey, T.J., Wampold, B.E., Lichtenberg, J.W., Goodyear, R. K., (2014) Expertise in Psychotherapy: An Elusive Goal, American Psychologist, Vol. 69, No. 3, 218-229. "In a review of expertise across professions, Shanteau, J. (1992). [Competence in experts: The role of task characteristics. *Organizational Behavior and Human Decision Processes, 53*(2), 252–266.] identified several professions in which practitioners develop expertise, which he defined as increased quality of performance that is gained with additional experience. These professions, which demonstrate there can be a relation

between experience and skill, include astronomers, test pilots, chess masters, mathematicians, accountants, and insurance analysts. Shanteau also identified several professions for which experiential expertise was not demonstrated, including [mental health professionals]. He attributed the differences between the two types of professions to the *predictability of their outcomes and the unavailability of quality feedback*." For example, airline pilots, or even more clearly Navy fighter pilots who land on aircraft carriers practice their professions in full view of hundreds of people. If they err, people die. If they are, off course, unstable, or inaccurate in their performance, immediate consequences, retraining or loss of profession is the immediate outcome. In contrast, a social worker, psychologist, or psychiatrist, sitting alone in a room with a troubled patient can make erroneous statements, use unreliable methodologies (e.g., naively believing whatever patients tell them or believing that they are "professional human lie detectors"), believe false and misleading notions about human memory, demonstrate ignorance of the serious defects in transgender treatment research, and fail to properly inform patients of the risks and benefits of treatments, etc. Mental health professionals can make such egregious errors for decades without receiving timely, accurate feedback. Without accurate feedback there is a failure of the learning process and improvements are difficult or not possible. Such limiting processes can continue for many years of practice. This is why mental health professions have been listed as doing the type of work that often does not lead to improvements in "clinical experience"—even over many years of practice. Gender discordant ("transgender") patients are rarely, if ever, informed of these limitations on mental health professionals' knowledge, training, or experience nor the limitations of mental health "assessments" based on unverified self-reported "memory" data.

38. The World Professional Association for Transgender Health (WPATH), the American Academy of Pediatrics (AAP), and the Endocrine Society: This methodological critique and

history of association errors and misadventures is quite informative when assessing the "professional association" consensus seeking methodologies including voting and political activities such as those of WPATH, the AAP, the American Endocrine Society and similar groups as they adopt support for the "politically correct" but scientifically defective, ideologically driven gender transition industry. Consensus seeking (voting) methods are not scientific evidence-based methodologies. Courts should take care not to be deceived by the "positions" of Associations—no matter how large or vocal. The net effect of many the gender transition industry's methods and procedures is the sterilization of tens of thousands of children, adolescents, and adults. This is a sobering reminder of previous, now infamous, medical misadventures. (See Hruz, PW, Mayer, LS, and McHugh, PR, "Growing Pains: Problems with Puberty Suppression in Treating Gender Dysphoria," The New Atlantis, Number 52, Spring 2017 pp. 3 -36; See also McHugh, P., Psychiatric Misadventures, The American Scholar, Vol. 62, No. 2 (Spring 1993), pp. 316-320).

39. The Diagnostic and Statistical Manual of the American Psychiatric Association (DSM): A final example of the methodological limitations of relying upon "association voting" methods is the Diagnostic and Statistical Manual of the American Psychiatric Association. The DSM (and also the International Classification of Diseases- ICD) system(s) have confused some courts in the past. Simply put, reliability data, validity methodological analyses, and error rates are not supplied nor supported by the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM).

The current American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (Version 5) employs the term "Gender Dysphoria" and defines it with separate sets of criteria for adolescents and adults on the one hand, and children on the other. It is important to appreciate the DSM for what it is and what it is not. The DSM began as an attempt to create a

dictionary for psychiatry. The process by which DSM classifications are created involves voting by committee—this is not a reliable-valid scientific process. The committees' recommendations are approved or rejected by superordinate committees. DSM content is largely decided by consensus-seeking methodologies—such as "voting" by small committees of (sometimes) advocates and activist practitioners whose judgment may suffer from significant financial conflicts of interest. The limitations of the DSM methodology are well known in the relevant scientific community. In my opinion, these views are generally accepted by the relevant scientific community.

In sum, professional association "positions" are not based upon competent, credible, reliable and valid scientific methodologies. Professional association "positions" on gender affirmation assessments and treatments remain very socially, medically, and scientifically controversial—and increasingly so. The association "positions"—since they are produced by voting and not methodologically reliable-valid evidence—have not been generally accepted by the relevant scientific community and they have no known, nor published, error rates.

40. PATIENTS' RIGHTS TO TESTED, PROVEN TREATMENTS and INFORMED CONSENT HAVE BEEN VIOLATED IN THE PAST BY ETHICAL FAILURES IN THE MEDICAL and MENTAL HEALTH SYSTEMS. Using experimental procedures on uninformed, vulnerable patients is unethical and improper. Some of the most tragic chapters in the history of medicine include violations of informed consent and improper experimentation on patients using methods and procedures that have not been tested and validated by methodologically sound science—such is the case with the gender transition industry. The history of the infamous Tuskegee studies, the Nazi and Imperial Japanese wartime experiments, lobotomies (e.g., Dr. Egas Moniz received the 1949 Nobel Prize in Medicine for inventing lobotomies as a "treatment" for schizophrenia. See https://www.nobelprize.org/prizes/medicine/1949/moniz/article/),

recovered memory therapy-multiple personality disorders, rebirthing therapy (see, e.g., Janofsky, M. Girl's Death Brings Ban on Kind of 'Therapy'. New York Times. April 18, 2001; see also Peggy Lowe, Rebirthing team convicted: Two therapists face mandatory terms of 16 to 48 years in jail, Rocky Mountain News, April 21, 2001), coercive holding therapy (see, Hyde, J. "Holding therapy appears finished, State orders the last practitioner of holding therapy to end controversial method" Deseret News, Feb 13, 2005), and other tragic examples should serve as a stark warning to medical providers to properly protect the rights of patients and their families to a proper informed consent process and to not be subjected to experimental, unproven interventions such as gender transition "treatments." It is now universally agreed that medical and psychotherapy patients have a right to proper informed consent. Professional ethics codes, licensing rules and regulations, hospital rules and regulations, state and federal laws, and biomedical conventions and declarations all protect patients' right to informed consent discussions of the risks and benefits of proposed treatments and alternative treatments including no treatment. See Jonson AR, Siegler M, Winslade, WJ: Clinical Ethics, New York: McGraw Hill, 1998, ("Informed consent is defined as the willing acceptance of a medical intervention by a patient after adequate disclosure by the physician of the nature of the intervention, its risks, and benefits, as well as of alternatives with their risks and benefits.") See also Katz, A., Webb, S., and Committee on Bioethics, Informed Consent in Decision-Making in Pediatric Practice, Pediatrics, August 2016, 138 (2) e20161485; DOI: https://doi.org/10.1542/peds.2016-1485 at https://pediatrics.aappublications.org/content/138/2/e20161485

Tragically, however, as I will discuss in detail below, we now have much evidence supporting increasing concerns that the true risks and benefits of Sex Discordant Gender

("transgender") transition "treatments" are NOT being properly and ethically presented to patients by providers (surgeons, endocrinologists, therapists, etc). Similarly, many of the published "pro-transition" research studies reviewed in this declaration have misrepresented to the public the actual risks and benefits of gender affirming medical interventions. The gender transition industry has produced research claiming evidence supporting the use of controversial "treatments" when, in fact, their own study data more likely support the alternative hypothesis that so-called "transition" intervention procedures might produce higher risks of anxiety and more serious suicide attempts requiring hospitalization**.** Expert witnesses in cases involving issues related to sex discordant gender transition interventions are duty bound and required by licensing rules to truthfully and fully disclose to courts and legal professionals the well-documented risks, international controversies, and published misrepresentations involving the still unproven gender transition methods and procedures.

42. ONE OF THE MOST SERIOUS OF ALL METHODOLOGICAL ERRORS, CONFIRMATION BIAS, PLAGUES THE RESEARCH OF THE GENDER TRANSITION INDUSTRY: Confirmation bias is one of the most serious and potentially dangerous errors in the assessment-diagnosis-treatment process of medicine. One of the key methodologies in science and in proper investigations-assessments of all kinds—including expert witness review and testimony—is the generation and testing of multiple alternative investigative hypotheses. From US Public Junior High Schools (typically first taught to 8th Graders) through competent M.A., M.S.W., and all Ph.D. and M.D. graduate programs, students and professionals at all levels are taught that the central methodology for science and for a proper assessment-diagnosis-treatment or expert witness report involves the generation and testing of alternative investigative hypotheses. Investigative hypotheses, once generated, should be rationally, properly, and fairly explored

to see if actual, factual evidence supports or refutes the hypotheses. A common and serious error in improper assessments-diagnoses-treatments is "confirmation bias," the failure to generate and then explore alternative hypotheses. With confirmation bias, the often poorly trained and/or biased physician, investigator, expert, or therapist applies a narrow "tunnel vision" process to support a single, favorite, biased, pre-conceived hypothesis in a case. (See Garb, H. N., & Boyle, P. A (2003). Understanding why some clinicians use pseudoscientific methods: Findings from research on clinical judgment. In S. O. Lilienfeld, S. J. Lynn, &. J. M. Lohr (Eds.), Science and pseudoscience in clinical psychology (pp. 17–38). New. York, NY: Guilford Press.; see also Plous, Scott (1993). The Psychology of Judgment and Decision Making. p. 233; Nickerson, Raymond S. (June 1998). "Confirmation Bias: A Ubiquitous Phenomenon in Many Guises". Review of General Psychology 2 (2): 175–220. doi:10.1037/1089-2680.2.2.17; Joshua Klayman and Young-Won Ha, Confirmation, Disconfirmation, and Information in Hypothesis Testing, Psychological Review, 1987, Vol.94, No. 2, 211-228.) Currently, too many gender transition industry providers appear to violate the requirement to properly generate, explore, and disclose alternative hypotheses for assessments/diagnoses and treatments. In my opinion such failures, including the demand that all alternative hypotheses and treatments be banned as forms of "conversion" therapy, risk institutionalizing confirmation bias —a dangerous form of negligent practice. See Smith, T. Summary of AMA Journal of Ethics article on cognitive biases, Four widespread cognitive biases and how doctors can overcome them (e.g., confirmation bias, anchoring bias, affect heuristic, and outcomes bias) at https://www.ama-assn.org/delivering-care/ethics/4-widespread-cognitive-biases-and-how-doctors-can-overcome-them. ("Physicians are human and, therefore, constantly vulnerable to cognitive bias. But this imperfection is not just theoretical. It can have huge effects on patient care.")

43. CONFIRMATION BIAS CAN PREVENT COMPLEX, COMPREHENSIVE DIAGNOSIS AND TREATMENT EXPLORING ALTERNATIVE HYPOTHESES: By demanding the immediate and un-investigated "affirmation" of a sex discordant gender identity patient's requests for so-called "transitioning"—without conducting a detailed, proper, medical assessment of alternative hypotheses—the gender transition industry is attempting to enforce and institutionalize the methodological failure of "confirmation bias." By disparaging as "conversion therapy" all forms of psychotherapy, coping-and-resilience training, cognitive behavioral therapy for depression/anxiety, the gender transition industry is failing to treat individual patients according to the basic requirements and principles of competent medical assessment, diagnosis, and treatment. The current scientific evidence does not support the current treatments nor methods endorsed and aggressively marketed and demanded by the gender transition industry. Its general refusal to properly investigate or even consider alternative hypotheses, alternative diagnoses, and alternative treatments is, in my view, unethical misconduct. For example, many peer reviewed, properly conducted, published research reports demonstrate that cognitive-behavioral therapy is a very low-risk, safe, and highly effective treatment for depression and anxiety disorders. See, e.g., Mor N, Haran D. Cognitive-behavioral therapy for depression. J Psychiatry Relat Sci. 2009;46(4):269-73. PMID: 20635774, https://pubmed.ncbi.nlm.nih.gov/20635774/; (A review of "Twenty-nine Random Control Trials were included in three separate meta-analyses. Results showed multi-modal CBT was more effective than no primary care treatment (d =0.59), and primary care treatment-as-usual (TAU) (d = 0.48) for anxiety and depression symptoms."). See, e.g., Twomey, C., O'Reilly, G. and Byrne, M. Effectiveness of cognitive behavioural therapy for anxiety and depression in primary care: a meta-analysis, Family Practice, Volume 32, Issue 1, February 2015, pp. 3–15, https://doi.org/10.1093/fampra/cmu060. The political taint is so strong

that some providers reportedly fail to offer and engage in CBT therapy with depressed/anxious gender dysphoric patients for fear of being attacked as engaging in "conversion" therapy. Again, the institutionalization of medical negligence (e.g., confirmation bias) harms vulnerable patients.

44. PROPER INVESTIGATIONS OF DECEPTIVE MISCONDUCT. Ideological over-reach can lead to unethical misconduct and licensing violations. Misrepresenting medical-scientific research, deceptively hiding methodological errors, or failing to honestly report ongoing international controversies to courts, patients, or guardians should be properly investigated as misconduct. Licensing boards and professional associations produce and should properly enforce ethics rules and requirements governing the conduct of health care professionals to protect the rights of patients and parents.

45. THE ACTUAL PREVALENCE OF GENDER DYSPHORIA and PATIENTS THAT IDENTIFY AS GENDER DISCORDANT ("transgender") IS UNKNOWN BUT IT APPEARS TO BE INCREASING AT A RAPIDLY ACCELERATING RATE THUS SUPPORTING AN ALTERNATIVE HYPOTHESIS OF SOCIAL CONTAGION: Estimates reported in in the DSM-V were between 0.005% to 0.014% for adult males and 0.002% to 0.003% for adult females. Thus, gender dysphoria was, until just a few years ago, a very rare condition. It is currently unknown whether these DSM estimates were falsely low due to under-reporting or:

- whether changing societal acceptance of transgendered identity and the growing number of medical centers providing interventions for gender dysphoria has led to increased reporting of persons who identify as transgender ;
- whether the reported educational programs aggressively promoting "non-binary" identification to elementary to high school students to college students have greatly increased the numbers of youth adopting a transgender identity;

- whether the reported wave of "trans You Tube influencers" watched by millions each day as they aggressively "sell" the transgender lifestyle has added to a social contagion effect with vulnerable lonely, depression, anxious, or autistic youth; or
- whether other causal processes are at play.

A key unanswered research question is whether a social contagion process is leading to vast and rapid increases in the numbers of patients identifying as gender discordant ("transgender"). How many of the new waves of thousands of cases are 'false reports' that will dissipate with time and normal development over time? For example, the Gender Identity Development Service in the United Kingdom, which treats only children under the age of 18, reported that it received 94 referrals of children in 2009/2010 and 1,986 referrals of children in 2016/2017, a relative increase of 2,000%. See "GIDS referrals figures for 2016/17," Gender Identity Development Service, GIDS. NHS.uk (undated), http://gids.nhs.uk/sites/default/files/content_uploads/referralfigures-2016-17.pdf.

Reportedly, similar social contagion processes led to tens of thousands of patients and families being harmed by controversial diagnoses such as multiple personality disorder (MPD) and controversial interventions including recovered memory therapy (RMT). RMT and MPD patients, once considered extremely rare (some 300 MPD patients reported worldwide prior to the 1980s-1990s social contagion epidemic) erupted into a flood of tens of thousands of patients and affected families in the 1990s. These very controversial disorders and treatments were greatly reduced by dozens of civil lawsuits against RMT-MPD therapists, international news exposure of scientific evidence debunking these notions, and international news reporting of the civil litigation, licensing prosecutions, and licensing revocations of well-known RMT-

MPD practitioners. (See, e.g., Belluck, P. Memory Therapy Leads to a Lawsuit and Big Settlement [$10.6 Million], The New York Times, Page 1, Column 1, Nov. 6, 1997; Pendergrast, M. (2017). The repressed memory epidemic: How it happened and what we need to learn from it. New York, NY: Springer).

Recent data indicates that the number of people seeking care for gender dysphoria is rapidly increasing with some estimates as high as 20-fold and more. See Chen, M., Fuqua, J. & Eugster, E. A. Characteristics of Referrals for Gender Dysphoria Over a 13-Year Period. Journal of Adolescent Health 58, 369-371, doi:https://doi.org/10.1016/j.jadohealth.2015.11.010 (2016); 4. "GIDS referrals figures for 2016/17," Gender Identity Development Service, GIDS.NHS.uk (undated), http://gids.nhs.uk/sites/default/files/content_uploads/referral-figures-2016-17.pdf). See Zucker K. J. (2017). Epidemiology of gender dysphoria and transgender identity. *Sexual health*, *14*(5), 404–411. https://doi.org/10.1071/SH17067. Data from England show *increases of 4,000%* for female to male patients and in America data show *increases of 20,000%* for young women (e.g. from .01 to 2%). Estimates vary considerably in relation to how sex-gender identity discordance is defined. See Zhang, Q., Goodman, M., Adams, N., Corneil, T., Hashemi, L., Kreukels, B., Motmans, J., Snyder, R., & Coleman, E. (2020). Epidemiological considerations in transgender health: A systematic review with focus on higher quality data. *International journal of transgender health*, *21*(2), 125–137. https://doi.org/10.1080; Poteat, T., Rachlin, K., Lare, S., Janssen, A. & Devor, A. in *Transgender Medicine: A Multidisciplinary Approach* (eds Leonid Poretsky & Wylie C. Hembree) 1-24 (Springer International Publishing, 2019); Flores AR, Herman JL, Gates, GJ, Brown TNT. How Many Adults Identify as Transgender in the United States? Los Angeles, CA: The Williams Institute; 2016. https://williamsinstitute.law.ucla.edu/wp-content/uploads/Trans-Adults-US-Aug-2016.pdf. Accessed April 28, 2021.

46. EVIDENCE SUPPORTS THE HYPOTHESIS THAT GENDER IDENTITY IS *NOT* GENETICALLY OR BIOLOGICALLY DETERMINED: There is strong disconfirming evidence (e.g., Popperian falsifiability) against the theory that gender identity is determined at or before birth and is unchangeable. This comes from A) identical twin studies where siblings share genetic complements and prenatal environmental exposure but have differing gender identities. See Heylens, G. et al. Gender identity disorder in twins: a review of the case report literature. J Sex Med 9, 751-757, doi:10.1111/j.1743-6109.2011.02567.x (2012) and B) the very recent and massive increase in the numbers of GD patients over a very short time span. This argues against a biological-genetic hypothesis. See Leinung MC, Joseph J. Changing Demographics in Transgender Individuals Seeking Hormonal Therapy: Are Trans Women More Common Than Trans Men? Transgend Health. 2020 Dec 11;5(4):241-245. doi: 10.1089/trgh.2019.0070. PMID: 33644314; PMCID: PMC7906237.

47. REPLICATED RESEARCH EVIDENCE SUPPORTS THE HYPOTHESIS THAT GENDER IDENTITY IS *NOT* IMMUTABLE: Further evidence that gender identity is not fixed and immutable comes from established peer reviewed literature demonstrating that the vast majority (80-95%) of children who express gender dysphoria revert to a gender identity concordant with their biological sex by late adolescence. This natural developmental "cure" of gender dysphoria requires no direct "treatment" and prevents the hormonal and surgical destruction of normal, healthy organs and bodily processes (e.g. prevents sterilization of the child). See Singh D, Bradley SJ, Zucker KJ. A Follow-Up Study of Boys With Gender Identity Disorder. Front Psychiatry. 2021 Mar 29;12:632784. doi: 10.3389/fpsyt.2021.632784. PMID: 33854450; PMCID: PMC8039393. It is not currently known whether individuals with gender dysphoria persistence have differing etiologies or severity of precipitating factors compared to desisting individuals.

See Drummond, K. D., Bradley, S. J., Peterson-Badali, M. & Zucker, K. J. A follow-up study of girls with gender identity disorder. Dev Psychol **44**, 34-45, doi:10.1037/0012-1649.44.1.34 (2008); Steensma, T. D., McGuire, J. K., Kreukels, B. P., Beekman, A. J. & Cohen-Kettenis, P. T. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. J Am Acad Child Adolesc Psychiatry **52**, 582-590, doi:10.1016/j.jaac.2013.03.016 (2013).

48. VIRTUALLY ALL TRANSGENDER PATIENTS ARE BORN WITH HEALTHY NORMAL SEX ORGANS AND NO KNOWN BRAIN OR GENETIC ABNORMALITIES: Most people with gender dysphoria, do not have a disorder of sexual development. As documented in their medical record, such patients typically have normally formed sexual organs. The presence of normal, functional sex organs prior to the initiation of hormone administration or surgical "transition" operations is typical in transgender patients. I note that both hormonal treatments and surgery to remove healthy, normal organs (the genitals of GD patients) destroy the function of healthy organs (e.g., producing the life-long sterilization of GD patients). Such injurious "treatments" are very controversial and occur nowhere else in medicine that I am aware of with the exception of requests for the amputation of healthy limbs in patients suffering from the very controversial "body integrity identity disorder". See Elliott, T., Body Dysmorphic Disorder, Radical Surgery and the Limits of Consent**,** *Medical Law Review*, Volume 17, Issue 2, Summer 2009, Pages 149–182, https://doi.org/10.1093/medlaw/fwp001. In 2000 there was a media furor when it was disclosed that a Scottish surgeon had operated upon two adult male patients reportedly suffering from a rare form of a psychological condition known as body integrity identity disorder, in each case amputating a healthy leg. Since then, the question of whether such surgery is ethically or legally permissible has been a matter of debate. The subject raises issues

as to the extent to which it is proper to treat adults with psychiatric or psychological disorders with radical surgery, particularly where the appropriate diagnosis and treatment of the underlying disorder is uncertain or disputed. Similarly, gender transition interventions also involve treating patients "with psychiatric or psychological disorders with radical surgery, where the appropriate diagnosis and treatment of the underlying disorder is uncertain or disputed."

The primary use of psychotherapy as a means to treat body dysmorphic disorder contrasts with the approaches used by the gender transition industry. See Hadley, S. J., Greenberg, J., & Hollander, E. (2002). Diagnosis and treatment of body dysmorphic disorder in adolescents. *Current psychiatry reports*, *4*(2), 108–113. https://doi.org/10.1007/s11920-002-0043-4; Allen, A., & Hollander, E. (2000). Body dysmorphic disorder. *The Psychiatric clinics of North America*, *23*(3), 617–628. https://doi.org/10.1016/s0193-953x(05)70184-2.

49. THE ETIOLOGY (CAUSE) OF GENDER DYSPHORIA IS CURRENTLY UNKNOWN and the "TREATMENTS" are of UNCERTAIN EFFICACY. The current theories and treatments remain experimental and controversial. The etiology of gender dysphoria in individuals with sex-gender identity discordance remains unknown. Alternative hypotheses include some as yet unidentified biological cause, prenatal hormone exposure, genetic variation, postnatal environmental influences, family dynamics, other forms of mental illness, an abnormal detour from developmental identity processes, social contagion effects on suggestible-vulnerable subjects, or a combination of multiple factors. Based upon the available evidence, it is most likely that sex-gender identity discordance is multifactorial with both genetic and environmental influences, differing in both kind and degree in any affected individual. Importantly, these potential contributing factors are hypothesized to be contributory, but not determinative of the condition.

See Saleem, Fatima, and Syed W. Rizvi. "Transgender Associations and Possible Etiology: A Literature Review." Cureus 9, no. 12 (2017): e1984.

50. THE CONCEPT OF "NEUROLOGICAL SEX" IS EXPERIMENTAL, UNVERIFIED, HAS NO KNOWN ERROR RATE and is NOT ACCEPTED BY THE RELEVANT SCIENTIFIC COMMUNITY. The recently coined concept of "neurological sex" as a distinct entity or a basis for classifying individuals as male or female has no scientific justification. Limited emerging data has suggested structural and functional differences between brains from normal and transgender individuals. These data do not establish whether these differences are innate and fixed or acquired and malleable. The remarkable neuronal plasticity of the brain is well known, well documented, and has been studied extensively in gender-independent contexts related to health and disease, learning, and behavior. See Fatima Yousif Ismail, Ali Fatemi, and Michael V. Johnston, "Cerebral Plasticity: Windows of Opportunity in the Developing Brain," European Journal of Paediatric Neurology 21, no. 1 (2017).

51. GENDER IDENTITY IDEOLOGY IS A POLITICAL, NOT SCIENTIFIC THEORY. A key alternative investigative hypothesis in efforts to understand the rise of reports of gender discordance and social-political-medical attempts to create a transgender movement is that such ideas are not based upon sound scientific biological, genetic, or related principles and data but rather are based upon ideology and driven by political advocacy. Although worldviews among scientists and physicians differ widely (similar to society at large), science must remain firmly grounded in testable, valid, and reliable assessments of physical reality—not ideologically tainted perceptions and belief systems. The inherent link between human sexual biology and teleology (e.g. human reproduction) is self-evident and fixed. Breithaupt H. The science of sex.

EMBO Rep. 2012;13(5):394. Published 2012 May 1. doi:10.1038/embor.2012.45. Activists often support clearly contradictory theories and arguments at the same time (e.g. the claim that Gender Dysphoria (GD) and "trans identity" are" immutable", "genetic", or based on "brain structures" while simultaneously claiming GD is also "fluid" and thus capable of changing on a daily basis). That is perhaps because the gender transition industry gains support from controversial ideological foundations. (See, e.g., Pluckrose, and Lindsay, J., Cynical Theories: How Activist Scholarship Made Everything about Race, Gender, and Identity—and Why This Harms Everybody, Pitchstone Publishing, August 25, 2020).

52. GENDER IDENTITY IDEOLOGY HAS NO SCIENTIFIC BASIS, HAS NEVER BEEN ACCEPTED BY THE RELEVANT SCIENTIFIC COMMUNITY, and HAS NO KNOWN NOR PUBLISHED ERROR RATE. The political-ideological claims of proponents of transgenderism, which include opinions such as "gender identity is the primary factor determining a person's sex," "gender is the only true determinant of sex," and individuals have "sex assigned at birth" must be viewed in their proper ideological context. There is no scientific basis for redefining sex on the basis of a person's subjective, psychological sense of "gender".

53. IN CONTRAST TO "TRANSGENDER" IDEOLOGY, THE BIOLOGICAL BASIS OF SEX IS FIRMLY GROUNDED IN SCIENCE, ACCEPTED BY THE RELEVANT SCIENTIFIC COMMUNITY, AND HAS A VERY LOW ERROR RATE: The prevailing, constant, tested, proven, and accurate designation of sex as a biological trait grounded in the inherent purpose of male and female anatomy and as manifested in the appearance of external genitalia at birth remains the proper scientific and medical standard. Redefinition of the classification and meaning of sex based upon pathologic variation is not established medical fact. See, e.g.,

Mittwoch, U. (2013), Sex determination. EMBO reports, 14: 588-592. https://doi.org/10.1038/embor.2013.84

54. THE ETHICAL FOUNDATIONS of MEDICINE—FIRST DO NO HARM: The fundamental purpose of the practice of medicine is to treat disease and alleviate suffering. An essential tenet of medical practice is to avoid doing harm in the process. Efforts to rely upon clear, valid, reliable, and definitive evidence on how to best accomplish treatment goals is the essential ethical, professional, scientific, and clinical goals of physicians. The gender transition industry violates this essential principle by using experimental treatments on vulnerable populations without properly informing them of the actual risks and limitations of the treatments. See Jonson AR, Siegler M, Winslade, WJ: Clinical Ethics, New York: McGraw Hill, 1998.

55. THE ETHICAL FOUNDATIONS of MEDICINE REQUIRE US TO STRIVE TO HELP THOSE IN DISTRESS WITH COMPASSION, KINDNESS, and EMPATHY WITHOUT VIOLATING PATIENTS' and PARENTS' RIGHTS BY ENGAGING IN EXPERIMENTAL, UNPROVEN INTERVENTIONS LEADING TO PERMANENT DAMAGE TO MANY PATIENTS—INCLUDING STERILIZATION: Persons with gender dysphoria as defined in the DSM-V report experiencing significant psychological distress related to their condition with elevated risk of depression, suicide, and other morbidities. Thus, attempts to provide effective medical care to affected persons are clearly warranted. Efforts to effectively treat persons with gender dysphoria require respect for the inherent dignity of those affected, sensitivity to their suffering, and maintenance of objectivity in assessing etiologies and long-term outcomes. In my opinion, the use of unproven, experimental treatments on vulnerable patients and the publication of grossly methodologically defective research are violations of the ethical foundations of medicine.

56. THREE CURRENT APPROACHES FOR MANAGING GENDER DYSPHORIA: To date, three approaches have been proposed for treating children with gender dysphoria. See Zucker, K. J. On the "natural history" of gender identity disorder in children. J Am Acad Child Adolesc Psychiatry 47, 1361-1363, doi:10.1097/CHI.0b013e31818960cf (2008).) The first approach, often referred to as "conversion" or "reparative therapy," is directed toward actively supporting and encouraging children to identify with their biological sex. The second "neutral" or "watchful waiting" approach, motivated by understanding of the natural history of transgender identification in children, is to neither encourage nor discourage transgender identification, recognizing that the vast majority of affected children if left alone are likely to eventually realign their reports of gender identification with their sex. This approach may also include the use of scientifically validated treatments (e.g. CBT) for the patient's anxiety, depression, social skills deficits or other issues. See van Bentum, J. S., van Bronswijk, S. C., Sijbrandij, M., Lemmens, L., Peeters, F., Drukker, M., & Huibers, M. (2021). Cognitive therapy and interpersonal psychotherapy reduce suicidal ideation independent from their effect on depression. *Depression and anxiety*, 10.1002/da.23151. Advance online publication. https://doi.org/10.1002/da.23151; Gallagher, M. W., Phillips, C. A., D'Souza, J., Richardson, A., Long, L. J., Boswell, J. F., Farchione, T. J., & Barlow, D. H. (2020). Trajectories of change in well-being during cognitive behavioral therapies for anxiety disorders: Quantifying the impact and covariation with improvements in anxiety. *Psychotherapy (Chicago, Ill.)*, *57*(3), 379–390. https://doi.org/10.1037/pst0000283. The third, "affirming," approach is to actively encourage children to embrace transgender identity with social transitioning followed by hormonal therapy leading to potential surgical interventions and life-long sterilization. See Walch A, Davidge-Pitts C, Safer JD, Lopez X, TangprichaV, Iwamoto SJ. Proper Care of Transgender and Gender Diverse Persons in the Setting of Proposed

Discrimination: A Policy Perspective J Clin Endocrinol Metab. 2021;106(2):305-308. doi:10.1210/clinem/dgaa816**.**

57. THE "WATCHFUL WAITING" TREATMENT MODALITY INVOLVES NO MEDICAL INTERVENTION AND IS CURRENTLY THE BEST SCIENTIFICALLY SUPPORTED INTERVENTION FOR YOUNG CHILDREN REPORTING GENDER DYSPHORIA: Desistance (i.e. realignment of expressed gender identity to be concordant with sex) provides the greatest lifelong benefit, is the outcome in the vast majority of patients, and should be maintained as a desired goal. Any scientifically untested intervention that unnecessarily interferes with the likelihood of a normal, non-traumatic, developmental resolution of gender dysphoria is unwarranted and potentially harmful. The gender affirming approach, which includes use of a child's preferred pronouns, use of sex-segregated bathrooms, other intimate facilities and sleeping accommodations corresponding to a child's gender identity, has limited, "very weak," "sparse" scientific support for short-term alleviation of dysphoria and *no long-term outcomes data demonstrating superiority over the other approaches*. (See national reviews of England, Sweden, Finland, the Cochrane review, the Griffin review, the Carmichael review and others). Claims that the other approaches have been scientifically disproven are simply false. Decades of peer-reviewed, published scientific research, including the pioneering work of Dr. Kenneth Zucker, have supported the efficacy of the "watchful waiting" approach for the majority of patients experiencing gender dysphoria. See Zucker, K. J. On the "natural history" of gender identity disorder in children. J Am Acad Child Adolesc Psychiatry 47, 1361-1363, doi:10.1097/CHI.0b013e31818960cf (2008); Bradley, S. J. & Zucker, K. J. Gender Identity Disorder: A Review of the Past 10 YearsG. Journal of the American Academy of Child & Adolescent Psychiatry 36, 872-880, doi:10.1097/00004583-199707000-00008.). In sum, the treatment

protocols and recommendations of politically influenced, non-science associations (WPATH, Pediatrics Assn, APA) who engaged in "voting", consensus-seeking methodologies (not science) are not accepted by the relevant *scientific* community, are not based upon competent-credible, methodologically sound science, and have no known, nor published, error rate.

58. THE HARMFUL EFFECTS OF "AFFIRMATIVE" TREATMENTS—INCLUDING PUBERTAL SUPPRESSION—ARE ESTABLISHED and ACCEPTED BY THE RELEVANT SCIENTIFIC COMMUNITY: "To sum up how puberty suppression works, a thought experiment might be helpful. Imagine two pairs of biologically and psychologically normal identical twins—a pair of boys and a pair of girls—where one child from each pair undergoes puberty suppression and the other twin does not. Doctors begin administering GnRH analogue treatments for the girl at, say, age 8, and for the boy at age 9. Stopping the gonadal hormone pathway of puberty does not stop time, so the puberty- suppressed twins will continue to age and grow—and because adrenal hormones associated with puberty will not be affected, the twins receiving GnRH analogue will even undergo some of the changes associated with puberty, such as the growth of pubic hair. However, there will be major, obvious differences within each set of twins. *The hormone suppressed twins' reproductive organs will not mature*: the testicles and penis of the boy undergoing puberty suppression will not mature, and the girl undergoing puberty suppression will not menstruate. The boy undergoing puberty suppression will have less muscle mass and narrower shoulders than his twin, while the breasts of the girl undergoing puberty suppression will not develop. The boy and girl undergoing puberty suppression will not have the same adolescent growth spurts as their twins. *So all told, by the time the untreated twins reach maturity, look like adults, and are biologically capable of having children, the twins undergoing puberty suppression will be several inches shorter, will physically look more androgynous and*

childlike, and will not be biologically capable of having children. This is a thought experiment, but it illustrates some of the effects that puberty suppression would be expected to have on the development of a growing adolescent's body." See Hruz, PW, Mayer, LS, and McHugh, PR, "Growing Pains: Problems with Puberty Suppression in Treating Gender Dysphoria," The New Atlantis, Number 52, Spring 2017 pp. 3-36.

59. THE ENDOCRINE SOCIETY RECOGNIZES THAT THE QUALITY OF EVIDENCE FOR "AFFIRMATIVE" TREATMENTS IS CURRENTLY ***"LOW OR VERY LOW"*** (*"estimate of effect is very uncertain*"). There is no general acceptance of these treatments in the relevant scientific community. The error rate is unknown and could be very high. The Endocrine Society published 2009 clinical guidelines for the treatment of patients with persistent gender dysphoria. See Hembree, W. C. et al. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 94, 3132-3154, doi:10.1210/jc.2009-0345 (2009). The recommendations include temporary suppression of pubertal development of children with GnRH agonists (hormone blockers normally used for children experiencing precocious puberty) followed by hormonal treatments to induce the development of secondary sexual traits consistent with one's gender identity. In developing these guidelines, the authors assessed the quality of evidence supporting the recommendations made with use of the GRADE (Recommendations, Assessment, Development, and Evaluation) system for rating clinical guidelines. As directly stated in the Endocrine Society publication, ***"the strength of recommendations and the quality of evidence was low or very low***." According to the GRADE system, low recommendations indicate that "[f]urther research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate." Very low recommendations mean that **"**any estimate of effect is very uncertain." (See

Guyatt G H, Oxman A D, Vist G E, Kunz R, Falck-Ytter Y, Alonso-Coello P et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations BMJ 2008; 336 :924 doi:10.1136/bmj.39489.470347.AD). An updated set of guidelines was published in September of 2017. See Hembree, W. C. et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab, doi:10.1210/jc.2017-01658 (2017). The low quality of evidence presented in this document persists to the current day, as the controversy over these "treatments" is accelerating in recent years.

60. THE WPATH GUIDELINES (7th version) NOTE SERIOUS LIMITATIONS OF THE EXISTING SCIENTIFIC DATA: Clinical Practice Guidelines published by the World Professional Association for Transgender Health (WPATH) - (an advocacy organization whose positions are based on voting and not a scientific, evidence-based process) which is currently in its 7th iteration, similarly, though less explicitly, acknowledge the limitation of existing scientific data supporting their recommendations given and "the value of harm-reduction approaches". Coleman, E., Bockting, W., Botzer, M., Cohen-Kettenis, P., DeCuypere, G., Feldman, J., Fraser, L., Green, J., Knudson, G., Meyer, W. J., Monstrey, S., Adler, R. K., Brown, G. R., Devor, A. H., Ehrbar, R., Ettner, R., Eyler, E., Garofalo, R., Karasic, D. H., . . . Zucker, K. (2012). Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. International Journal of Transgenderism, 13(4), 165–232. https://doi.org/10.1080/15532739.2011.700873.

61. ADMINISTERING HORMONES TO A CHILD WHOSE GENDER DYSPHORIA IS HIGHLY LIKELY (80%+) TO RESOLVE IS RISKY, UNSCIENTIFIC and UNETHICAL. Iatrogenic damages, including life-long sterility, stunted growth, increased heart attack risk, etc.,

are often irreversible. Treatment of gender dysphoric children who experience persistence of symptoms with hormones (pubertal suppression and cross-hormone therapy) carries significant risk. It is generally accepted, even by advocates of transgender hormone therapy, that hormonal treatment impairs fertility and often result in sterility, which in many cases is irreversible. See Nahata, L., Tishelman, A. C., Caltabellotta, N. M. & Quinn, G. P. Low Fertility Preservation Utilization Among Transgender Youth. Journal of Adolescent Health 61, 40-44, doi:https://doi.org/10.1016/j.jadohealth.2016.12.012 (2017)). Emerging data also show that treated patients have lower bone density which may lead to increased fracture risk later in life. See Klink, D., Caris, M., Heijboer, A., van Trotsenburg, M. & Rotteveel, J. Bone Mass in Young Adulthood Following Gonadotropin-Releasing Hormone Analog Treatment and Cross-Sex Hormone Treatment in Adolescents With Gender Dysphoria. The Journal of Clinical Endocrinology & Metabolism 100, E270-E275, doi:10.1210/jc.2014-2439 (2015)). Other potential adverse effects include disfiguring acne, high blood pressure, weight gain, abnormal glucose tolerance, breast cancer, liver disease, thrombosis, and cardiovascular disease. See Seal, L. J. A review of the physical and metabolic effects of cross-sex hormonal therapy in the treatment of gender dysphoria. Annals of Clinical Biochemistry 53, 10-20, doi:10.1177/0004563215587763 (2016); Banks, K., Kyinn, M., Leemaqz, S. Y., Sarkodie, E., Goldstein, D., & Irwig, M. S. (2021). See also, Blood Pressure Effects of Gender-Affirming Hormone Therapy in Transgender and Gender-Diverse Adults. *Hypertension (Dallas, Tex.: 1979)*, HYPERTENSIONAHA12016839. Advance online publication. https://doi.org/10.1161/HYPERTENSIONAHA.120.16839; Getahun, D., Nash, R., Flanders, W. D., Baird, T. C., Becerra-Culqui, T. A., Cromwell, L., Hunkeler, E., Lash, T. L., Millman, A., Quinn, V. P., Robinson, B., Roblin, D., Silverberg, M. J., Safer, J., Slovis, J., Tangpricha, V., & Goodman, M. (2018). Cross-sex Hormones and Acute Cardiovascular

Events in Transgender Persons: A Cohort Study. *Annals of internal medicine*, *169*(4), 205–213. https://doi.org/10.7326/M17-2785; Spyridoula Maraka, Naykky Singh Ospina, Rene Rodriguez-Gutierrez, Caroline J Davidge-Pitts, Todd B Nippoldt, Larry J Prokop, M Hassan Murad, Sex Steroids and Cardiovascular Outcomes in Transgender Individuals: A Systematic Review and Meta-Analysis, *The Journal of Clinical Endocrinology & Metabolism*, Volume 102, Issue 11, 1 November 2017, Pages 3914–3923, https://doi.org/10.1210/jc.2017-01643.

62. LONG TERM EFFECTS ARE UNKNOWN. Such treatments are not generally accepted by the relevant scientific community and have no known nor published error rate. Since strategies for the treatment of transgender children as summarized by the Endocrine Society guidelines are relatively new, long-term outcomes are unknown. Evidence presented as support for short-term reductions in psychological distress following social transition in a "gender affirming" environment remains inconclusive. When considered apart from advocacy-based agendas, multiple potential confounders are evident. The most notable deficiencies of existing research are the absence of proper control subjects and lack of randomization in study design. See Hruz, P. W. Deficiencies in Scientific Evidence for Medical Management of Gender Dysphoria. *Linacre Q* 87, 34-42, doi:10.1177/0024363919873762 (2020). Although appropriate caution is warranted in extrapolating the outcomes observed from prior studies with current treatments, adults who have undergone social transition with or without surgical modification of external genitalia continue to have *rates of depression, anxiety, substance abuse and suicide far above the background population*. See Adams, N., Hitomi, M. & Moody, C. Varied Reports of Adult Transgender Suicidality: Synthesizing and Describing the Peer-Reviewed and Gray Literature. Transgend Health 2, 60-75, doi:10.1089/trgh.2016.0036 (2017); see also Dhejne, C. et al. Long-

term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. PLoS One 6, e16885, doi:10.1371/journal.pone.0016885 (2011)).

63. MEDICAL TREATMENTS CONTRARY TO THE SCIENCE COULD RESULT IN IRREVERSIBLE HARMS TO MANY PATIENTS WHO WOULD OTHERWISE HAVE RECOVERED NATURALLY FROM GENDER DYSPHORIA: Of particular concern is the likelihood that naively requested gender transition "treatments" and social changes could interfere with known very high rates of natural-untreated resolution of sex-gender discordance. Any activity that encourages or perpetuates transgender persistence for those who would otherwise desist could cause significant harm, particularly in light of the current treatment paradigm for persisting individuals. As noted, sterility can often be expected with hormonal or surgical disruption of normal gonadal function. See Cheng PJ, Pastuszak AW, Myers JB, Goodwin IA, Hotaling JM. Fertility concerns of the transgender patient. Transl Androl Urol. 2019 Jun;8(3):209-218. doi: 10.21037/tau.2019.05.09. PMID: 31380227; PMCID: PMC6626312.

64. YOUNG CHILDREN and PARENTS ARE OFTEN NOT PROPERLY INFORMED or ARE NOT COMPETENT TO GIVE INFORMED CONSENT TO PROCEED WITH EXPERIMENTAL, HAZARDOUS TREATMENTS THAT COULD POTENTIALLY RESULT IN PERMANENT STERILITY: This is a particularly concerning issue given that children are likely to be incapable of giving truly informed consent. See Geier, C. F. Adolescent cognitive control and reward processing: Implications for risk taking and substance use. Hormones and Behavior 64, 333-342, doi:https://doi.org/10.1016/j.yhbeh.2013.02.008 (2013). This concern remains valid when applied to hormonal or surgical treatments that will result in lifelong sterility. In addition, parents are often manipulated and coerced by misinformed political activists or providers who threaten them with dire warnings that the only two options are "treatment or suicide".

These "threats" ignore data that challenge this biased assumption. See D'Angelo, R., Syrulnik, E., Ayad, S. *et al.* One Size Does Not Fit All: In Support of Psychotherapy for Gender Dysphoria. *Arch Sex Behav* 50**,** 7–16 (2021). https://doi.org/10.1007/s10508-020-01844-2

65. SOCIAL CONTAGION HAS BEEN IMPROPERLY IGNORED BY PROVIDERS: Social and psychological support with dignity for adolescents with gender dysphoria does not necessitate acceptance of a unproven, experimental understanding of human sexuality. Rather, policy requirements including social contagion promoting educational processes that can increase the prevalence and persistence of transgender identification have significant potential for inducing long-term harm to affected children.

66. COMPETENT, METHODOLOGICALLY SOUND, LONG-TERM TREATMENT OUTCOME RESEARCH ON GENDER DYSPHORIA INTERVENTIONS HAS NEVER BEEN DONE: There remains a significant and unmet need to improve our understand of the biological, psychological, and environmental basis for the manifestation of patient reports of discordance of gender identity and biological sex in affected individuals. (Olson-Kennedy, J. et al. Research priorities for gender nonconforming/transgender youth: gender identity development and biopsychosocial outcomes. Current Opinion in Endocrinology, Diabetes and Obesity 23, 172-179, (2016)). In particular, there is a concerning lack of randomized controlled trials comparing outcomes of youth with gender dysphoria who are provided public encouragement for "affirming" social gender transition and how such transitioning affects the usual and natural progression to resolution of gender dysphoria in most affected children. Such studies can be ethically designed and executed with provisions for other dignity affirming measures to both treatment groups. See Sugarman J. Ethics in the design and conduct of clinical trials. Epidemiol Rev.

2002;24(1):54-8. doi: 10.1093/epirev/24.1.54. PMID: 12119856; And https://clinicalcenter.nih.gov/recruit/ethics.html

67. DUE TO THE LACK OF QUALITY, CREDIBLE SUPPORTIVE RESEARCH GENDER AFFIRMING INTERVENTIONS REMAIN EXPERIMENTAL and HIGHLY CONTROVERSIAL. Gender identity is consolidated during puberty and adolescence as young people's bodies become more sexually differentiated and mature. How this normally happens is not well understood, so it is imperative to be cautious about interfering with this complex natural process. Far from being cautious and prudent in using puberty blockers to treat gender dysphoria, too many providers engaged in gender affirming medical interventions are conducting an unethical and risky experiment that does not come close to the ethical standards demanded in other areas of medicine. No one really knows all the potential consequences of puberty blocking as a treatment for gender dysphoria, but there are some known effects of pubertal suppression on children who are physiologically normal, and these carry long-term health risks. Children placed on puberty blockers have slower rates of growth in height, and an elevated risk of low bone-mineral density. Another possible effect of blocking normally timed puberty is alteration of normal adolescent brain maturation. (See Arain, M., Haque, M., Johal, L., Mathur, P., Nel, W., Rais, A., Sandhu, R., & Sharma, S. (2013). Maturation of the adolescent brain. *Neuropsychiatric disease and treatment*, *9*, 449–461. https://doi.org/10.2147/NDT.S39776).

When followed by cross-sex hormones, known and potential effects include disfiguring acne, high blood pressure, weight gain, abnormal glucose tolerance, breast cancer, liver disease, thrombosis, and cardiovascular disease. Tragically, those children who persist in their transgender identity and take puberty blockers and cross-sex hormones are *expected to become sterile*. Given what we already know about puberty blocking and how much remains unknown, it

is not surprising that the use of GnRH analogues for puberty suppression in children with gender dysphoria is not FDA-approved. The off-label prescription of these drugs is legal *but unethical* outside the setting of a carefully controlled and supervised clinical trial. See Hruz, Mayer, and McHugh, "Growing Pains." Trans activist professionals act as if there is a firm scientific consensus that it is safe and effective to treat gender dysphoria by using GnRH analogues to suppress normal puberty indefinitely. But this is far from the reality, as I, together with Mayer and McHugh, have pointed out: "Whether puberty suppression is safe and effective when used for gender dysphoria remains unclear and unsupported by rigorous scientific evidence." Thus, it is not generally accepted by the relevant scientific community. Instead of regarding puberty blocking as a "prudent and scientifically proven treatment option," courts of law, parents, and the medical community *should view it as a "drastic and experimental measure*." (See Hruz, Mayer, and McHugh, 2017.) The use of any experimental medical treatment on children calls for "especially intense scrutiny, since children cannot provide proper legal consent to experimental medical treatments—especially treatments that may harm natural gender processes and produce sterility.

The rapid acceptance of puberty suppression as a treatment for gender dysphoria with little scientific support or scrutiny should raise concerns about the welfare of the children who receive such treatments. In particular, we should question the claim that it is both physiologically and psychologically "reversible." This includes the alteration of a temporally dependent developmental process. After an extended period of pubertal suppression one cannot "turn back the clock" and reverse changes in the normal coordinated pattern of adolescent psychological development and puberty. (See Hruz, Mayer, and McHugh, "Growing Pains, The New Atlantis: A Journal of Technology and Society, Spring 2017, pg 3-36; see also Vijayakumar N, Op de Macks

Z, Shirtcliff EA, Pfeifer JH. Puberty and the human brain: Insights into adolescent development. Neurosci Biobehav Rev. 2018 Sep;92:417-436. doi: 10.1016/j.neubiorev.2018.06.004. Epub 2018 Jul 1. PMID: 29972766; PMCID: PMC6234123; see also Choudhury S, Culturing the adolescent brain: what can neuroscience learn from anthropology?, *Social Cognitive and Affective Neuroscience*, Volume 5, Issue 2-3, June/September 2010, Pages 159–167, https://doi.org/10.1093/scan/nsp030

68. ACTIVIST ATTEMPTS TO CONTROL PUBLIC DISCUSSION ARE HARMFUL TO SCIENCE: The controversies regarding the risks and potential dangers of the transgender industry cannot be resolved by "cancel culture." As Steven Levine, MD of Case Western has noted, "Among psychiatrists and psychotherapists who practice in the area, *there are currently widely varying views* concerning both the causes of, and appropriate therapeutic responses to, gender dysphoria in children. Dr. Levine went on to state, "Existing studies do not provide a basis for a scientific conclusion as to which therapeutic response results in the best long-term outcomes for affected individuals." Although political advocates have asserted that the "affirmation therapy" model is accepted and agreed with by the overwhelming majority of mental health professionals, many respected academics and providers in the field strongly disagree. For example, J. Cantor, Ph.D. (McGill) published the following opinion in 2019, "almost all clinics and professional associations in the world" do not use "gender affirmation" for prepubescent children and instead "delay any transitions until after the onset of puberty." See J. Cantor (2019), Transgender and Gender Diverse Children and Adolescents: Fact-Checking of AAP Policy, J. of Sex& Marital Therapy, 1, DOI: 10.1080.0092623X.2019.1698481.

69. In the midst of this ongoing international, raging controversy, transgender and allied political activists have attempted to silence open public debate on the risks and benefits of

transgender medical procedures and political ideologies. For example, Ryan Anderson, Ph.D., a policy analyst, wrote a book analyzing the scientific and policy issues involved in assessing the risks and benefits of the current practices of the transgender treatment industry. See Anderson, R., *When Harry Became Sally: Responding to the Transgender Moment*, Encounter Books. Despite widespread scientific interest and positive reviews, the book was banned from sale by the Amazon Corporation. Too many lives are at stake for such blatant suppression of open scientific discussion. Several positive reviews of Dr Ryan's book were posted by notable members of the relevant scientific-ethical community including: Paul McHugh, MD, University Distinguished Professor of Psychiatry, Johns Hopkins University School of Medicine (Dr McHugh was trained at Harvard College and Harvard Medical School. He served as the Chairman of Psychiatry at Johns Hopkins Medical School for decades) and Melissa Moschella, PhD, who served at Columbia University as Director of the Center for Biomedical Ethics in the Department of Medicine and currently at The Catholic University of America. (Dr. Moschella was trained at Harvard College and her PhD is from Princeton University) and Maureen Condic, Associate Professor of Neurobiology and Adjunct Professor of Pediatrics, University of Utah Medical School. (Dr. Condic's training includes a B.A. from the University of Chicago, and a Ph.D. from the University of California, Berkeley) and John Finnis, Ph.D., Professor of Law at Oxford University for 40 years, now Emeritus. (LL.B. from Adelaide University (Australia) and Ph.D. in 1965 from Oxford University as a Rhodes Scholar at University College Oxford.)

International experts from a variety of relevant fields consider the issue of proper and harmful transgender treatments to be a serious controversy that must not be silenced. Other scholars in this contentious field have been threatened and/or silenced by the political and ideo-

logical allies of the gender transition industry. Consider, for example, the case of Alan Josephson, MD, a distinguished psychiatrist. See Kearns, M., Gender Dissenter Gets Fired, National Review, Jan 12, 2019. "Allan M. Josephson is a distinguished psychiatrist who, since 2003, has transformed the division of child and adolescent psychiatry and psychology at the University of Louisville from a struggling department to a nationally acclaimed program. In the fall of 2017 he appeared on a panel at the Heritage Foundation and shared his professional opinion on the medicalization of gender-confused youth. The university responded by demoting him and then effectively firing him." See https://www.nationalreview.com/2019/07/allen-josephson-gender-dissenter-gets-fired/. Theories in the midst of an international firestorm of controversy are clearly not "generally accepted" by the relevant scientific community. The ongoing attempts to ban books and aggressively silence academic debate or "cancel" professionals with alternative views are clear demonstrations of the ongoing and intense controversies surrounding the gender transition industry.

70. Consider also the example of Dr. Lisa Littman at Brown University Medical School. Dr. Littman conducted extensive surveys to assess the experiences of parents involved in an online community for parents of transgender children or "gender skeptical" parents and children. There were 256 completed surveys. Their children were mostly adolescents or young adults. The parents reported that about 80 percent of their (mostly adolescent) children announced their transgender identity "out of the blue" without the long-term history generally associated with gender dysphoria. The parents also reported that transgender identity was linked with mental health issues (an often repeated, reliable finding in multiple studies from multiple nations). The parents also reported that after their children came out as transgender, their children's mental health worsened, as did relationships with family members. The parents also reported a *decline*

in the children's social adjustment after the announcement (e.g., more isolation, more distrust of non-transgender information sources, etc.).

The publication of the Littman paper was greeted by the outrage of trans activists who denounced the paper and Dr. Littman, calling it "hate speech and transphobic." Brown University had initially produced a press release for the paper stating the Littman research provided bold new insights into transgender issues. Once the political attacks began, the University removed it from their announcements. Fortunately, in this case, there was also a counter-outcry from scientists decrying Brown University and the political activists for threatening academic freedom and censoring scientific research that might assist in the treatment of gender dysphoria.

There was also reportedly an academic petition signed by members of the relevant scientific community. For example, Lee Jussim, PhD., Chair of the Psychology Department at Rutgers University wrote, "If the Littman study is wrong, let someone produce evidence that it is wrong. Until that time, if the research p*sses some people off, who cares? Galileo and Darwin p*ssed people off too. Brown University should be ashamed of itself for caving to sociopolitical pressure. Science denial, anyone?" Similarly, Richard B. Krueger, MD (a Harvard Medical School graduate) of Columbia University College of Physicians and Surgeons, board certified psychiatrist specializing in the treatment of sexual disorders wrote, "Brown University's actions in its failure to support Dr. Littman's peer reviewed research are abhorrent." Similarly, Nicholas Wolfinger, PhD (UC Berkeley, UCLA), currently Professor of Family and Consumer Studies at the University of Utah wrote: "The well-being of trans youth and other sexual minorities is best served by more research, not less."

The onslaught of attacks resulted in the journal asking Dr. Littman to publish a "corrected" version of the paper. After careful review, the paper was again published with additional

information but no methodological nor data corrections—as no such errors were found. See https://www.psychologytoday.com/us/blog/rabble-rouser/201903/rapid-onset-gender-dysphoria. See also Littman, L., Correction: Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria, PLOS ONE March 19, 2019, https://doi.org/10.1371/journal.pone.0214157. Dr. Littman's paper was a key initial step in the alternative investigative hypothesis that the very recent and enormous increase in teenage girls seeking "gender transitioning" is due to a social contagion process at school, in peer groups, and on the internet. This theory has yet to be tested in detail.

71. UNDERLYING BIOLOGY IS NOT CHANGED BY ALTERING BODILY FEATURES TO "PASS" AS THE OPPOSITE SEX, NOR DO SUCH ALTERATIONS CHANGE DISEASE VULNERABILITIES ASSOCIATED WITH GENETICALLY-DEFINED SEX: Despite the increasing ability of hormones and various surgical procedures to reconfigure some male bodies to visually pass as female, or vice versa, the biology of the person remains as defined by genetic makeup, normatively by his (XY) or her (XX) chromosomes, including cellular, anatomic, and physiologic characteristics and the particular disease vulnerabilities associated with that chromosomally-defined sex. (See "Institute of Medicine (US) Committee on Understanding the Biology of Sex and Gender Differences. Exploring the Biological Contributions to Human Health: Does Sex Matter?" Wizemann TM, Pardue ML, editors. Washington (DC): National Academies Press (US); 2001. PMID: 25057540.) For instance, the XX (genetically female) individual who takes testosterone to stimulate certain male secondary sex characteristics will nevertheless remain unable to produce sperm and father children. Contrary to assertions and hopes that medicine and society can fulfill the aspiration of the individual with sex-discordant

gender identity to become "a complete man" or "a complete woman," this is not biologically attainable. It is possible for some adolescents and adults to pass unnoticed as the opposite gender that they aspire to be—but with limitations, costs, and risks, as I detail later. See S. Levine (2018), Informed Consent for Transgendered Patients, J. of Sex & Marital Therapy, at 6, DOI: 10.1080/0092623X.2018.1518885 ("Informed Consent"); S. Levine (2016), Reflections on the Legal Battles Over Prisoners with Gender Dysphoria, J. Am. Acad Psychiatry Law 44, 236 at 238 ("Reflections").

72. ONE OF THE MOST CONTROVERSIAL AND CONTENTIOUS ISSUES IN TRANSGENDER SCIENCE IS THE RECENT EPIDEMIC OF ADOLESCENT FEMALE TO MALE GENDER DISCORDANT PATIENTS: How prevalent is the Sudden Onset Gender Dysphoria Epidemic in Teen Girls first described by the research of Dr. Littman at Brown University? In the UK, where centralized medical care provides data to track health care phenomenon, the number of adolescent girls seeking sex transitioning exploded *over 4,000% in the last decade.* Similarly, in the US, where we lack the same kinds of centralized health care data, it has been reported that in 2018 2% (2 in 100) of high school students identified on surveys as "transgender"—this is 200 times greater response— a 20,000% increase—over reports during past decades which showed a rate of only .01 percent (one in 10,000 people). See Johns MM, Lowry R, Andrzejewski J, et al. Transgender Identity and Experiences of Violence Victimization, Substance Use, Suicide Risk, and Sexual Risk Behaviors Among High School Students—19 States and Large Urban School Districts, 2017. MMWR Morb Mortal Wkly Rep 2019; 68:67–71.

Along with this increase in transgender patients and identifiers, has come *a radical and recent transformation of the patient population* from early onset males to rapid onset adolescent girls. Thus currently the majority of new patients with sex-gender discordance are not males with a long, stable history of gender dysphoria since early childhood—as they were for decades—but instead adolescent females with no documented long-term history of gender dysphoria—thus they experienced "rapid onset" transgender identification. Whole groups of female friends in colleges, high schools, and even middle schools across the country are reportedly coming out together in peer group clusters as "transgender." These are girls who — by detailed parental reports and self-reports—had never experienced any discomfort in their biological sex until they heard a coming-out story from a speaker at a school assembly or discovered the internet (YouTube) community of trans "influencer video stars."

This extraordinary change in new patient demographics appears more consistent with a theory of social contagion than of "immutable identification," "brain structures," "genetics," or other biological hypotheses. Many unsuspecting parents, whose children have never shown any signs for gender discordant feelings or ideas, are awakening to find their daughters in thrall to hip trans YouTube stars and "gender-affirming" educators and activist therapists who push life-changing interventions on these young girls—including double mastectomies and hormonal puberty blockers that can potentially cause permanent infertility. See Littman L. Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria. PLoS One. 2018 Aug 16;13(8):e0202330. doi: 10.1371/journal.pone.0202330. Erratum in: PLoS One. 2019 Mar 19;14(3):e0214157. PMID: 30114286; PMCID: PMC6095578.

73. GENERATING, CONSIDERING, AND TESTING ALTERNATIVE THEORIES PREVENTS CONFIRMATION BIAS. Several theories should be considered, as the science is currently unclear:

We should consider the genetics theory of transgender identity. But his theory cannot explain the rapid expansion of new GD cases (a 4,000% to 20,000% increase), as our genome is simply not changing that fast.

We should consider the "brain structures" theory of transgender identity. Yet there is only weak medical evidence to support this theory, and it cannot explain the rapid expansion of new gender dysphoria cases because brain structures are not changing that fast.

We should consider the theory that increased social acceptance of the transgender lifestyle is leading many people who were transgender all along to come out. Yet this theory fails to explain why *males and older women are not also coming out in the same huge numbers* and not coming out in "social peer group clusters," as adolescent females are reportedly doing.

We should consider the "immutable gender identity" theory. Yet this theory fails to explain the rapid expansion of patients. In addition, the "immutable" theory fails to explain the rapid expansion of "Rapid Onset Gender Dysphoria" reports—newly "trans" adolescent girl patients who reportedly showed no indication of gender dysphoria previously.

Having considered alternative theories—to avoid confirmation bias—it appears that another alternative theory might well be the most applicable, rational theory to explain the extreme, recent increases in the GD patient population: the Social Contagion hypothesis. Social contagion effects are also reportedly responsible for the massive, rapid increase in "recovered repressed memory" cases and also the extraordinary expansion of "multiple personality disorder"

cases in the 1990s. I also note the alternative investigative hypothesis that *social contagion effects would appear to be psychological/psychiatric problems and NOT physical medical problems requiring hormonal or surgical "treatments."*

74. ADOLESCENT FEMALE PSYCHOLOGY RESEARCH SHOWS WELL-DOCUMENTED PEER INFLUENCES on ANOREXIA, BULIMIA, DRUG ABUSE, and now GENDER DISCORDANT ("TRANSGENDER") SYMPTOMS. The Social Contagion theory for the large increase in reported Rapid Onset Gender Dysphoria in adolescent girls appears to be the most rational explanation for the reportedly dramatic (rapid, media related, hundreds of times increase, YouTube influenced, Peer Group influenced) explosion of gender discordant patients among adolescent female friend groups.

Adolescent female social contagion effects in psychiatric illness are well-known and well documented. Consider, for example, Bulimia and Anorexia — both of which spread rapidly in adolescent female friend groups. Se Allison S, Warin M, Bastiampillai T. Anorexia nervosa and social contagion: clinical implications. Aust N Z J Psychiatry. 2014 Feb;48(2):116-20. doi: 10.1177/0004867413502092. Epub 2013 Aug 22. PMID: 23969627.

It has been known for decades that adolescent females are highly prone to social contagion effects spreading psychiatric symptoms—e.g., Anorexia, Bulimia, Drug Abuse, etc.) are well known to be subject to "cluster" and "friendship" contagions as teens girls (and especially troubled teen girls) co-ruminate and share feelings at very high rates and with emotional depth. See, e.g., Crandall CS. Social contagion of binge eating. J Pers Soc Psychol. 1988 Oct;55(4):588-98. doi: 10.1037//0022-3514.55.4.588. PMID: 3193348.

For example, Prof. Amanda Rose at the University of Missouri has conducted research to understand why adolescent girls show such susceptibility to social contagion with psychiatric symptoms—"Teenage girls share symptoms via social contagions because their friendship processes involve "co-rumination," that is, taking on the emotional pain and concerns of their friends." See R. Schwatz-Mette and A. Rose, Co-Rumination Mediates Contagion of Internalizing Symptoms Within Youths' Friendships, Developmental Psychology 48(5):1355-65, February 2012, DOI: 10.1037/a0027484 Developmental Psychology, Vol. 48, No. 5, 1355–1365 0012-1649/12/$12.00 DOI: 10.1037/a0027484. This could be one explanation for why we are hearing increasing reports of" clusters" and "friend groups" of teen girls who are adopting a "transgender identity" and "transitioning" as friends together.

75. IDEOLOGICAL-POLITICAL PRESSURE SEEKS TO INSTITUTIONALIZE THE SYSTEMATIC NEGLIGENCE and METHODOLOGICAL ERROR OF CONFIRMATION BIAS: Because of the efforts of ill-informed legal and medical professionals and the intense activity of political trans activists— health providers (in many fields) are now NOT permitted to openly asks questions, properly investigate alternative diagnoses, or explore alternative hypotheses for the symptoms of gender dysphoria patients. They are compelled (sometimes under fear of employment termination or legal attacks) to adopt a patient's self-diagnosis and only support "transgender affirming" medical interventions. These providers are thus being pressured and/or compelled to commit the scientific and medical malpractice of Confirmation Bias. (See detailed discussion above on confirmation bias.) Unexamined "affirming" medical interventions—based on uncorroborated patient self-reports, assessed by mental health professionals with no methodology for discerning true from false patient reports, with no ability to decipher accurate from contaminated "memories," with no alternative treatments offered, and no alternative explanations

(e.g., social contagion) explored—are medical, psychological, surgical, and endocrinological negligence and a violation of the most basic, essential scientific and medical practices and methods requiring the generation and testing of alternative hypotheses. In sum, the industry actually requires "confirmation bias"—one of the most serious of all methodological diagnostic failures. See e.g. Mendel, R. et. al., Confirmation bias: why psychiatrists stick to wrong preliminary diagnoses, Psychological Medicine, Oxford University Press, 20 May 2011 ("Diagnostic errors can have tremendous consequences because they can result in a fatal chain of wrong decisions. Experts assume that physicians' desire to confirm a preliminary diagnosis while failing to seek contradictory evidence is an important reason for wrong diagnoses. This tendency is called 'confirmation bias."); see also, Doherty, T.S. and Carroll, A.E., Believing in Overcoming Cognitive Biases, American Medical Association Journal of Ethics, 2020;22(9):E773-778 ("Like all humans, health professionals are subject to cognitive biases that can render diagnoses and treatment decisions vulnerable to error. Learning effective debiasing strategies and cultivating awareness of confirmation, anchoring, and outcomes biases and the affect heuristic, among others, and their effects on clinical decision making should be prioritized in all stages of medical education…. Confirmation bias is the selective gathering and interpretation of evidence consistent with current beliefs and the neglect of evidence that contradicts them."); see also, Hershberger PJ, Part HM, Markert RJ, Cohen SM, Finger WW. Teaching awareness of cognitive bias in medical decision making. *Acad Med*. 1995;70(8):661.

76. GIVEN THE LACK OF RESEARCH, IT IS RECKLESS TO PERMIT CHILDREN TO SELF-DIAGNOSE WHEN THE "TREATMENTS" WILL PRODUCE LIFE-LONG STERILIZATION and/or OTHER PERMANANT INJURIES TO NORMAL, HEALTHY ORGANS: In some jurisdictions in America now child or adolescent patients can—without parental

permission or even parental notification—receive hormones to begin the experimental treatment of "transitioning" with no competent diagnostic investigation or professional assessment of gender dysphoria and no competent medical investigation, testing, or consideration of alternative hypotheses. Worst of all, providers can be coerced by law, collegial pressures, or "cancel culture" ideology to comply with the troubled child's/teen's/patient's amateur self-diagnosis or be faced with potentially career ending allegations of "conversion therapy." Politically tainted, pseudo-science, experimental, unproven medical practices have caused grave harm to millions in the past. (See the discussion of lobotomies, repressed memory therapy, multiple personality therapy, rebirthing therapy, etc. above.) Unethical, politically driven, experimental medical errors should not be repeated today.

77. EXPERIMENTATION on SEX-GENDER DISCORDANT PATIENTS IS ESPECIALLY LIKELY TO CAUSE HARM TO MINORITY PATIENTS FROM HISTORICALLY MARGINALIZED COMMUNITIES. The development of effective strategies to impact long-term physical and psychological health in patients who experience sex-discordant gender identity should be undertaken with recognition of the disproportionate burden of this condition in a number of vulnerable minority populations of children. These include:

- children with a prior history of psychiatric illness (See, e.g., Kaltiala-Heino, R., Sumia, M., Työläjärvi, M., & Lindberg, N. (2015). Two years of gender identity service for minors: overrepresentation of natal girls with severe problems in adolescent development. *Child and adolescent psychiatry and mental health*, *9*, 9. https://doi.org/10.1186/s13034-015-0042-y

- children of color (See, e.g., G. Rider et al. (2018), Health and Care Utilization of Transgender/Gender Non-Conforming Youth: A Population Based Study, Pediatrics at 4, DOI: 10.1542/peds.2017-1683.
- children with mental developmental disabilities (See, e.g., Bedard, C., Zhang, H.L. & Zucker, K.J. Gender Identity and Sexual Orientation in People with Developmental Disabilities. *Sex Disabil* 28**,** 165–175 (2010). https://doi.org/10.1007/s11195-010-9155-7
- children on the autistic spectrum (See, e.g., de Vries, A. L., Noens, I. L., Cohen-Kettenis, P. T., van Berckelaer-Onnes, I. A. & Doreleijers, T. A. Autism spectrum disorders in gender dysphoric children and adolescents. *J Autism Dev Disord* 40, 930-936, doi:10.1007/s10803-010-0935-9 (2010).
- children residing in foster care homes and adopted children (See, e.g., See e.g., D. Shumer et al. (2017), Overrepresentation of Adopted Adolescents at a Hospital-Based Gender Dysphoria Clinic, Transgender Health Vol. 2(1).

78. "GENDER AFFIRMATIVE" TREATMENTS DAMAGE or DESTROY HEALTHY BODILY ORGANS, LEADING TO LOSS OF ESSENTIAL BODILY FUNCTIONS (e.g. Medically Induced Sterilization): Despite the fact that gender dysphoria represents a psychological condition (as catalogued in the DSM since the third edition of this publication), some conceptualize the condition as a medical illness similar to cancer. When considered from this viewpoint, the goal of "treatment" is to alter the appearance of the body to conform to a patient's perceived sexual identity, including the physical removal of unwanted "diseased" sexual organs. Since undesired body parts are fully formed and functional prior to hormonal or surgical intervention, the

result of these "therapies" is injury to innate sexual ability. In particular, loss or alteration of primary sexual organs leads directly to impairment of reproductive potential. Recognition of this obvious consequence is the basis for the development of new arenas of medical practice where there is an attempt to restore what has been intentionally destroyed. See, e.g., Ainsworth AJ, Allyse M, Khan Z. Fertility Preservation for Transgender Individuals: A Review. Mayo Clin Proc. 2020 Apr; 95(4):784-792. doi: 10.1016/j.mayocp.2019.10.040. Epub 2020 Feb 27. PMID: 32115195. As correctly noted by Dr. Levine, gender dysphoria is unique in that it is "the only psychiatric condition to be treated by surgery, even though no endocrine or surgical intervention package corrects any identified biological abnormality." See, e.g., S. Levine (2016), Reflections on the Legal Battles Over Prisoners with Gender Dysphoria, J. American Academy of Psychiatry and Law, 44, 236 at 238 ("Reflections"), at 240.)

79. A DEVELOPMENTAL MODEL PROVIDES ALTERNATIVE HYPOTHESES TO THE UNEXAMINED "AFFIRMATON" MODEL: The diagnosis of "gender dysphoria" encompasses a diverse array of conditions. While the etiologic contributors to sex discordant gender identity remain to be fully identified and characterized, differences both in kind and degree within individuals and across varied populations creates challenges in establishing specific approaches to alleviate associated suffering. For example, data from adults cannot be assumed to apply equally to children. Nor can data from children who present with sex discordant gender pre-pubertally be presumed to apply to the growing number of post-pubertal adolescent females presenting with this condition.

80. NO COMPETENT, SCIENTIFICALLY VALID and RELIABLE COST-BENEFIT ANALYSIS HAS BEEN DONE ON "GENDER AFFIRMATIVE" TREATMENTS. When the FDA tests a drug, the safety analysis looks at all related risks. Specifically, the drug must not

only be effective, but it must not cause side effects that are more damaging than the proposed treatment. This is one of the gender transition industry's key weaknesses. Not only have the "treatments" *not* been proven reliably effective compared to *no* treatment, they are designed with existing knowledge of well-documented, long-term health problems and damages (e.g., testosterone use by transgender men increases the risk of fatal heart disease, estrogen use by transgender women increases risk of blood clots and strokes, gender transition industry treatments—if completed—can cause life-long sterility, etc.).

81. LACK OF INTEGRATION OF CARE BY PROVIDERS IN THE GENDER TRANSITION INDUSTRY INCREASES DANGERS TO PATIENTS: It is too often the case in the gender transition industry that "nobody is in charge" of a patient's care. The mental health professionals know little about the risks of surgery and the surgeons know little about the defects in mental health methodologies and the endocrinologists are only following the hormonal treatments and many are not aware of the serious methodological research defects in this field. Such disjointed care can increase dangers to patients. On cases showing such a lack of integration and uncertain chain of command, reliable measurements of the divergent, multi-disciplinary risks to patients of these treatments (e.g. hormones, incomplete therapy, or surgical side effects) are precluded and too often ignored. The plaintiffs' expert witness reports in this case appear to ignore this issue.

82. SUMMARY OPINIONS:

- There are no long-term, peer-reviewed published, reliable and valid, research studies documenting the number or percentage of patients receiving gender affirming medical interventions who are helped by such procedures.

- There are no long-term, peer-reviewed published, reliable and valid, research studies documenting the number or percentage of patients receiving gender affirming medical interventions who are injured or harmed by such procedures.
- There are no long-term, peer-reviewed published, reliable and valid, research studies documenting the reliability and validity of assessing gender identity by relying solely upon the expressed desires of a patient.
- There are no long-term, peer-reviewed published, reliable and valid, research studies documenting any valid and reliable biological, medical, surgical, radiological, psychological, or other objective assessment of gender identity or gender dysphoria.
- A currently unknown percentage and number of patients reporting gender dysphoria suffer from mental illness(es) that complicate and may distort their judgments and perceptions of gender identity.
- A currently unknown percentage and number of patients reporting gender dysphoria are being manipulated by a—peer group, social media, YouTube role modeling, and/or parental—social contagion and social pressure processes.
- Patients suffering from gender dysphoria or related issues have a right to be protected from experimental, potentially harmful treatments lacking reliable and valid, peer reviewed, published, long-term scientific evidence of safety and effectiveness.
- It would be a serious violation of licensing rules, ethical rules, and professional standards of care for a health care professional to provide gender transition or related procedures to any patient without first properly obtaining informed consent

including informing the patient and/or guardian(s) of the lack of valid and reliable on the long-term risks and benefits of "affirmation" treatments.

- A large percentage of children (over 80% in some studies) who questioned their gender identity will, if left alone, develop an acceptance of their natal (biological) sex.
- Medical treatments may differ significantly by sex according to chromosomal assessment but not gender identity. Misinforming physicians of a patient's biological sex can have deleterious effects on treatment for medical conditions.
- Affirmation medical treatments—hormones and surgery—for gender dysphoria and "transitioning" have not been accepted by the relevant scientific communities (biology, genetics, neonatolgy, medicine, psychology, etc).
- Gender transition "affirmation" medical assessments and treatments—hormones and surgery—for gender dysphoria and "transitioning" have no known, peer reviewed and published error rates—the treatments and assessment methods lack demonstrated, reliable and valid error rates.
- Political activists, political activist physicians, and politically active medical organizations that operate by voting methodologies (e.g, WPATH, the American Medical Association, the American Academy of Pediatrics, the American Endocrine Society) are not the relevant scientific community, they are politically active professional organizations. These organizations operate via consensus-seeking methodology (voting) and political ideologies rather than evidence-based scientific methodologies.

- Experts in legal cases have an ethical obligation to honestly, fairly, and accurately discuss the international controversy regarding the safety, effectiveness, reliability, and credibility of the gender transition industry.
- With the limited and poor quality data currently available on the purported efficacy of blocking normally timed puberty, administering of cross-sex hormones and gender affirming surgeries in alleviating psychological morbidity for youth who experience sex-discordant gender identity and the associated serious medical risks associated with these interventions, it cannot be concluded that this approach is "medically necessary."

83. LIMITATIONS ON EXPERT REPORTS: My opinions and hypotheses in this matter are—as all expert reports—subject to the limitations of documentary and related evidence, the impossibility of absolute predictions, as well as the limitations of social, biological, and medical science. I have not met with, nor personally interviewed, anyone in this case. As always, I have no expert opinions regarding the veracity of witnesses in this case. I have not yet reviewed all of the evidence in this case and my opinions are subject to change at any time as new information becomes available to me. Only the trier of fact can determine the credibility of witnesses and how scientific research may or may not be related to the specific facts of any particular case. In my opinion, a key role of an expert witness is to help the court, lawyers, parties, and the public understand and apply reliable scientific, technical, and investigative principles, hypotheses, methods, and information.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on May 1, 2022.

Paul W. Hruz, M.D., Ph.D.

Curriculum Vitae

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Present Position

Associate Professor of Pediatrics, Endocrinology and Diabetes
Associate Professor of Pediatrics, Cell Biology & Physiology

Education

1987	BS, Chemistry, Marquette University, Milwaukee, WI
1993	PhD, Biochemistry, Medical College of Wisconsin, Milwaukee, WI Elucidation of Structural, Mechanistic, and Regulatory Elements in 3-Hydroxy-3-Methlyglutaryl-Coenzyme A Lyase, Henry Miziorko
1994	MD, Medicine, Medical College of Wisconsin, Milwaukee, WI
1994 - 1997	Pediatric Residency, University of Washington, Seattle, Washington
1997 - 2000	Pediatric Endocrinology Fellowship, Washington University, Saint Louis, MO
2017	Certification in Healthcare Ethics, National Catholic Bioethics Center, Philadelphia, PA

Academic Positions / Employment

1996 - 1997	Locum Tenens Physician, Group Health of Puget Sound Eastside Hospital, Group Health of Puget Sound Eastside Hospital, Seattle , WA
2000 - 2003	Instructor in Pediatrics, Endocrinology and Diabetes, Washington University in St. Louis, St. Louis, MO
2003 - 2011	Assistant Professor of Pediatrics, Endocrinology and Diabetes, Washington University in St. Louis, St. Louis, MO
2004 - 2011	Assistant Professor of Pediatrics, Cell Biology & Physiology, Washington University in St. Louis, St. Louis, MO
2011 - Pres	Associate Professor of Pediatrics, Cell Biology & Physiology, Washington University in St. Louis, St. Louis, MO

2011 - Pres	Associate Professor of Pediatrics, Endocrinology and Diabetes, Washington University in St. Louis, St. Louis, MO
2012 - 2017	Division Chief, Endocrinology and Diabetes, Washington University in St. Louis, St. Louis, MO

Clinical Title and Responsibilities

	General Pediatrician, General Pediatric Ward Attending: 2-4 weeks per year, St. Louis Children's Hospital
2000 - Pres	Pediatric Endocrinologist, Endocrinology Night Telephone Consult Service: Average of 2-6 weeks/per yr, St. Louis Children's Hosptial
2000 - Pres	Pediatric Endocrinologist, Inpatient Endocrinology Consult Service: 3-6 weeks per year, St. Louis Children's Hospital
2000 - Pres	Pediatric Endocrinologist, Outpatient Endocrinology Clinic: Approximately 50 patient visits per month, St. Louis Children's Hospital

Teaching Title and Responsibilities

2009 - Pres	Lecturer, Markey Course-Diabetes Module
2020 - 2020	Facilitator, Reading Elective-Interdisciplinary/Miscellaneous Course #M80-800, Washington University School of Medicine

University, School of Medicine and Hospital Appointments and Committees

University

2012 - 2020	Disorders of Sexual Development Multidisciplinary Care Program

School of Medicine

2013 - 2020	Molecular Cell Biology Graduate Student Admissions Committee
2014 - Pres	Research Consultant, ICTS Research Forum - Child Health

Hospital

2000 - Pres	Attending Physician, St. Louis Children's Hospital

Medical Licensure and Certifications

1997 - Pres	Board Certified in General Pediatrics
2000 - Pres	MO Stae License #2000155004
2001 - Pres	Board Certified in Pediatric Endocrinology & Metabolism

Honors and Awards

1987	National Institute of Chemists Research and Recognition Award
1987	Phi Beta Kappa
1987	Phi Lambda Upsilon (Honorary Chemical Society)
1988	American Heart Association Predoctoral Fellowship Award
1994	Alpha Omega Alpha
1994	Armond J. Quick Award for Excellence in Biochemistry

1994	NIDDK/Diabetes Branch Most Outstanding Resident
1998	Pfizer Postdoctoral Fellowship Award
2002	Scholar, Child Health Research Center of Excellence in Developmental Biology at Washington University
2013	Julio V Santiago, M.D. Scholar in Pediatrics
2017	Redemptor Hominis Award for Outstanding Contributions to the Study of Bioethics
2018	Eli Lilly Outstanding Contribution to Drug Discovery: Emerging Biology Award
2018	Scholar-Innovator Award, Harrington Discovery Institute
2021	Linacre Award

Editorial Responsibilities

Editorial Ad Hoc Reviews

AIDS
AIDS Research and Human Retroviruses
American Journal of Pathology
American Journal of Physiology
British Journal of Pharmacology
Circulation Research
Clinical Pharmacology & Therapeutics
Comparative Biochemistry and Physiology
Diabetes
Experimental Biology and Medicine
Future Virology
Journal of Antimicrobial Chemotherapy
Journal of Clinical Endocrinology & Metabolism
Journal of Molecular and Cellular Cardiology
Obesity Research

2000 - Pres	Journal of Biological Chemistry
2013 - Pres	PlosOne
2016 - Pres	Scientific Reports
2018 - Pres	Nutrients

Editorial Boards

2014 - 2015	Endocrinology and Metabolism Clinics of North America

National Panels, Committees

2017 - Pres	Consultant, Catholic Health Association
2021 - Pres	Consulting Fellow, National Catholic Bioethics Center

National Boards

2020 - Pres	WU ICTS Clinical and Translational Research Funding Program (CTRFP) Review Committee

Community Service Contributions

Professional Societies and Organizations

1992 - 2004	American Medical Association
1994 - 2005	American Academy of Pediatrics
1995 - 2014	American Association for the Advancement of Science
1998 - Pres	American Diabetes Association
1998 - Pres	Endocrine Society
1999 - Pres	Pediatric Endocrine Society
2004 - 2007	American Chemical Society
2004 - 2018	American Society for Biochemistry and Molecular Biology
2004 - 2020	Society for Pediatric Research
2005 - 2020	Full Fellow of the American Academy of Pediatrics
2013 - Pres	International Society for Pediatric and Adolescent Diabetes
2018 - Pres	American College of Pediatricians

Major Invited Professorships and Lectures

2002	Pediatric Grand Rounds, St. Louis Children's Hospital, St Louis, MO
2004	National Disease Research Interchange, Human Islet Cell Research Conference, Philadelphia, PA
2004	NIDA-NIH Sponsored National Meeting on Hormones, Drug Abuse and Infections, Bethesda, MD
2005	Endocrine Grand Rounds, University of Indiana, Indianapolis, IN
2005	The Collaborative Institute of Virology, Complications Committee Meeting, Boston, MA
2006	Metabolic Syndrome Advisory Board Meeting, Bristol-Meyers Squibb, Pennington, NJ
2007	American Heart Association and American Academy of HIV Medicine State of the Science Conference: Initiative to Decrease Cardiovascular Risk and Increase Quality of Care for Patients Living with HIV/AIDS, Chicago, IL
2007	Minority Access to Research Careers Seminar, University of Arizona, Tucson, AZ
2007	MSTP Annual Visiting Alumnus Lecture, Medical College of Wisconsin , Milwaukee, WI
2007	Pediatric Grand Rounds, St Louis Children’s Hospital, St Louis, MO
2008	Division of Endocrinology, Diabetes and Nutrition Grand Rounds, Boston University, Boston, MA
2009	Pediatric Grand Rounds, St Louis Children's Hospital, St. Louis, MO
2010	American Diabetes Association Scientific Sessions, Symposium Lecture Orlando, FL
2010	School of Biological Sciences Conference Series, University of Missouri Kansas City, Kansas City, MO
2011	Life Cycle Management Advisory Board Meeting, Bristol-Myers Squibb,, Chicago, IL
2013	Pediatric Grand Rounds, St Louis Children's Hospital, ST LOUIS, MO
2013	Clinical Practice Update Lecture, St Louis Children's Hospital, St Louis, MO
2014	Pediatric Academic Societies Meeting,, Vancouver, Canada
2014	American Diabetes Association 74th Scientific Sessions, , San Francisco, CA
2017	Division of Pediatric Endocrinology Metabolism Rounds, University of Michigan, Ann Arbor, MI

2017	Catholic Medical Association National Conference, Denver, CO
2018	Obstetrics, Gynecology & Women's Health Grand Rounds, Saint Louis University, St. Louis, MO
2018	Medical Grand Rounds, Sindicato Médico del Uruguay, Montevideo, Uraquay
2018	Internal Medicine Grand Rounds, Texas Tech , Lubbock, TX
2019	Veritas Center for Ethics in Public Life Conference, Franciscan University, Steubenville, OH
2019	MaterCare International Conference, Rome, Italy
2019	Child Health Policy Forum, Notre Dame University, South Bend , IN
2021	Obstetrics & Gynecology Grand Rounds, University of Tennessee, Knoxville , TN

Consulting Relationships and Board Memberships

1996 - 2012	Consultant, Bristol Myers Squibb
1997 - 2012	Consultant, Gilead Sciences

Research Support

Completed Governmental Support

2001 - 2006	K-08 A149747, NIH Mechanism of GLUT4 Inhibition by HIV Protease Inhibitors Role: Principal Investigator
2007 - 2012	R01 Mechanisms for Altered Glucose Homeostasis During HAART Role: Principal Investigator Total cost: $800,000.00
2009 - 2011	R01 Student Supp Mechanisms for Altered Glucose Homeostasis During HAART Role: Principal Investigator Total cost: $25,128.00
2009 - 2014	R01 Direct Effects of Antiretroviral Therapy on Cardiac Energy Homeostasis Role: Principal Investigator Total cost: $1,250,000.00
2017 - 2019	R-21 1R21AI130584 , National Institutes of Health SELECTIVE INHIBITION OF THE P. FALCIPARUM GLUCOSE TRANSPORTER PFHT Role: Principal Investigator Total cost: $228,750.00

Completed Non-Governmental Support

2015	Novel HIV Protease Inhibitors and GLUT4 Role: Principal Investigator
2008 - 2011	II Insulin Resistance and Myocardial Glucose Metabolism in Pediatric Heart Failure Role: Co-Investigator PI: Hruz Total cost: $249,999.00

2009 - 2012 Research Program
Regulation of GLUT4 Intrinsic Activity
Role: Principal Investigator
Total cost: $268,262.00

2010 - 2011 Protective Effect of Saxagliptin on a Progressive Deterioration of Cardiovascular Function
Role: Principal Investigator

2012 - 2015 II
Solution-State NMR Structure and Dynamics of Facilitative Glucose Transport Proteins
Role: Principal Investigator
Total cost: $375,000.00

2017 - 2020 Prevention And Treatment Of Hepatic Steatosis Through Selective Targeting Of GLUT8
Role: Co-Principal Investigator
PI: DeBosch
Total cost: $450,000.00

2017 - 2021 Matching Micro Grant
Novel Treatment of Fatty Liver Disease (CDD/LEAP)
Role: Principal Investigator
Total cost: $68,500.00

2018 - 2021 LEAP Innovator Challenge
Novel Treatment of Fatty Liver Disease
Role: Principal Investigator
Total cost: $68,500.00

2019 - 2021 Scholar-Innovator Award HDI2019-SI-4555 , Harrington Foundation
Novel Treatment of Non-Alcoholic Fatty Liver Disease
Role: Principal Investigator
Total cost: $379,000.00

Current Governmental Support

2021 - 2025 R-01 DK126622 (Co-investigator), 8/25/2021-7/31/2025, NIH-NIDDK, , NIH
Leveraging glucose transport and the adaptive fasting response to modulate hepatic metabolism
Role: Co-Investigator
PI: DeBosch

Pending Non-Governmental Support

2015 Novel HIV Protease Inhibitors and GLUT4
Role: Principal Investigator

Trainee/Mentee/Sponsorship Record

Current Trainees

2019 Ava Suda, Other, Pre-med

Past Trainees

2002 - 2002 Nishant Raj- Undergraduate Student, Other
Study area: Researcher

2002 - 2010 Joseph Koster, PhD, Postdoctoral Fellow
Study area: Researcher

2003 - 2004 Johann Hertel, Medical Student
Study area: Research
Present position: Assistant Professor, University of North Carolina, Chapel Hill, NC

2003 - 2003 John Paul Shen, Medical Student
Study area: Research

2004 - 2005 Carl Cassel- High School Student, Other
Study area: Research

2004 - 2004 Christopher Hawkins- Undergraduate Student, Other
Study area: Researcher

2004 - 2004 Kaiming Wu- High School Student, Other
Study area: Research

2005 - 2005 Helena Johnson, Graduate Student

2005 - 2005 Jeremy Etzkorn, Medical Student
Study area: Researcher

2005 - 2005 Dominic Doran, DSc, Postdoctoral Fellow
Study area: HIV Protease Inhibitor Effects on Exercize Tolerance

2006 - 2006 Ramon Jin, Graduate Student
Study area: Research

2006 - 2006 Taekyung Kim, Graduate Student
Study area: Research

2007 - 2007 Jan Freiss- Undergraduate Student, Other
Study area: Researcher

2007 - 2008 Kai-Chien Yang, Graduate Student
Study area: Research
Present position: Postdoctoral Research Associate, University of Chicago

2007 - 2007 Paul Buske, Graduate Student
Study area: Research

2007 - 2007 Randy Colvin, Medical Student
Study area: Researcher

2008 - 2011 Arpita Vyas, MD, Clinical Fellow
Study area: Research
Present position: Assistant Professor, Michigan State University, Lansing MI

2008 - 2009 Candace Reno, Graduate Student
Study area: Research
Present position: Research Associate, University of Utah

2008 - 2012 Dennis Woo- Undergraduate Student, Other
Study area: Researcher
Present position: MSTP Student, USC, Los Angeles CA

2008 - 2008 Temitope Aiyejorun, Graduate Student
Study area: Research

2009 - 2009 Anne-Sophie Stolle- Undergraduate Student, Other
Study area: Research

2009 - 2009 Matthew Hruz- High School Student, Other
Study area: Research
Present position: Computer Programmer, Consumer Affairs, Tulsa OK

2009 - 2009 Stephanie Scherer, Graduate Student
Study area: Research

2010 - 2014 Lauren Flessner, PhD, Postdoctoral Fellow
Present position: Instructor, Syracuse University

2010 - 2010 Constance Haufe- Undergraduate Student, Other
Study area: Researcher

2010 - 2011 Corinna Wilde- Undergraduate Student, Other
Study area: Researcher

2010 - 2010 Samuel Lite- High School Student, Other
Study area: Research

2011 - 2016 Thomas Kraft, Graduate Student
Study area: Glucose transporter structure/function
Present position: Postdoctoral Fellow, Roche, Penzberg, Germany

2011 - 2011 Amanda Koenig- High School Student, Other
Study area: Research

2011 - 2012 Lisa Becker- Undergraduate Student, Other

2011 - 2011 Melissa Al-Jaoude- High School Students, Other

2014 - 2014 David Hannibal, Clinical Research Trainee

Bibliography

A. Journal Articles

1. Hruz PW, Narasimhan C, Miziorko HM. 3-Hydroxy-3-methylglutaryl coenzyme A lyase: affinity labeling of the Pseudomonas mevalonii enzyme and assignment of cysteine-237 to the active site. *Biochemistry*. 1992;31(29):6842-7. PMID:1637819
2. Hruz PW, Miziorko HM. Avian 3-hydroxy-3-methylglutaryl-CoA lyase: sensitivity of enzyme activity to thiol/disulfide exchange and identification of proximal reactive cysteines. *Protein Sci*. 1992;1(9):1144-53. doi:10.1002/pro.5560010908 PMCID:PMC2142181 PMID:1304393
3. Mitchell GA, Robert MF, Hruz PW, Wang S, Fontaine G, Behnke CE, Mende-Mueller LM, Schappert K, Lee C, Gibson KM, Miziorko HM. 3-Hydroxy-3-methylglutaryl coenzyme A lyase (HL). Cloning of human and chicken liver HL cDNAs and characterization of a mutation causing human HL deficiency. *J Biol Chem*. 1993;268(6):4376-81. PMID:8440722
4. Hruz PW, Anderson VE, Miziorko HM. 3-Hydroxy-3-methylglutaryldithio-CoA: utility of an alternative substrate in elucidation of a role for HMG-CoA lyase's cation activator. *Biochim Biophys Acta*. 1993;1162(1-2):149-54. PMID:8095409
5. Roberts JR, Narasimhan C, Hruz PW, Mitchell GA, Miziorko HM. 3-Hydroxy-3-methylglutaryl-CoA lyase: expression and isolation of the recombinant human enzyme and investigation of a mechanism for regulation of enzyme activity. *J Biol Chem*. 1994;269(27):17841-6. PMID:8027038
6. Hruz PW, Mueckler MM. Cysteine-scanning mutagenesis of transmembrane segment 7 of the GLUT1 glucose transporter. *J Biol Chem*. 1999;274(51):36176-80. PMID:10593902
7. Murata H, Hruz PW, Mueckler M. The mechanism of insulin resistance caused by HIV protease inhibitor therapy. *J Biol Chem*. 2000;275(27):20251-4. doi:10.1074/jbc.C000228200 PMID:10806189
8. Hruz PW, Mueckler MM. Cysteine-scanning mutagenesis of transmembrane segment 11 of the GLUT1 facilitative glucose transporter. *Biochemistry*. 2000;39(31):9367-72. PMID:10924131
9. Hruz PW, Mueckler MM. Structural analysis of the GLUT1 facilitative glucose transporter (review). *Mol Membr Biol*. 2001;18(3):183-93. PMID:11681785

10. Murata H, Hruz PW, Mueckler M. Investigating the cellular targets of HIV protease inhibitors: implications for metabolic disorders and improvements in drug therapy. *Curr Drug Targets Infect Disord*. 2002;2(1):1-8. PMID:12462148
11. Hruz PW, Murata H, Qiu H, Mueckler M. Indinavir induces acute and reversible peripheral insulin resistance in rats. *Diabetes*. 2002;51(4):937-42. PMID:11916910
12. Murata H, Hruz PW, Mueckler M. Indinavir inhibits the glucose transporter isoform Glut4 at physiologic concentrations. *AIDS*. 2002;16(6):859-63. PMID:11919487
13. Koster JC, Remedi MS, Qiu H, Nichols CG, Hruz PW. HIV protease inhibitors acutely impair glucose-stimulated insulin release. *Diabetes*. 2003;52(7):1695-700. PMCID:PMC1403824 PMID:12829635
14. Liao Y, Shikapwashya ON, Shteyer E, Dieckgraefe BK, Hruz PW, Rudnick DA. Delayed hepatocellular mitotic progression and impaired liver regeneration in early growth response-1-deficient mice. *J Biol Chem*. 2004;279(41):43107-16. doi:10.1074/jbc.M407969200 PMID:15265859
15. Shteyer E, Liao Y, Muglia LJ, Hruz PW, Rudnick DA. Disruption of hepatic adipogenesis is associated with impaired liver regeneration in mice. *Hepatology*. 2004;40(6):1322-32. doi:10.1002/hep.20462 PMID:15565660
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17. Yan Q, Hruz PW. Direct comparison of the acute in vivo effects of HIV protease inhibitors on peripheral glucose disposal. *J Acquir Immune Defic Syndr*. 2005;40(4):398-403. PMCID:PMC1360159 PMID:16280693
18. Hruz PW. Molecular Mechanisms for Altered Glucose Homeostasis in HIV Infection. *Am J Infect Dis*. 2006;2(3):187-192. PMCID:PMC1716153 PMID:17186064
19. Turmelle YP, Shikapwashya O, Tu S, Hruz PW, Yan Q, Rudnick DA. Rosiglitazone inhibits mouse liver regeneration. *FASEB J*. 2006;20(14):2609-11. doi:10.1096/fj.06-6511fje PMID:17077279
20. Hruz PW, Yan Q, Struthers H, Jay PY. HIV protease inhibitors that block GLUT4 precipitate acute, decompensated heart failure in a mouse model of dilated cardiomyopathy. *FASEB J*. 2008;22(7):2161-7. doi:10.1096/fj.07-102269 PMID:18256305
21. Hruz PW. HIV protease inhibitors and insulin resistance: lessons from in-vitro, rodent and healthy human volunteer models. *Curr Opin HIV AIDS*. 2008;3(6):660-5. doi:10.1097/COH.0b013e3283139134 PMCID:PMC2680222 PMID:19373039
22. Flint OP, Noor MA, Hruz PW, Hylemon PB, Yarasheski K, Kotler DP, Parker RA, Bellamine A. The role of protease inhibitors in the pathogenesis of HIV-associated lipodystrophy: cellular mechanisms and clinical implications. *Toxicol Pathol*. 2009;37(1):65-77. doi:10.1177/0192623308327119 PMCID:PMC3170409 PMID:19171928
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27. Hresko RC, Hruz PW. HIV protease inhibitors act as competitive inhibitors of the cytoplasmic glucose binding site of GLUTs with differing affinities for GLUT1 and GLUT4. *PLoS One*. 2011;6(9):e25237. doi:10.1371/journal.pone.0025237 PMCID:PMC3179492 PMID:21966466
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43. Wei C, Heitmeier M, Hruz PW, Shanmugam M. Evaluating the Efficacy of GLUT Inhibitors Using a Seahorse Extracellular Flux Analyzer. *Methods Mol Biol*. 2018;1713:69-75. PMID:29218518
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45. Zhang Y, Higgins CB, Mayer AL, Mysorekar IU, Razani BB, Graham MJ, Hruz PW, DeBosch BJ. TFEB-dependent Induction of Thermogenesis by the Hepatocyte SLC2A Inhibitor Trehalose. *Autophagy*. 2018. PMID:29996716
46. Emfinger CH, Yan Z, Welscher A, Hung P, McAllister W, Hruz PW, Nichols CG, Remedi MS. Contribution of systemic inflammation to permanence of K_{ATP}-induced neonatal diabetes in mice. *Am J Physiol Endocrinol Metab*. 2018;315(6):E1121-E1132. PMCID:PMC6336961 PMID:30226997
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49. Zhang Y, Shaikh N, Ferey JL, Wankhade UD, Chintapalli SV, Higgins CB, Crowley JR, Heitmeier MR, Stothard AI, Mihi B, Good M, Higashiyama T, Swarts BM, Hruz PW, Shankar K, Tarr PI, DeBosch BJ. Lactotrehalose, an Analog of Trehalose, Increases Energy Metabolism Without Promoting Clostridioides difficile Infection in Mice. *Gastroenterology*. 2020;158(5):1402-1416.e2. PMCID:PMC7103499 PMID:31838076
50. Malone WJ, Hruz PW, Mason JW, Beck S. Letter to the Editor from William J. Malone: "Proper Care of Transgender and Gender Diverse Persons in the Setting of Proposed Discrimination: A Policy Perspective". *J Clin Endocrinol Metab*. 2021. PMID:33772300

C2. Chapters

1. Henderson KE, Baranski TJ, Bickel PE, Clutter PE, Clutter WE, McGill JB. Endocrine Disorders in HIV/AIDS. In: *The Washington Manual Endocrinology Subspecialty Consult* Philadelphia, PA; 2008:321-328.
2. Paul W Hruz. Medical Approaches to Alleviating Gender Dysphoria In: Edward J Furton, eds. *Transgender Issues in Catholic Health Care* Philadelphia PA; 2021:1-42.

C4. Invited Publications

1. Grunfeld C, Kotler DP, Arnett DK, Falutz JM, Haffner SM, Hruz P, Masur H, Meigs JB, Mulligan K, Reiss P, Samaras K, Working Group 1. Contribution of metabolic and anthropometric abnormalities to cardiovascular disease risk factors. *Circulation*. 2008;118(2):e20-8. PMCID: PMC3170411 PMID: 18566314
2. Hruz PW. HIV protease inhibitors and insulin resistance: lessons from in-vitro, rodent and healthy human volunteer models. *Curr Opin HIV AIDS*. 2008;3(6):660-5. PMCID: PMC2680222 PMID: 19373039
3. Hruz PW. Molecular mechanisms for insulin resistance in treated HIV-infection. *Best Pract Res Clin Endocrinol Metab*. 2011;25(3):459-68. PMCID: PMC3115529 PMID: 21663839
4. Hruz PW. HIV and endocrine disorders. *Endocrinol Metab Clin North Am*. 2014;43(3): xvii–xviii. PMID: 25169571
5. Hruz PW. Commentary. *Clin Chem*. 2015;61(12):1444. PMID: 26614228
6. Hruz PW, Mayer LS, and McHugh PR. Growing Pains: Problems with Pubertal Suppression in Treating Gender Dysphoria *The New Atlantis*. 2017;52:3-36.
7. Hruz, PW. The Use of Cross-Sex Steroids in Treating Gender Dysphoria *Natl Cathol Bioeth Q*. 2018;17(4):1-11.
8. Hruz, PW. Experimental Approaches to Alleviating Gender Dysphoria in Children *Nat Cathol Bioeth Q*. 2019;19(1):89-104.

Clinician Educator Portfolio

CLINICAL CONTRIBUTIONS

Summaries of ongoing clinical activities

	General Pediatrician, General Pediatric Ward Attending: 2-4 weeks per year, St. Louis Children's Hospital
2000 - Pres	Pediatric Endocrinologist, Endocrinology Night Telephone Consult Service: Average of 2-6 weeks/per yr, St. Louis Children's Hosptial
2000 - Pres	Pediatric Endocrinologist, Inpatient Endocrinology Consult Service: 3-6 weeks per year, St. Louis Children's Hospital
2000 - Pres	Pediatric Endocrinologist, Outpatient Endocrinology Clinic: Approximately 50 patient visits per month, St. Louis Children's Hospital

EDUCATIONAL CONTRIBUTIONS

Direct teaching

Classroom

2009 - Pres	Lecturer, Markey Course-Diabetes Module
2020 - 2020	Facilitator, Reading Elective-Interdisciplinary/Miscellaneous Course #M80-800, Washington University School of Medicine

Clinical

2000 - Pres	Lecturer, Medical Student Growth Lecture (Women and Children's Health Rotation): Variable
2000 - Pres	Lecturer, Pediatric Endocrinology Journal Club: Presentations yearly
2009 - Pres	Facilitator, Medical Student Endocrinology and Metabolism Course, Small group
2016 - Pres	Facilitator, Medical Student Endocrinology and Metabolism Course, Small group

Other

	Facilitator, Cell Biology Graduate Student Journal Club, 4 hour/year
	Facilitator, Discussion: Pituitary, Growth & Gonadal Cases, 2 hours/year
2000 - Pres	Lecturer, Metabolism Clinical Rounds/Research Seminar: Presentations twice yearly
2009 - Pres	Facilitator, Biology 5011- Ethics and Research Science, 6 hours/year
2016 - Pres	Lecturer, Cell Signaling Course, Diabetes module, 3 hours/year

ANNUAL SUMMARIES

OTHER

Participated in research studies

Pres	Development of Novel Small Molecule Hexose Transport Inhibitors for Glucose-Dependent Disesases Paul W Hruz.

DEFENDANT'S EXHIBIT 6

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER, *et al.*,	)	
Plaintiffs,	)	
v.	)	No. 2:22-cv-00184-LCB-SRW
KAY IVEY, in her official capacity as Governor of the State of Alabama, *et al.*,	)	
Defendants.	)	

DECLARATION OF PATRICK HUNTER

My name is Patrick Hunter MD. I am over the age of 19, I am qualified to give this declaration, and, I have personal knowledge of the matters set forth herein. My CV is attached to this declaration.

In the past four years, I have not provided expert testimony in any case.

I am compensated the rate of $ 450 per hour for my work on this matter. My compensation is not dependent upon the substance of my opinions or the outcome of the case.

1. I submit this expert declaration based upon my personal knowledge, my experience as a pediatrician with an advanced degree in bioethics, and my review of the literature discussed below.
2. If called to testify in this matter, I would testify truthfully based on my expert opinion.

I. Qualifications and Experience

3. I am a pediatrician with a master's degree in bioethics. I received my medical degree from the University of Louisville School of Medicine in 1992 and completed a pediatric residency at Tripler Army Medical Center in 1995. I obtained board certification in general pediatrics in 1995 and have continuously maintained that certification. I obtained a Master of Science degree in bioethics from the University of Mary in 2020. I have served on the ethics committee at Nemours Children Hospital, Orlando.
4. At Scotland Memorial Hospital, I served as pediatric department chair, medical executive committee chair, chief of the medical staff, and on the physician effectiveness committee. This physician effectiveness committee addressed physician professionalism and ethics. I also served on this hospital's governing board and operating committee.
5. I have held teaching positions at the rank of clinical and associate professors at the University of Hawaii and the Uniformed Services University of the Health Sciences. I currently hold academic positions at the University of Central Florida and Florida State University. I have taught pediatrics and bioethics to medical students and resident physicians at Tripler Army Medical Center, the University of Central Florida, and Nemours Children's Hospital in Orlando, Florida.
6. My path into the field of gender medicine is unique. For my first 20 plus years in practice, young people with transgender identity were an extremely rare phenomenon. While gay,

lesbian, and gender non-conforming patients were not uncommon, none of the patients in my care were declaring a transgender identity.

7. However, in 2015, I began to see young patients, exclusively adolescent females, who asserted that they were transgender. I was surprised that the cases I was seeing had "come out" around and after puberty. This sudden epidemiological change did not agree with what I had learned.

8. Historically, gender identity disorder and gender dysphoria affected primarily pre-pubescent boys. These young boys were adamant about their female identity. Gender dysphoria was obvious to the family, and had begun at a young age (approximately 3-5 year old), long before children are developmentally capable of hiding facts from their parents. This presentation of cross-sex identification has been described in the literature as "persistent, insistent and consistent." The rare cases of such young boys (and on an even rarer occasion, girls) did not have to "come out."

9. I now know that my experience with seeing this unusual cohort of adolescents with no history of "persistent, insistent and consistent" cross-sex identity in early childhood closely mirrors the trends seen by other clinicians. In the last eight years there has been an unexplained, dramatic rise in adolescents declaring distress with their sexed bodies and seeking hormones and surgeries to stop the development of secondary sex characteristics.

10. These puzzling epidemiological shifts made me eager to learn what is known about pediatric gender transition. This has involved reading hundreds of papers in this field that have encompassed research, practice guidelines, epidemiology, opinions, history, and ethics. This reading has been from journals that include the NEJM, JAMA, Pediatrics, British Medical Journal, Lancet, Archives of Sexual Behavior, Journal of Homosexuality, Sexual Medicine,

the Journal of American Academy of Child and Adolescent Psychiatry, American Psychologist, PLOS ONE, the Journal of Clinical Endocrinology and Metabolism, and many others. I have also studied professional guidelines from Finland, Sweden, Australia, New Zealand, England, France, and The Netherlands.

11. Importantly, I have also read the first-person accounts of patients in the lay literature, where patient stories and professional concerns are increasingly being voiced. It is my opinion that concerns regarding the so-called "gender-affirmative care model" are often barred from the medical literature.

12. My comprehensive review of the literature revealed that public health authorities in a number of progressive European countries have conducted independent evaluations of the evidence. They have found the evidence for youth transition to be lacking, any benefits to be of very low certainty, and the harms significant.

13. The risks of "gender-affirmative care" in youth are real and the harms are considerable. The most self-evident risk is that the treatment frequently leads to infertility. In fact, if the Endocrine Society's treatment recommendations for youth are followed, and puberty blockers are followed by cross-sex hormones, sterility is nearly assured. Other risks are less certain, but alarming evidence is emerging that bone health is adversely affected. A growing list of concerns includes the effect on developing brains, cardiovascular complications of cross-sex hormones, increased risk for cancer, and others. Arguably the greatest harms are regret and detransition after irreversible bodily changes, sterilization, and impairment of sexual function that is wrought by hormones and surgery.

14. The unfavorable risk/benefit ratio of pediatric transition is the reason why a growing number of liberal western countries are now sharply scaling back the practice of pediatric gender transition.

15. I have always had a keen interest in medical ethics and often considered formal education in the field. I originally wanted to explore the merging of medicine and business—hospital systems dominating the marketplace and physicians becoming employees—and how this evolution was impacting the ethics of medical care. What I was learning about gender dysphoria further propelled my interest in an ethics degree. I undertook a study of bioethics, completing my master's degree in bioethics in 2020.

16. In my degree, much effort was focused on the growing popularity of the so-called "gender-affirmative care," which delivers life-altering, permanent interventions to minors that involve sterilizing procedures. I have focused on ethical dilemmas, such as whether minors have the capacity to give a meaningful informed consent.

17. My research has given me the opportunity to work with experts in the field of gender medicine from all over the world, including Sweden, Finland, England, Australia, Canada, and the United States. I have lectured with Dr. Rittakerttu Kaltiala, a child and adolescent psychiatrist and a leading world expert in transgender care for youth. Dr. Kaltiala was instrumental in recently changing Finland's national transgender practice guidelines, when they recognized the harms being done to youth. I have also lectured on this topic to The National Academy of Science in France. I am a member of the group's scientific council. Recently, my letter outlining concerns with the practice of pediatric gender transition was

published by JAMA Pediatrics. [1] I have authored several recent manuscripts that are currently under review.

18. To round out my academic grasp of the ethical issues, I have also engaged with individuals who transitioned as youth. Some have detransitioned. Some have remained transitioned. I have learned a lot from these brave patients who have been the trailblazers in the highly experimental field of pediatric gender transition.

19. I approach gender dysphoria, gender medicine, and transgender patients from both the clinical and the ethical perspectives. First and foremost, clinical care for patients that suffer from gender dysphoria must offer the greatest benefits. Care must aim for optimal psychological, physical, sexual, and reproductive well-being. Benefits must exceed harms. The well-respected medical truism must prevail: First, do no harm.

20. I will devote part of this declaration to the profound ethical concerns that all physicians should have when treating children with gender dysphoria with medical interventions. It is my conclusion as a bioethicist that the practice of prescribing puberty blockers, cross-sex-hormones, and surgeries to minors violates every key principle of biomedical ethics.

21. Based on numerous conversations and interactions with other pediatricians, it is my opinion that many share my concerns about the unusually high numbers of adolescents requesting gender reassignment and the "gender-affirming care" they are given. Many providers are concerned about the irreversible, profound, life-long changes that these poorly evidenced interventions entail. However, in our current climate, where political activism has taken over

[1] Hunter PK. Political Issues Surrounding Gender-Affirming Care for Transgender Youth. *JAMA Pediatr*. Published online December 20, 2021. doi:10.1001/jamapediatrics.2021.5348

the medical profession, my colleagues are too afraid to speak out publicly. They fear being accused of "transphobia," or fear losing their employment.

22. Gender-dysphoric youth are suffering, and they deserve our compassion and care. The question is not *whether to treat them*, but rather, *how to treat them* in a way that promotes their long-term health and well-being. It is my strong opinion, supported by a growing number of leading pediatric gender clinics and public health authorities in the western world, that hormonal and surgical interventions should be reserved for mature adults, while minors should be treated with supportive psychological care.

23. This is because many minors will find that their trans identity is a transient phase in their identity formation—a realization that is increasingly common among previously trans-identified youth. There is a growing visibility of detransitioned young adults. They regret that they were allowed to get the interventions they so disparately desired at the time, but now realize these interventions were a mistake. Those who persist in their transgender identity can undergo interventions as adults and can be highly successful in their transition. We have many visible examples of successful transitioned adults.

24. One symbol of the medical profession is Asclepias's Rod, with a single snake wrapped around the rod. The rod is the walking stick that the physician uses to travel from home to home to care for those in need. The snake as a reminder, to both physician and patient, that the physician has the power to both heal and to harm.[2]

25. Below, I outline my position that "gender-affirmative" hormonal and surgical interventions for minors on the balance do more harm than good, and that these interventions should be

[2] Cavanaugh TA. *Hippocrates' Oath and Asclepius' Snake*. Vol 1. Oxford University Press; 2017. doi:10.1093/med/9780190673673.001.0001

delayed until a young person's identity is stabilized, full maturity is reached, and true informed consent is attainable.

II. Summary of Key Positions

Below is a summary of my key opinions. I will expand on these opinions further.

- Gender identity is not biologically predetermined
- Transgender identity in young people typically resolves
- The original research on which the practice of pediatric transition rests no longer applies to the currently presenting cases
- There is no established standard of care for transgender-identified youth
- "Gender-affirming" interventions for youth cannot be ethically justified

III. Key Positions

A. Gender Identity is not biologically predetermined

26. Proponents of treating young people with "gender-affirming" hormones and surgeries assert that gender identity is biologically predetermined and, therefore, immutable. They argue that gender-dysphoric adolescents were born "transgender" and will always be "transgender"—much like children born with a congenital disorder such as a cleft palate. Thus, they argue that it is cruel and nonsensical to delay physical alterations to the bodies needed to make their future lives easier.

27. If one is to believe gender identity is biologically predetermined and immutable, and children presenting with gender dysphoria are simply "transgender children" who were born with a

brain-body mismatch, a person holding such beliefs would reason that medical doctors should try to intervene as early as possible to "fix" the body. This is exactly the rationale that the expert witnesses for the plaintiffs in this case are presenting.

28. However, these claims are patently untrue. Despite decades of trying to prove that gender identity is biologically predetermined, the body of evidence points to something entirely different: that biology is far from deterministic, and that a transgender identity arises instead in response to is a combination of factors.

29. Below I present some of the arguments that demonstrate decisively that "gender identity" is not biologically predetermined.

i. Brain studies have not been able to demonstrate a "transgender brain"

30. Despite a number of brain studies that attempted to demonstrate that there is a distinctive brain structure that differentiates people with a transgender identity from the rest, no study has been able to demonstrate a pattern or structure unique to the "transgender brain." The few differences that have been noted disappear after researchers control for sexual orientation and exposure to hormonal interventions that gender dysphoric people undergo, or the studies are too small or unable to control for these or other known confounding factors. Brain

researchers clearly state that their findings do not justify statements suggesting gender dysphoria is a biological condition. [3, 4, 5, 6]

ii. Identical twin studies challenge the notion that gender identity is biologically predetermined

31. Identical twin studies represent one the best available methods to test biological determinism. If gender identity were to be predetermined by one's biology whereby certain children are simply born with a "transgender brain," we would expect both identical twins to have a concordant gender identity majority of the time. Instead, the research into pairs of identical twins shows that if one of the identical twins has a transgender identity the chance that the other twin is also transgender identified is less than 30%.[7]

32. It should be noted that a 30% transgender identity concordance found in identical twins is much higher than would occur by chance, which raises the possibility of biological influence for the formation of a transgender identity, alongside other possibilities. However, the 70% discordance in identical twins' transgender identity strongly signals that a transgender identity is not predetermined by one's genes or prenatal factors.

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[3] Mueller SC, De Cuypere G, T'Sjoen G. Transgender Research in the 21st Century: A Selective Critical Review From a Neurocognitive Perspective. *AJP*. 2017;174(12):1155-1162. doi:10.1176/appi.ajp.2017.17060626

[4] Frigerio A, Ballerini L, Valdés Hernández M. Structural, Functional, and Metabolic Brain Differences as a Function of Gender Identity or Sexual Orientation: A Systematic Review of the Human Neuroimaging Literature. *Arch Sex Behav*. 2021;50(8):3329-3352. doi:10.1007/s10508-021-02005-9

[5] Mueller SC, Guillamon A, Zubiaurre-Elorza L, et al. The Neuroanatomy of Transgender Identity: Mega-Analytic Findings From the ENIGMA Transgender Persons Working Group. *The Journal of Sexual Medicine*. 2021;18(6):1122-1129. doi:10.1016/j.jsxm.2021.03.079

[6] Mueller SC, Guillamon A, Zubiaurre-Elorza L, et al. The Neuroanatomy of Transgender Identity: Mega-Analytic Findings From the ENIGMA Transgender Persons Working Group. *The Journal of Sexual Medicine*. 2021;18(6):1122-1129. doi:10.1016/j.jsxm.2021.03.079

[7] Diamond M. Transsexuality Among Twins: Identity Concordance, Transition, Rearing, and Orientation. *International Journal of Transgenderism*. 2013;14(1):24-38. doi:10.1080/15532739.2013.750222

iii. Peer-reviewed publications acknowledge that transgender identity arises in response to a complex interplay of multiple factors

33. The fact that transgender identity emerges due to the interplay of a multitude of factors, rather than having a biological cause, is widely recognized. In fact, Dr. Rosenthal, one of the expert witnesses for the plaintiffs acknowledged this in his 2014 study:[8]

> *... studies have demonstrated that "gender identity"—a person's inner sense of self as male, female, or occasionally a category other than male or female—...likely reflects a complex interplay of biological, environmental, and cultural factors."* (*Rosenthal, 2014, p. 4379*)

iv. The "gender identity" theory has never been properly tested

34. While it is evident that some people have a transgender identity, and "gender dysphoria" is a diagnosable DSM-5 psychological disorder, what "gender identity" is more generally, and whether and how it varies from one's awareness of one's sex for the rest of the population, is yet to be elucidated. The claims that "everyone has a gender identity," and that one's gender identity is a different entity than one's awareness of one's own sex, have never been put to test.

35. It is worth noting that the very concept of a "gender identity" is relatively new, popularized by the psychologist Dr. John Money in the 1960's. Dr. Money's theories about gender identity developed as he experimented on identical twin boys, one of whom was being raised

[8] Rosenthal SM. Approach to the Patient: Transgender Youth: Endocrine Considerations. *The Journal of Clinical Endocrinology & Metabolism*. 2014;99(12):4379-4389. doi:10.1210/jc.2014-1919

as a girl at Dr. Money's advice. Dr. Money made this recommendation following a circumcision accident that left the boy without a penis. To help the twin raised as a girl embrace his female gender role, Dr. Money performed highly unethical experiments on the boys, including making the siblings examine each other's genitals and perform simulated sexual acts with one another.

36. Initially, the twin boy raised as a girl appeared to have embraced the female identity, which Dr. Money took as validation of his gender identity theory. However, the twin raised in the female gender role eventually re-identified with his biological sex. Tragically, both twins died young, one from a suicide, and the other from a drug overdose. [9] The parents of the twins blamed Dr. Money's experiments as contributing to their sons' mental health struggles and premature death.

37. The proponents of "gender-affirming" hormonal and surgical interventions for minors claim that Dr. Money's experiments proved that gender identity is biologically predetermined and immutable (since the child raised as a girl eventually identified as a boy, despite the psychologist's efforts to the contrary). However, few conclusions can be drawn from a single case that involved such unusual circumstances.

38. More than anything, this experiment demonstrates the problematic origins of the gender identity theory and highlights the profound ethical problems with the currently ongoing social, medical, and surgical experimentation on minors in an attempt to deny or obfuscate their sex.

[9] John Colapinto., 2013. *As nature made him: the boy who was raised as a girl*. HarperCollins Publishers.

B. Transgender identity in young people typically resolves

39. During childhood, adolescence, and young adulthood, an individual's identity continues to develop and change. Historical data shows that most cases of a cross-sex identity in children resolve before they reach mature adulthood. Research confirms that the majority of such youth grow up to be gay, lesbian, or bisexual adults. In fact, a period of cross-sex identification in childhood is a common developmental pathway of gay adults.[10, 11]

40. Contrary to the assertions of the proponents of "gender affirmation," the tendency of a cross-sex identity to resolve is not coerced, but rather happens through the natural course of undergoing puberty and reaching maturity. While the mechanism by which this change occurs is not exactly known, it has been observed that experiencing romantic and sexual encounters and undergoing physical changes of puberty play a key role. [12,13]

41. In talking about the permanent vs. transient nature of transgender identity, is important to differentiate between two known variants of gender dysphoria in young people: the "classical" presentation where gender dysphoria begins in early childhood (typically between ages 3-5), and the novel and now-predominant variant where older children "come out" as transgender around or after the onset of puberty.

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[10] *See* Cantor, 2020

[11] Korte A, Goecker D, Krude H, Lehmkuhl U, Grüters-Kieslich A, Beier KM. Gender Identity Disorders in Childhood and Adolescence. *Dtsch Arztebl Int*. 2008;105(48):834-841. doi:10.3238/arztebl.2008.0834

[12] Steensma TD, Biemond R, de Boer F, Cohen-Kettenis PT. Desisting and persisting gender dysphoria after childhood: A qualitative follow-up study. *Clin Child Psychol Psychiatry*. 2011;16(4):499-516. doi:10.1177/1359104510378303

[13] Kaltiala-Heino R, Bergman H, Työläjärvi M, Frisen L. Gender dysphoria in adolescence: current perspectives. *AHMT*. 2018;Volume 9:31-41. doi:10.2147/AHMT.S135432

i. Childhood-onset gender dysphoria typically remits naturally

42. To date, the total of 11 studies have been conducted to determine the trajectories of children with early-childhood onset of gender dysphoria. All 11 demonstrated that for a majority of such children (61%-98%), early childhood-onset gender dysphoria resolves without any interventions by late adolescence or young adulthood. [14, 15,16]

43. Proponents of pediatric "gender-affirmation" reject this proven high rate of desistance. The fact that desistence happens so frequently in gender-dysphoric children is a threat to the premise of pediatric gender transition. In fact, the expert witnesses for the plaintiffs go to great lengths to preemptively discredit the statistic.

44. For example, Dr. Hawkins attempts to discredit the overwhelming evidence that pediatric gender dysphoria typically self-resolves by claiming that the prior studies dealt with merely gender-non-conforming "non-transgender children," rather than "true transgender children." Hawkins says, "*Historically, earlier studies included a wide range of gender nonconforming children, rather than differentiating between transgender and non-transgender children, and also suffered from other serious methodological flaws that make them unreliable."* (Hawkins, para 22)

45. This claim is not credible at face value. The studies in question have been authored by the very same researchers who are their countries' respective leaders in pediatric gender

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[14] Cantor JM. Transgender and Gender Diverse Children and Adolescents: Fact-Checking of AAP Policy. *Journal of Sex & Marital Therapy*. 2020;46(4):307-313. doi:10.1080/0092623X.2019.1698481

[15] Ristori J, Steensma TD. Gender dysphoria in childhood. *International Review of Psychiatry*. 2016;28(1):13-20. doi:10.3109/09540261.2015.1115754

[16] Singh D, Bradley SJ, Zucker KJ. A Follow-Up Study of Boys With Gender Identity Disorder. *Front Psychiatry*. 2021;12. doi:10.3389/fpsyt.2021.632784

transition. These are the very same authors who have produced much of the currently available literature upon which the entire field of pediatric gender transition rests. To suggest that these clinicians and researchers were somehow confused about their own study subjects, and accidentally studied children who were merely "tomboy girls" or "feminine boys," rather than children with significant gender identity issues, is to imply that the entire body of evidence in the field of pediatric gender medicine came from highly confused clinicians and researchers.

46. Hawken's argument is not original—the proponents of pediatric gender transition have been making it for some time. In response to their critique, a prominent researcher in the field of pediatric gender medicine, Dr. Ken Zucker, re-analyzed the studies in question and split the study subjects into two cohorts: those who were extremely gender non-conforming but did not meet the full diagnostic criteria for Gender Identity Disorder (which was the name of the respective DSM diagnosis at the time), and those who actually met the full diagnostic criteria for having Gender Identity Disorder.

47. The reanalysis confirmed the original finding that most children diagnosed with a gender issue per DSM—nearly 7 in 10—naturally stopped identifying as transgender by the time they reached adulthood. The rate of natural resolution for gender dysphoria is even higher, more than 9 in 10, for those who gender distress was significant enough to warrant a consult with a pediatric gender clinic, but not enough to meet the full diagnostic DSM criteria. [17]

[17] Zucker KJ. The myth of persistence: Response to "A critical commentary on follow-up studies and 'desistance' theories about transgender and gender non-conforming children" by Temple Newhook et al. (2018). *International Journal of Transgenderism*. 2018;19(2):231-245. doi:10.1080/15532739.2018.1468293

48. Yet another way that pro-transition activists have tried to discredit the well-established fact that childhood gender dysphoria eventually remits, is by claiming that DSM-IV criteria used at the time were so flawed as to be totally invalid. These claims assert that even those properly diagnosed with "Gender Identity Disorder" in DSM-IV were not "transgender" at all, but were merely gender-non-conforming.

49. While it is true that the updated DSM-5 criteria in use today made some changes to the childhood diagnosis, these changes have proven to be minor and not clinically significant. Both of the diagnostic manuals (the prior DSM-IV and the current DSM-5) were recently field-tested and were found to be equivalent in terms of which children they flagged as meeting the diagnostic criteria: [18]

> "*…both editions (DSM-IV and DSM-5 and ICD-10 and ICD-11) of gender identity-related diagnoses seem reliable and convenient for clinical use."*

50. The Chair of the DSM-5 Work Group for Sexual and Gender Identity Disorders also concurs that the change in the diagnostic criteria for children from DSM-IV to DSM-5 was not significant: [19]

> *"It is my clinical opinion that the similarities across the various iterations of the DSM are far greater than the differences (Zucker, 2010) and, as part of the work done by the Subcommittee on Gender Identity Disorders for the DSM-IV, provided one example of this (Zucker et al., 1998)*

[18] de Vries ALC, Beek TF, Dhondt K, et al. Reliability and Clinical Utility of Gender Identity-Related Diagnoses: Comparisons Between the ICD-11, ICD-10, DSM-IV, and DSM-5. *LGBT Health*. 2021;8(2):133-142. P.1 doi:10.1089/lgbt.2020.0272

[19] Zucker KJ. The myth of persistence: Response to "A critical commentary on follow-up studies and 'desistance' theories about transgender and gender non-conforming children" by Temple Newhook et al. (2018). *International Journal of Transgenderism*. 2018;19(2):231-245. doi:10.1080/15532739.2018.1468293

51. Thus, the argument that the high desistance rates of pediatric gender dysphoria recorded in all the studies to date were due to the mistaken inclusion of merely gender-non-conforming, rather than "truly transgender" children, does not hold up. It is undeniable that most gender dysphoric children will not grow up to be transgender identified adults, as long as they are allowed to naturally develop without undergoing social and medical transition.

52. Further, contrary to the unfounded plaintiff expert witnesses' claims, no clinician can accurately predict which of the trans-identified children will continue to identify as transgender in mature adulthood vs. those that will desist. This is recognized by the seminal study evaluating the development trajectories of gender-distressed children.[20]

> *"When considering the development of children with GD [gender dysphoria]; studies show that gender dysphoric feelings eventually desist for the majority of children with GD, and that their psychosexual outcome is strongly associated with a lesbian, gay, or bisexual sexuality which does not require any medical intervention, instead of an outcome where medical intervention is required (e.g. Drummond et al., 2008; Wallien & Cohen-Kettenis, 2008; Singh, 2012). Factors predictive for the persistence of GD have been identified on a group level, with higher intensity of GD in childhood identified as the strongest predictor for a future gender dysphoric outcome (Steensma et al., 2013).* ***The predictive value of the identified factors for persistence are, however, on an individual level less clear cut, and the clinical utility of currently identified factors is low****" (Ristori and Steensma, 2016, p. 6)*

[20] Ristori J, Steensma TD. Gender dysphoria in childhood. *International Review of Psychiatry*. 2016;28(1):13-20. doi:10.3109/09540261.2015.1115754

53. This very inability to predict who will persist vs. desist raises serious ethical questions regarding the provision of any irreversible procedures, and particularly those that result in sterilization.

54. The common claim by medicalization activists that once a gender-dysphoric minor reaches adolescence, their gender identity is fixed, is not supported by the evidence. In the 11 desistance studies, the age at which the subjects were followed ranged from adolescence into young adulthood. Some desisted in puberty and others in young adulthood. The Endocrine Society's treatment guidelines acknowledge this:[21]

> *"With current knowledge, we cannot predict the psychosexual outcome for any specific child. Prospective follow-up studies show that childhood GD/gender incongruence does not invariably persist into adolescence* ***and adulthood*** *(so-called "desisters"). (Hembree et al., 2017, p. 3876)*

ii. Transgender identity in adolescents has an unknown developmental trajectory, but high rates of mutability are increasingly evident

55. It is now well recognized that a new variant of transgender identity emerged in the mid 2015's, represented by young people who were not cross-sex identified in childhood. Such cases were virtually unseen until about 7-10 years ago. This is the very population I, and many of my colleagues in the US and internationally, are now seeing in our practices. If one can develop a transgender identity for the first time in adolescence, it demonstrates that a transgender identity is not fixed.

[21] Hembree WC, Cohen-Kettenis PT, Gooren L, et al. ENDOCRINE TREATMENT OF GENDER-DYSPHORIC/GENDER-INCONGRUENT PERSONS: AN ENDOCRINE SOCIETY CLINICAL PRACTICE GUIDELINE. *Endocrine Practice*. 2017;23(12):1437-1437. doi:10.4158/1934-2403-23.12.1437

56. The UK has one of the biggest pediatric gender clinics in the world. The UK clinicians made this observation recently regarding adolescents declaring a trans identity without any childhood history: [22]

> *'...some of us have informally tended toward describing the phenomenon we witness as "adolescent-onset" gender dysphoria, that is,* ***without any notable symptom history prior to or during the early stages of puberty*** *(certainly nothing of clinical significance.)"*(Hutchinson et al., 2020, p. 1)

57. The lead researcher for the Finnish national pediatric gender services program, one of the most respected in the world, has stated the following: [23]

> *"In Finland most adolescents seeking medical treatment in order for their body to conform with their gender identity do not fulfil the eligibility criteria ... for example because they initially* ***experienced onset of gender dysphoria in the late stages of pubertal development*** *or suffer from severe mental disorders which predate the onset of gender dysphoria. Research on adolescent onset gender dysphoria is scarce, and optimal treatment options have not been established [12]. The reasons for the sudden increase in treatment-seeking due to* ***adolescent onset gender dysphoria*** */ transgender identification are not known [13]"* (Kaltiala-Heino and Lindberg, 2019, p. 62)

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[22] Hutchinson A, Midgen M, Spiliadis A. In Support of Research Into Rapid-Onset Gender Dysphoria. *Arch Sex Behav*. 2020;49(1):79-80. p.1 doi:10.1007/s10508-019-01517-9

[23] Kaltiala-Heino R, Lindberg N. Gender identities in adolescent population: Methodological issues and prevalence across age groups. *Eur psychiatr*. 2019;55:61-66. p.62 doi:10.1016/j.eurpsy.2018.09.003

58. A leading Canadian pediatric gender expert made a similar observation: [24]

> *".. it is my view (and that of others) that a new subgroup of adolescents with gender dysphoria has appeared on the clinical scene. This subgroup appears to be comprised—at least so far—of a disproportionate percentage of birth-assigned females* ***who do not have a history of gender dysphoria in childhood or even evidence of marked gender-variant or gender nonconforming behavior****."* (Zucker, 2019, p. 4)

59. Last but not least, even the principal investigator of the medical protocol for transitioning minors (known as the Dutch Protocol) recently acknowledged that a fundamental shift has occurred where adolescents are "coming out" with a trans identity around puberty:[25]

> *"... gender identity development is diverse, and a new developmental pathway is proposed involving youth with postpuberty* ***adolescent-onset transgender histories****.6–8 These youth did not yet participate in the early evaluation studies.5,9" (de Vries, 2020, p. 1)*

[24] Zucker KJ. Adolescents with Gender Dysphoria: Reflections on Some Contemporary Clinical and Research Issues. *Arch Sex Behav*. 2019;48(7):1983-1992. doi:10.1007/s10508-019-01518-8

[25] de Vries ALC. Challenges in Timing Puberty Suppression for Gender-Nonconforming Adolescents. *Pediatrics*. 2020;146(4):e2020010611. doi:10.1542/peds.2020-010611

60. Finally, the growing visibility of young adult detransitioners confirms that a transgender identity can desist in young people. [26, 27, 28, 29]

61. A recent study from a UK adult gender clinic showed that over 10% of young people treated with gender-affirmative interventions detransitioned within 16 months of starting treatment. Another 22% of patients disengaged from the clinic without completing their treatment plan.[30]

62. Another clinic population study found that over 12% of those who had started hormonal treatments either detransitioned or documented regret, while 20% stopped the treatments for a wider range of reasons. These patients presented to the clinics as young adults (mean age of 20) and it took them on average 5 years from beginning treatment to stopping it. Notably, the UK researchers said this: [31]

> *"Thus, the detransition rate found in this population is novel and questions may be raised about the phenomenon of overdiagnosis, overtreatment, or iatrogenic harm as found in other medical fields." (Boyd et al., 2021, p.12)*

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[26] Entwistle K. Debate: Reality check – Detransitioner's testimonies require us to rethink gender dysphoria. *Child Adolesc Ment Health*. Published online May 14, 2020:camh.12380. doi:10.1111/camh.12380

[27] Littman L. Individuals Treated for Gender Dysphoria with Medical and/or Surgical Transition Who Subsequently Detransitioned: A Survey of 100 Detransitioners. *Arch Sex Behav*. Published online October 19, 2021. doi:10.1007/s10508-021-02163-w

[28] Levine SB, Abbruzzese E, Mason JM. Reconsidering Informed Consent for Trans-Identified Children, Adolescents, and Young Adults. *Journal of Sex & Marital Therapy*. Published online March 17, 2022:1-22. doi:10.1080/0092623X.2022.2046221

[29] Vandenbussche E. Detransition-Related Needs and Support: A Cross-Sectional Online Survey. *Journal of Homosexuality*. Published online April 30, 2021:20. doi:10.1080/00918369.2021.1919479

[30] Hall R, Mitchell L, Sachdeva J. Access to care and frequency of detransition among a cohort discharged by a UK national adult gender identity clinic: retrospective case-note review. *BJPsych open*. 2021;7(6):e184. doi:10.1192/bjo.2021.1022

[31] Boyd IL, Hackett T, Bewley S. Care of Transgender Patients: A General Practice Quality Improvement Approach. *SSRN Journal*. Published online 2021. p. 12 doi:10.3390/healthcare10010121

63. Further, we have direct evidence that adolescents with a transgender identity who desire to undergo medical interventions but are told to wait will likely desist. While the studies into this subject are scarce, in the early 2000's Dutch researchers (who pioneered the practice of pediatric gender transition) followed 14 adolescents who were rejected from hormonal and surgical interventions due to presenting with co-morbid mental health issues. [32]

64. At follow-up when the subjects were in their 20's, approximately 1-7 years after being rejected from medical transition as minors, the researchers discovered that 11 of 14 cases no longer wished to transition at all, two subjects only slightly regretted not being able to transition, and only one subject continued to strongly wish to transition. This single subject only wanted breast augmentation, but no other surgery in order to preserve sexual function.[33] Had that one individual been transitioned as a minor under the Dutch protocol, the loss of fertility and sexual function would have ensued.

65. Thus, all 14 of the 14 who were rejected from gender reassignment as teens benefitted from the intervention being delayed until they reached mature adulthood. These 14 young adults simultaneously prove three things: (i) Desistance frequently occurs. (ii) Desistence occurs even when gender dysphoria persists into adolescence. And (iii) a transgender identity is not immutable.

[32] Smith YLS, Van Goozen SHM, Cohen-Kettenis PT. Adolescents With Gender Identity Disorder Who Were Accepted or Rejected for Sex Reassignment Surgery: A Prospective Follow-up Study. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2001;40(4):472-481. doi:10.1097/00004583-200104000-00017

[33] Malone W, D'Angelo R, Beck S, Mason J, Evans M. Puberty blockers for gender dysphoria: the science is far from settled. *The Lancet Child & Adolescent Health*. 2021;5(9):e33-e34. doi:10.1016/S2352-4642(21)00235-2

iii. The terms "transgender child" or "transgender adolescent" are poorly defined

66. Precisely because no clinician can reliably predict which young person will desist from their transgender identification vs. who will persist, the notion of a "transgender child/adolescent" extensively used by the plaintiff's witnesses is not a valid one.

67. "Transgender" is not a diagnosis found in any of the existing diagnostic classifications (either DSM or ICD). It's a lay term that has a wide range of definitions that vary depending on each person's unique understanding of this phenomenon.

68. I maintain that the use of the adjective "transgender" by the plaintiffs' expert witnesses, whenever they talk about gender-dysphoric youth, aims to create an emotional response, implies immutability not supported by evidence, and generally does not belong in a legal document dealing with medical interventions as it lacks a clinical definition. The proper terms in medical contexts are "gender-dysphoric" or "diagnosed with gender dysphoria," based on the diagnostic DSM-5 criteria that are currently in use in the United States.

C. The original research on which the practice of pediatric transition rests no longer applies to the currently presenting cases

i. The Protocol for gender-transitioning minors suffers from serious problems.

69. The practice of pediatric gender transition, known as "gender-affirmative care," rests on a single experiment from the Netherlands conducted circa 2010. This small, single-site, uncontrolled experiment showed that carefully selecting only the highest-functioning children with no mental health problems aside, from being cross-sex identified from early childhood on, and providing them with puberty blockers and cross-sex hormones upon reaching mid-adolescence, followed by surgeries after reaching the 18th birthday, allows

these children to continue to be high-functioning approximately 1.5 years after the completion of final surgery. [34,35]

70. However, the only attempt to replicate the Dutch experiment outside the Netherlands, in the world's largest gender clinic in the UK, failed to show any positive outcomes of the first phase of the Dutch protocol (puberty blockers).[36] The latter phases of the Dutch protocol (following puberty blockers with cross-sex hormones and surgery) have never been attempted to be replicated.

71. Further, new information came into light recently that suggests that the Dutch experiment was both misunderstood and misrepresented as providing "proof" that gender reassignment for minors leads to successful outcomes, when in fact, the study's conclusions are highly questionable. For example, while the Dutch researchers took credit for the adolescents' high level of functioning after transition, these adolescents were high functioning before transition due to the study's stringent participant selection criteria.

72. In fact, for half of the psychological measures tracked, there were no statistically significant improvements before vs. after the treatment protocol. The positive changes in the rest of the psychological measures were so small as to be of highly questionable clinical significance,

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[34] de Vries ALC, Steensma TD, Doreleijers TAH, Cohen-Kettenis PT. Puberty Suppression in Adolescents With Gender Identity Disorder: A Prospective Follow-Up Study. *The Journal of Sexual Medicine*. 2011;8(8):2276-2283. doi:10.1111/j.1743-6109.2010.01943.x

[35] de Vries ALC, McGuire JK, Steensma TD, Wagenaar ECF, Doreleijers TAH, Cohen-Kettenis PT. Young Adult Psychological Outcome After Puberty Suppression and Gender Reassignment. *Pediatrics*. 2014;134(4):696-704. doi:10.1542/peds.2013-2958

[36] Carmichael P, Butler G, Masic U, et al. Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK. Santana GL, ed. *PLoS ONE*. 2021;16(2):e0243894. doi:10.1371/journal.pone.0243894

and could not be attributed to the hormones and surgeries alone since all the subjects also received extensive psychological support. [37]

73. More generally, the lack of a control group rendered the study findings "very low certainty," the rating assigned to the study by the recent comprehensive systematic review of evidence conducted by the UK's National Institute for Health and Care Excellence (NICE). [38]

74. Even the study's most-lauded finding, the marked drop in the "gender dysphoria" score, is now in question, as it has come to light that the researchers did not have an appropriate scale to capture changes in gender dysphoria, and they used the scale that they did have access to in a highly questionable way (by "flipping" the male and female versions of the scales between baseline and final measurement time periods).[39]

75. Further, the Dutch team had very strict screening criteria, which would have excluded the vast majority of young people who request gender reassignment today. For example, the Dutch excluded from their experiment any adolescent whose transgender identity emerged only around and after puberty—they required that clear cross-sex identification be present from very early childhood on. The Dutch also excluded the adolescents who were suicidal or had any significant unaddressed mental illness. Adolescents with a non-binary identity were not eligible. In addition, the Dutch researchers insisted that the adolescents have a firm grasp

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[37] *See* Levine, 2020

[38] National Institute for Health and Care Excellence. Evidence review: Gonadotrophin releasing hormone analogues for children and adolescents with gender dysphoria. https://web.archive.org/web/20220414202655/https://arms.nice.org.uk/resources/hub/1070905/attachment

[39] *See* Levine, 2020

of biological reality and realize they will never be able to become the "opposite sex" despite the hormonal and surgical interventions. [40, 41]

76. Several children in the small sample of 70 cases (which, by the end of the study, shrank to 55) experienced severe adverse events while under treatment, including one young adult who died followed surgical complications, several cases of new diabetes and obesity, and at least one case of detransition, although the study is vague on this point.[42]

77. This study, and the modest psychological improvements reported, came at the cost of sterility for 100% of the subjects (mandatory removal of ovaries and testes was part of the protocol), and were associated with severe adverse, raising serious ethical concerns that I will address later on in more detail.

78. The concern that I would like to focus on here is that the presentation of gender dysphoria in youth has markedly changed since the Dutch protocol's final results were published in 2014. As a result, the continued application of this protocol to the populations for which it was never intended in the first place is not justified under any circumstances. This misapplication of the Dutch protocol directly contradicts the principle of evidence-based medicine.

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[40] Delemarre-van de Waal HA, Cohen-Kettenis PT. Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects. *eur j endocrinol*. 2006;155(suppl_1):S131-S137. doi:10.1530/eje.1.02231

[41] Cohen-Kettenis PT, Delemarre-van de Waal HA, Gooren LJG. The treatment of adolescent transsexuals: changing insights. *J Sex Med*. 2008;5(8):1892-1897. doi:10.1111/j.1743-6109.2008.00870.x

[42] *See* de Vries et al., 2014

ii. The vast majority of currently presenting cases of gender dysphoric youth no longer meet the strict criteria of the Dutch protocol

79. Currently, approximately 2%-9% of minors in the US identify as transgender.[43,44] Most are adolescent females who "came out" as transgender around the time of puberty, and very often have significant mental health comorbidities that pre-date the onset of transgender identity. [45, 46, 47] Increasingly, these minors are identifying as "non-binary": neither male nor female, or both as male and female.[48] Recent research estimates that as many as 67% of trans-identified adolescents today identify as non-binary. [49]

80. The new clinical presentation and skyrocketing numbers are totally new phenomena. As recently as eight or ten years ago, seeing a child with a cross-gender identity was extremely rare, and most were prepubescent boys, the majority of whom outgrew their trans

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[43] Johns MM, Lowry R, Andrzejewski J, et al. Transgender Identity and Experiences of Violence Victimization, Substance Use, Suicide Risk, and Sexual Risk Behaviors Among High School Students - 19 States and Large Urban School Districts, 2017. *MMWR Morb Mortal Wkly Rep*. 2019;68(3):67-71. doi:10.15585/mmwr.mm6803a3

[44] Kidd KM, Sequeira GM, Douglas C, et al. Prevalence of Gender-Diverse Youth in an Urban School District. *Pediatrics*. 2021;147(6):e2020049823. doi:10.1542/peds.2020-049823

[45] Becerra-Culqui TA, Liu Y, Nash R, et al. Mental Health of Transgender and Gender Nonconforming Youth Compared With Their Peers. *Pediatrics*. 2018;141(5):e20173845. doi:10.1542/peds.2017-3845

[46] Kaltiala-Heino R, Sumia M, Työläjärvi M, Lindberg N. Two years of gender identity service for minors: overrepresentation of natal girls with severe problems in adolescent development. *Child Adolesc Psychiatry Ment Health*. 2015;9(1):9. doi:10.1186/s13034-015-0042-y

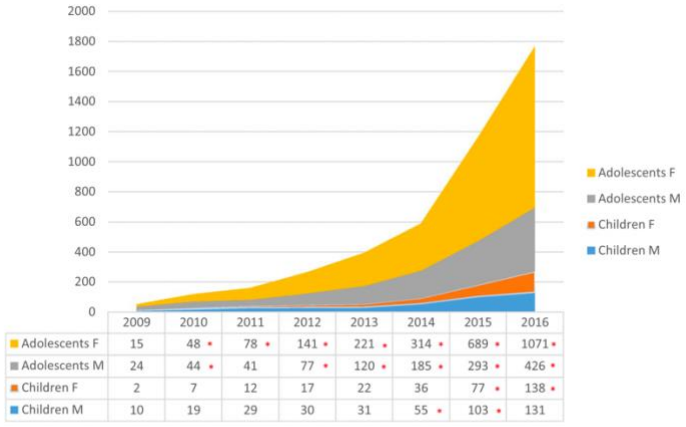
[47] Kaltiala-Heino R, Lindberg N. Gender identities in adolescent population: Methodological issues and prevalence across age groups. *Eur psychiatr*. 2019;55:61-66. doi:10.1016/j.eurpsy.2018.09.003

[48] Chew D, Tollit MA, Poulakis Z, Zwickl S, Cheung AS, Pang KC. Youths with a non-binary gender identity: a review of their sociodemographic and clinical profile. *The Lancet Child & Adolescent Health*. 2020;4(4):322-330. doi:10.1016/S2352-4642(19)30403-1

[49] Green AE, DeChants JP, Price MN, Davis CK. Association of Gender-Affirming Hormone Therapy With Depression, Thoughts of Suicide, and Attempted Suicide Among Transgender and Nonbinary Youth. *Journal of Adolescent Health*. Published online December 2021:S1054139X21005681. doi:10.1016/j.jadohealth.2021.10.036

identification sometime before mature adulthood. Many of these youths grew up to be gay. [50] [51]

81. The graph shown here from the Gender Identity Service in England is but one example of this worldwide phenomenon.[52]



	2009	2010	2011	2012	2013	2014	2015	2016
Adolescents F	15	48 *	78 *	141 *	221 *	314 *	689 *	1071 *
Adolescents M	24	44 *	41	77 *	120 *	185 *	293 *	426 *
Children F	2	7	12	17	22	36	77 *	138 *
Children M	10	19	29	30	31	55 *	103 *	131

AFAB = assigned female at birth; AMAB = assigned male at birth
* Indicates $p < .05$ which shows a significant increase of referrals compared to the previous year

82. In my own practice, I am also struck by the similarities in the patient stories of trans-identified youth. Most are adolescent females who have had a normative childhood from the gender standpoint, but have felt isolated from their peers. They have had pre-existing anxiety and depression. Several have had a history of psychiatric hospitalizations.

83. What is particularly striking is that that my patients arrive at my office well-versed in gender-related terminology. The trans-identified youth I see use terms that I did not expect to hear from late elementary, middle school, and high school students. Without prompting or questioning, I often hear about self-diagnoses of depression, anxiety, PTSD, autism, and

[50] *See* Cantor, 2020, Appendix

[51] *See* Korte, 2008

[52] de Graaf NM, Giovanardi G, Zitz C, Carmichael P. Sex Ratio in Children and Adolescents Referred to the Gender Identity Development Service in the UK (2009–2016). *Arch Sex Behav*. 2018;47(5):1301-1304. doi:10.1007/s10508-018-1204-9

dissociative disorders. Terms such as *puberty blockers*, *cross sex hormones*, *fully reversible*, *partially reversible, irreversible, suicidality, allyship*, *misgendering*, *minority stress*, and *transphobia* are often mentioned. The patient familiarity with terminology in this field is remarkable.

84. The advocates of medicalization may celebrate this as patient empowerment and patient education. To me this suggests a heavy influence from others. These youth self-diagnose and arrive in my office certain of their condition and the need for treatment, which is usually a request for hormones.

85. The emergence of a new clinical entity, and to an unprecedented scale, would normally give us pause. A pause to better understand what's causing the exponential rise in gender dysphoria and how best to understand it and address it. Several national health systems in progressive countries have indeed done this very thing. They include Finland, Sweden, and the UK, all of which have recently conducted systematic reviews of evidence and have begun to sharply limit pediatric transition over the concerns about this new trend.

86. Instead of a pause and critical analysis of the situation, as other countries are now doing, the US presses on, oblivious to these changes, and even actively suppressing concerns. The researcher who first raised the key question of why suddenly so many teenagers, and especially females with pre-existing mental health problems, are declaring a trans identity and seeking "gender-affirming" hormones, and hypothesized that peer pressure and social influence may be playing a key role, has been subject to intimidation, abuse, and silencing.[53]

87. It should also be noted that we are currently experiencing a well-recognized and new phenomenon of high numbers of children, particularly adolescent females, developing the

[53] https://quillette.com/2018/08/31/as-a-former-dean-of-harvard-medical-school-i-question-browns-failure-to-defend-lisa-littman/

sudden onset of tics that has been tied to social contagion via social networks.[54] Other well-researched socially-mediated psychological phenomena are eating disorders. It is known that bulimia and anorexia can spread through human social networks. These human social networks existed prior to the internet, can spread these conditions, and have disproportionately affected adolescent females. [55,56]

88. I am not asserting that adolescent-onset gender dysphoria spreads through social circles or is socially contagious—however this hypothesis and others need to be investigated. It is reasonable and prudent to ask why this is happening—as many as 1 in 10 youth currently claim a transgender identity —before a growing number of children are subjected to irreversible and highly experimental medical interventions. [57]

D. There is no established standard of care for transgender-identified youth

i. Current treatment guidelines do not represent a standard of care

89. Contrary to the plaintiffs' expert reports, there is currently no established standard of care for transgender-identified youth. Instead, multiple professional societies have come up with various treatment guidelines which are increasingly divergent in terms of how to approach the management of gender dysphoria in youth.

[54] https://ipmh.duke.edu/news/pediatric-presentation-tics-potential-role-tiktok
[55] Allison S, Warin M, Bastiampillai T. Anorexia nervosa and social contagion: Clinical implications. *Aust N Z J Psychiatry*. 2014;48(2):116-120. doi:10.1177/0004867413502092

[56] Forman-Hoffman VL, Cunningham CL. Geographical clustering of eating disordered behaviors in U.S. high school students. *Int J Eat Disord*. 2008;41(3):209-214. doi:10.1002/eat.20491

[57] Littman L. Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria. Romer D, ed. *PLoS ONE*. 2018;13(8):e0202330. doi:10.1371/journal.pone.0202330

90. Unlike standards of care, which should be authoritative, unbiased consensus positions designed to produce optimal outcomes, practice guidelines are suggestions or recommendations. Depending on their sponsor, practice guidelines may be biased. [58]

91. The World Professional Association for Transgender Health (WPATH), an advocacy organization with a mission to remove barriers to insurance coverage for "gender-affirming" hormones and surgeries, is one of several organizations that authors guidelines in this space. Although WPATH named its guidelines "Standards of Care," it recently had to acknowledge that their recommendations are merely practice guidelines, rather than standards of care.[59]

92. The "Standards of Care 7" acknowledges that it was not evidence-based and did not utilize any systematic reviews of evidence, but rather was based on the emerging cultural changes and expert opinions of clinicians, many of whom derive a significant proportion of their income from delivering transgender medicine. A recent systematic review of treatment guidelines in this space found that "Standards of Care 7" were generally unfit for clinical decision-making, and it described several recommendations in the document as incoherent.[60]

93. The upcoming "Standards of Care 8" have not yet been finalized, but the draft version signals even more aggressive lowering of age of eligibility for hormonal and surgical interventions than that found in "Standards of Care 7," clearly signaling that the values and preferences of

[58] Malone WJ, Hruz PW, Mason JW, Beck S. Letter to the Editor from William J. Malone et al: "Proper Care of Transgender and Gender-diverse Persons in the Setting of Proposed Discrimination: A Policy Perspective." *The Journal of Clinical Endocrinology & Metabolism*. Published online March 27, 2021:dgab205. doi:10.1210/clinem/dgab205

[59] *See* Malone et al., 2021

[60] Dahlen S, Connolly D, Arif I, Junejo MH, Bewley S, Meads C. International clinical practice guidelines for gender minority/trans people: systematic review and quality assessment. *BMJ Open*. 2021;11(4):e048943. doi:10.1136/bmjopen-2021-048943

WPATH clinicians are strongly aligned with medicalization even when the evidence for it is low-quality and non-existent entirely.

94. Another guideline that the plaintiffs' expert witnesses erroneously cite as representing the standard of care is that by the Endocrine Society. However, the Endocrine Society's guidelines clearly state: [61]

> *"…the guidelines cannot guarantee any specific outcome, nor do they establish a standard of care." (Hembree et al., 2017, p. 3895)*

95. The Endocrine Society's recommendation to halt gender dysphoric minors' puberty and treat them with cross-sex hormones is rated as "weak," and is recognized as coming from low quality evidence by the guidelines itself.[62] The "weak" grading indicates that it is not known whether the benefits outweigh the risks.

96. Notably, the only studies cited in the two key recommendations to treat minors hormonally are the two Dutch studies I described earlier.[63] Thus, the entire foundation of the Endocrine Society's recommendations to medically intervene with gender-dysphoric minors comes from a single small-scale experiment with significant problems, as described earlier.

ii. The National Institutes of Health (NIH)-funded research acknowledges that little is known about pediatric gender transition

97. According to the research protocol filed by the researchers for a recent NIH grant, the data on pediatric gender transitions are almost entirely lacking. The need to conduct this research

[61] *See* Hembree et al., 2017
[62] *See* Hembree et al., 2017
[63] *See* de Vries et al., 2011 and de Vries et al., 2014

demonstrates that this care pathway remains largely experimental, with an unknown risk-benefit ratio. [64]

98. The following quotes from the NIH grant from 2019 clearly demonstrate how immature the field of pediatric gender medicine is: [65]

- *"Although the Endocrine Society Clinical Practice Guidelines are widely adopted by providers around the United States and worldwide, there are no formal empirical studies of related clinical outcomes in transgender children and adolescents."*
- "*…existing models of care for transgender youth…have been used in clinical settings for close to a decade, although with limited empirical research to support them"*
- *"Although these [current clinical practice] guidelines have informed care at academic and community centers across the United States, they are based on very limited data. Furthermore, there is minimal available data examining the long-term physiologic and metabolic consequences of gender-affirming hormone treatment in youth. This represents a critical gap in knowledge that has significant implications for clinical practice across the United States."*
- *"The gap in existing knowledge about the impact of these practices leaves providers and caretakers uncertain about moving forward with the recommended medical interventions for transgender youth seeking phenotypic transition."*

[64] Olson-Kennedy J, Chan YM, Garofalo R, et al. Impact of Early Medical Treatment for Transgender Youth: Protocol for the Longitudinal, Observational Trans Youth Care Study. *JMIR Res Protoc*. 2019;8(7):e14434. doi:10.2196/14434

[65] *See* Olson-Kennedy et al., 2019

99. These quotes, and the substantial amount of money paid by the NIH to fund this research, clearly demonstrate that "gender-affirmative" interventions are still in the experimental stage and are not yet ready to deemed either "safe" or "effective."

100. When there is no data of the benefits, and the risks are substantial, the onus is on the research community to first demonstrate that benefits that outweigh the risks. Until such evidence exists, no standard of care can be claimed.

iii. The United States is increasingly becoming an outlier in its non-evidence-based stance that transitioning minors is a safe and effective practice

101. Sweden is the first country in the world to recognize the legal status of transgender adults. In May of 2021, Sweden's flagship children's hospital, which is affiliated with the Karolinska Institute that grants the Nobel Prize of Medicine, announced that they were discontinuing all new pediatric transitions due to concerns over the lack of efficacy and the potential for significant harm. In May 2022, Sweden's Health Authority (National Board of Health and Welfare/NBHW) issued a country-wide policy that states that going forward, pediatric gender transitions will not be available in general medical practice to those <18. Such interventions will only be provided in strictly controlled clinical trial settings with a focus on the strictest ethical safeguards for youth, given the significant risk of harm.

102. It is noteworthy that the official English translation of Sweden's health authority's decision states:[66]

[66] https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2022-3-7799.pdf

"For adolescents with gender incongruence, the NBHW deems that the ***risks of puberty suppressing treatment with GnRH-analogues and gender-affirming hormonal treatment currently outweigh the possible benefits****... This judgement is based mainly on three factors: the continued lack of reliable scientific evidence concerning the efficacy and the safety of both treatments, the new knowledge that detransition occurs among young adults, and the uncertainty that follows from the yet unexplained increase in the number of care seekers, an increase particularly large among adolescents registered as females at birth."*

103. Increasingly, a number of western countries with significant experience in pediatric gender transition are turning away from WPATH and the Endocrine Society's guidelines. In the last 24 months, not just Sweden, but also Finland, the UK, and France, after independently reviewing evidence, have issued their own guidelines that are far more conservative than the stances promoted by the US-based medical societies. [67,68,69]

104. However, in the US, the proponents of medical interventions of minors continue to assert that if a child on the verge of puberty, or an older adolescent meets the diagnostic criteria for gender dysphoria, then medical interventions are without question "medically necessary."

105. This confidence by US clinicians extends to medical interventions for "non-binary" youth who are an even less well-understood population. Procedures viewed as "medically necessary" by some of the proponents of "gender-affirmative care" for minors now include

[67] https://segm.org/Finland_deviates_from_WPATH_prioritizing_psychotherapy_no_surgery_for_minors

[68] https://cass.independent-review.uk/publications/interim-report/

[69] https://segm.org/France-cautions-regarding-puberty-blockers-and-cross-sex-hormones-for-youth

the suppression of puberty indefinitely in order to present as an ambiguous sex, [70,71] mastectomy on youth as young as 13 years of age,[72] and "non-binary" breast surgeries that preserve a feminine appearance while changing the placement of the nipples to be more reminiscent of a male chest, should the minor's identity reside somewhere along the "male to female spectrum." [73]

106. It is my belief that the highly politicized nature of the US debate about transgender healthcare has pushed our country toward an increasingly pro-medicalization position, at the same time the rest of the world is making a U-turn. The failure of the US-based medical societies to recognize the harms that are currently occurring to vulnerable minors is hard to understand, and raises serious ethical questions.

IV. Ethical Considerations and Conclusions

107. Medical ethics rests on four key pillars: the principles of patient autonomy, justice, beneficence, and nonmaleficence.[74] It is my belief as a bioethicist that providing youth with hormones and surgeries directly violates all of these principles. For this reason, it is my belief that true informed consent to "gender-affirming" hormones and surgeries for minors is not possible.

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[70] Notini L, Earp BD, Gillam L, et al. Forever young? The ethics of ongoing puberty suppression for non-binary adults. *J Med Ethics*. Published online July 24, 2020:medethics-2019-106012. doi:10.1136/medethics-2019-106012

[71] Pang KC, Notini L, McDougall R, et al. Long-term Puberty Suppression for a Nonbinary Teenager. *Pediatrics*. 2020;145(2):e20191606. doi:10.1542/peds.2019-1606

[72] Olson-Kennedy J, Warus J, Okonta V, Belzer M, Clark LF. Chest Reconstruction and Chest Dysphoria in Transmasculine Minors and Young Adults: Comparisons of Nonsurgical and Postsurgical Cohorts. *JAMA Pediatr*. 2018;172(5):431. doi:10.1001/jamapediatrics.2017.5440

[73] https://cranects.com/non-binary-surgery/

[74] Varkey B. Principles of clinical ethics and their application to practice. *Med Princ Pract*. Published online June 4, 2020. doi:10.1159/000509119

A. The principle of "Patient Autonomy" is not respected when "gender-affirming" hormones and surgeries are provided to minors

108. Patient autonomy is a bedrock principle of medical ethics, having a long and well-respected history in both medical ethics and the law. In the context of providing hormones and surgeries to gender-dysphoric minors who wish for these interventions, the advocates of medical interventions are misrepresenting the nature of patient autonomy.

109. Rather than the right to *demand and receive* any treatment, patient autonomy is rightfully understood as the patient's right to *consent to* and to *refuse* treatment. Medical care cannot be done without a valid informed consent. It cannot be provided against the patient's will. The court stated this clearly in *Schloendorff v Society of New York Hospital*:

> *"Every human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault for which he is liable in damages."* [75]

110. Patient autonomy has never meant that a patient or their guardian have the right to *demand and receive* treatment that is inappropriate or harmful. For example, pediatricians routinely decline to provide antibiotics to children with viral infections. Well-meaning and deeply concerned parents may be looking for, and even demand, antibiotics as a solution to a child's viral illness. However, we do not prescribe antibiotics in these cases because they have no role in viral infections, carry risks to the child, and the inappropriate use of antibiotics create resistance in the community. Likewise, when worried parents implore physicians for a CT scan of their child's head following a minor head trauma, a conscientious physician will decline such a request. There is no benefit to imaging for

[75] Schloendorff v. Society of New York Hospital, 1914 https://biotech.law.lsu.edu/cases/consent/schoendorff.htm

minor head trauma and there are well-recognized risks that are not insignificant, including sedation and radiation exposure. In these cases, we are not "denying care." We are providing the patients with appropriate medical care and safeguarding them from the risk of harm.

111. Like antibiotics for viral infections or CT scans for minor head injuries, puberty blockers, cross sex hormones, and surgeries do not have proven psychological or physical health benefits for gender-dysphoric youth. This lack of benefit has been the conclusion of recent quality systematic reviews by the UK, Sweden's, and Finland's public health authorities.[76,77,78,79] Sweden's National Health and Welfare Board has determined that risks of gender affirming care "currently outweigh the benefits." [80]

112. The medical risks of "gender-affirming" interventions are substantial. The most recent evidence shows that a gender-dysphoric child with normally timed puberty who is started on puberty blockers has a nearly 100% chance of continuing to cross-sex hormones.[81,82,83] This medical sequence will render the child sterile.

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[76] https://web.archive.org/web/20220414202655/https://arms.nice.org.uk/resources/hub/1070905/attachment

[77] https://web.archive.org/web/20220215111922/https://arms.nice.org.uk/resources/hub/1070871/attachment

[78] SBU. *Hormonbehandling Vid Könsdysfori - Barn Och Unga [Hormonal Treatment of Gender Dysphoria - Children and Adolescents]*. SBU; 2022. https://www.sbu.se/342

[79] Pasternack I, Söderström I, Saijonkari M, Mäkelä M. Lääketieteelliset menetelmät sukupuolivariaatioihin liittyvän dysforian hoidossa. Systemaattinen katsaus. [Appendix 1 Systematic Review]. Published online 2019:106. Accessed May 1, 2022. https://app.box.com/s/y9u791np8v9gsunwgpr2kqn8swd9vdtx

[80] https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2022-3-7799.pdf

[81] Wiepjes CM, Nota NM, de Blok CJM, et al. The Amsterdam Cohort of Gender Dysphoria Study (1972–2015): Trends in Prevalence, Treatment, and Regrets. *The Journal of Sexual Medicine*. 2018;15(4):582-590. doi:10.1016/j.jsxm.2018.01.016

[82] Carmichael P, Butler G, Masic U, et al. Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK. Santana GL, ed. *PLoS ONE*. 2021;16(2):e0243894. doi:10.1371/journal.pone.0243894

[83] Brik T, Vrouenraets LJJJ, de Vries MC, Hannema SE. Trajectories of Adolescents Treated with Gonadotropin-Releasing Hormone Analogues for Gender Dysphoria. *Arch Sex Behav*. 2020;49(7):2611-2618. doi:10.1007/s10508-020-01660-8

113. Other medical harms also ensue. These include harms to bone health, cardiovascular health, brain development, and other problems. [84,85,86]

114. A physician who grants a minor's wish for these interventions is not respecting patient autonomy. That physician is misusing the principle of patient autonomy to justify unethical experimentation on minors.

115. Another key ethical dilemma regarding patient autonomy is whether the wishes of the 13-year-old should be privileged over the wishes of the future adult self. Can the 13-year-old self fully and truly know what the 25-year-old self will desire regarding the questions of sexual function and reproductive rights? We do not know what the 25-year-old will say about the loss of sexual function or fertility. A price may be paid that can never be recouped, all for bodily change that may or may not comport with the 25-year-old's future identity and desires.

116. It is a well-known fact that many adult trans-identified individuals choose not to undergo "gender-affirming" procedures that threaten their sexual function. While adults chose to preserve their fertility and sexual function, children at Tanner stage 2, which can occur in females as young as 8, are asked to contemplate, decide, and then consent to treatments with puberty blockers followed by cross sex hormones, which will cause sterility. Fertility

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[84] Klink D, Caris M, Heijboer A, van Trotsenburg M, Rotteveel J. Bone Mass in Young Adulthood Following Gonadotropin-Releasing Hormone Analog Treatment and Cross-Sex Hormone Treatment in Adolescents With Gender Dysphoria. *The Journal of Clinical Endocrinology & Metabolism*. 2015;100(2):E270-E275. doi:10.1210/jc.2014-2439

[85] Alzahrani T, Nguyen T, Ryan A, et al. Cardiovascular Disease Risk Factors and Myocardial Infarction in the Transgender Population. *Circ: Cardiovascular Quality and Outcomes*. 2019;12(4). doi:10.1161/CIRCOUTCOMES.119.005597

[86] Schneider MA, Spritzer PM, Soll BMB, et al. Brain Maturation, Cognition and Voice Pattern in a Gender Dysphoria Case under Pubertal Suppression. *Front Hum Neurosci*. 2017;11:528. doi:10.3389/fnhum.2017.00528

preservation – harvesting of egg or sperm – may be discussed by the proponents of medicalization. However, there are no mature egg or sperm to harvest at Tanner stage 2. Sterility is guaranteed with oophorectomy and removal of testes (castration).

117. It is important to note that a number of individuals who identified as transgender in their teen years and no longer identify as transgender upon reaching maturity have expressed gratitude that they did not undergo medical and surgical interventions that would have rendered them infertile. This sentiment is echoed by detransitioners who did receive these interventions and express disappointment, grief, and anger that nobody resisted their desires. No one challenged them. No one slowed down the younger version of themselves. [87,88]

118. The principle of patient autonomy also requires a fiduciary, trusting relationship between physician and patient. Truthfulness and full disclosure of information must occur for the patient and parent to exercise autonomy. As my arguments demonstrate, the low-quality evidence, lack of long-term follow-up, and increasing reports of harm, regret, and detransition, all raise grave concerns about "gender-affirmative care."

119. In my experience of having reviewed informed consent forms, speaking to physicians and therapists involved in "gender affirmative" care that refer for or prescribe puberty blockers and cross sex hormones, and talking to patients and parents who have transitioned or are seeking to transition, many of these concerns are not disclosed to patients and families. While some well-established risks are mentioned, the profound uncertainties are not acknowledged, and even denied by proponents of "gender-affirmative" care.[89]

[87] *See* Vandenbussche (2021)
[88] *See* Littman (2021)
[89] *See* Levine, 2022

120. For example, puberty blockers are often misrepresented as fully reversible despite mounting evidence that they irreversibly impeded bone growth, impact cognitive development, change the psycho-sexual profile toward a diminished sexual desire, and likely have a host of other yet unknown consequences. The relative safety record of puberty blockers administered for precocious puberty (e.g., a 5-year old who is starting to develop pubic hair and develop breasts) is being misrepresented as evidence that this intervention will be safe and fully reversible when used off-label to stop normally-timed puberty.

121. Puberty is the developmentally appropriate time when every organ system benefits from sex hormones to reach its optimal adult function. We do not know the long-term effects of stopping the biologically vital, normally timed process of puberty for several years. This is the reason why the UK's National Health Service recently replaced its statement that puberty blockers are reversible and now states: [90,91]

> "*Little is known about the long-term side effects of hormone or puberty blockers in children with gender dysphoria*." (NHS)

122. Also, it is typically not disclosed to the patients that the population on which the Dutch protocol was originally tested does not match most of the cases presenting today and that most cases treated with the protocol today would have been disqualified by the original study. Specifically, the Dutch excluded from transition adolescents whose transgender identity was not clearly established in early childhood, and those with significant mental

[90] https://www.spectator.co.uk/article/the-nhs-has-quietly-changed-its-trans-guidance-to-reflect-reality
[91] https://www.nhs.uk/conditions/gender-dysphoria/treatment/#:~:text=Puberty%20blockers%20and%20cross%2Dsex%20hormones&text=Little%20is%20known%20about%20the,the%20psychological%20effects%20may%20be.

health problems. [92] Nor is it typically disclosed to the patients and parents that the mental health of the Dutch study participants did not statistically or meaningfully improve after gender reassignment. Instead, these treatments are misrepresented as "life-saving."

123. Finally, patient autonomy is correctly understood as the freedom to act towards one's objective good. "Gender-affirming care" leads to sterilization, increased risk to general health (bone, cardiac, others), surgical complications, the potential for worsened mental health, and in a growing number of instances, future regret. These outcomes are objectively bad.

124. Thus, it is my opinion as a bioethicist that "gender-affirming" interventions with hormones and surgery for minors not only fail to support the core principle of Autonomy, but they directly violate it.

B. The principle of "Justice" is violated when minors are provided with "gender-affirming" hormones and surgery

125. The right to control one's reproduction and sexual function is well recognized by United States law and court rulings. Article 16 of the United Nations Universal Declaration of Human Rights recognizes that "men and woman of full age have the right…to found a family."

126. It is now well recognized that puberty blockers followed by cross sex hormones are, in effect, chemical castration, which is likely irreversible. The removal of testicles, which WPATH supports as early as 17 years of age in the draft of its upcoming guidelines, is irreversible castration.

[92] *See* Delemarre-van de Waal & Cohen-Kettenis, 2006 and Cohen-Kettenis et al., 2008.

127. It is unjust and unethical to sterilize a gender-non-conforming, mentally distressed adolescent. In my opinion, this is precisely what "gender-affirmative care" is doing to children. Children and adolescents do not have the capacity—the knowledge, understanding, and judgement—to comprehend the gravity of the decision they are making regarding their fertility.

128. The United States medical profession has a shameful history regarding forced and coerced sterilization of minors and adults without informed consent. All people of goodwill now agree that the court erred when it upheld these unethical sterilization practices in Buck v Bell (274 U.S. 200, 1927). [93]

129. It is my opinion as a bioethicist that "gender-affirming" interventions for minors violates the core ethical principle of Justice.

C. The ethical principles of "Beneficence" and "Non-Maleficence" are violated by providing minors with "gender-affirming" hormones and surgeries

130. The principles of beneficence and non-maleficence are fundamental principles of medical ethics. They require that medicine must do good and avoid harm. The Dutch Study[94] on which the practice of pediatric transition rests (as evidenced by the Endocrine Society Guidelines' citations [95]) has demonstrated that the "good" was narrowly defined and remains highly uncertain, while the "harm" was self-evident.

131. The Dutch Study claimed the greater "good" by claiming (correctly) that post-surgery the young adults who emerged after transition were functioning well, or even better, than the

[93] https://supreme.justia.com/cases/federal/us/274/200/

[94] *See* de Vries et al., 2014

[95] *See* Hembree et al., 2017

average 21-year-old Dutch peer. However, the study authors did not reflect on the fact that their screening methods nearly guaranteed such an outcome, since their carefully-selected 70 study subjects were already extremely high functioning before treatment.

132. Their beneficial claims also fail to address the harm to the patient with postoperative death after genital surgery and several instances of diabetes and obesity that developed during treatment.[96]

133. It has been longer than 10 years since these adolescents were transitioned, and we have no long-term follow up on this cohort. However, another study by the Dutch of an adolescent treated with the same protocol several years earlier did follow that individual into their mature adult years and the results are not reassuring. When this individual was first followed as a young 20-year old shortly after surgery, he was happy with the transition and the appearance of his genitals.[97] However, when followed up again at the age of thirty-five the situation had changed.

134. The patient was living alone and unable to form a loving relationship with a partner. He attributed the inability to form a long-lasting stable relationship to the shame about his genitalia. [98] This case does not lend confidence to the notion that the youth in the Dutch Study will be thriving in key aspects of their lives once they reach a mature adult age.

135. The Endocrine Society relies heavily on the Dutch Protocol in writing their guidelines, yet they fail to address the serious harms that were present and reported in the Dutch Study.

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[96] *See* de Vries et al., 2014

[97] Cohen-Kettenis PT, van Goozen SHM. Pubertal delay as an aid in diagnosis and treatment of a transsexual adolescent. *European Child & Adolescent Psychiatry*. 1998;7(4):246-248. doi:10.1007/s007870050073

[98] Cohen-Kettenis PT, Schagen SEE, Steensma TD, de Vries ALC, Delemarre-van de Waal HA. Puberty Suppression in a Gender-Dysphoric Adolescent: A 22-Year Follow-Up. *Arch Sex Behav*. 2011;40(4):843-847. doi:10.1007/s10508-011-9758-9

They fail to mention or address the fact that fertility was destroyed in 100% of the youth transitioned in the Dutch Study. Nor are the 3 cases of new onset diabetes and obesity that developed during the Dutch Study addressed by the Endocrine Society. It cannot be said for certain that transition caused these effects, but a 4.3% rate of diabetes in a pediatric population is highly unusual and should lead to further concern and study. Another adolescent in the Dutch Study stopped short of gender confirming surgery. This patient has had irreversible changes from puberty blockers followed by cross-sex hormones. We do not know the effects of these permanent changes on this young person's life.

136. The one young person who tragically died as a result of surgical complications has already been mentioned. Death was due to tissue necrosis as a complication of a vaginoplasty: a procedure to construct a neo-vagina from the penis after castration. This translates into a 1%-2% death rate.

137. The evidence of regret is now emerging from newer research. The first large study of detransitioners in 2021 reported on 237 people. They stopped transitioning on average 4 years after starting. [99] Another study of 100 people who regretted their sex transition stopped the process on average 3.9 years after it began.[100] These numbers dwarf the participants in the Dutch Study, which ended their report 18 months after transition.

138. Many of the studies that purport benefit of transition recruit participants from online pro-transition activist sites. [101,102] At the same time, little attention is paid to the emerging

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[99] See Vandenbussche, 2021.

[100] Littman, 2021

[101] Turban JL, King D, Carswell JM, Keuroghlian AS. Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation. *Pediatrics*. 2020;145(2):e20191725. doi:10.1542/peds.2019-1725

[102] D'Angelo R, Syrulnik E, Ayad S, Marchiano L, Kenny DT, Clarke P. One Size Does Not Fit All: In Support of Psychotherapy for Gender Dysphoria. *Arch Sex Behav*. Published online October 21, 2020. doi:10.1007/s10508-020-01844-2

online communities of detransitioners and their stories are readily dismissed by proponents of affirmative care. One such community has over 28,000 subscribers, at least half of whom are estimated to be actual detransitioned patients.[103] The sheer numbers of people on the site sharing their devastating transition stories, their regret, and their harms dwarfs the Dutch case series of 55. The stories posted here are heart wrenching and indisputable evidence of the great harm being done.

139. There is no doubt in my mind that parents of children receiving "gender-affirming" interventions want the best for their children, and they are acting on advice of professionals. It is the physicians and counselors whom I believe have failed these parents and their children, falsely asserting that gender transition will help their children long-term. Many of these professionals themselves are misled by the activism that has taken over US-based professional bodies.

140. No matter how well-meaning the advocates of pediatric gender transition are, their actions lack beneficence. The experiment of medically and surgically transitioning minors lacks long-term outcome data. There is no meaningful evidence of long-term benefits. There are many demonstrable harms. And there remain many unknowns and uncertainties.

D. True informed consent for "gender-affirming care" for minors is not possible

141. Informed consent is another foundational principle of bioethics. It rests on all the other principles and requires a trusting and truthful relationship with one's physician. Physician-patient relationships must respect personal autonomy, promote the patient good, avoid harms, and seek justice. As a bioethicist, I am deeply concerned that valid informed

[103] https://www.reddit.com/r/detrans/

consent, a prerequisite of ethical care, is not possible in the context of "gender-affirmative care" for minors.

142. For informed consent to be valid the minor child or parent must understand the proposed procedure. The possible benefits, risks, limitations, and alternatives must be disclosed to the minor patient and parent. Since the information regarding "gender-affirmative care" is of low quality, unreliable, and very uncertain, a true understanding is not possible.

143. Also, for the consent to be valid, alternative approaches, including the approach to not medically intervene with one's gender non-conformity, must be discussed. However, alternative approaches such as psychotherapy,[104] which are now recommended as the first line and often the only treatment for gender dysphoric youth in European countries, are often withheld from US children and misrepresented as "conversion." This is dishonest and further undermines the informed consent process.

144. In addition, informed consent is not valid if decisions are made under coercion or duress (The Nuremberg Code, 1946).[105] It is highly problematic that the so-called "gender specialists" raise the specter of suicide. This can only alarm parents and their children, with wrongful and unsupported claims that these radical interventions are "lifesaving." These claims wrongly imply that transgender patients will commit suicide if not permitted to transition.

145. It is true that self-harm and suicidal thoughts are increased in trans-identified youth, but the suicide risk is on par with youth who have other mental health conditions, and thankfully,

[104] Schwartz D. Clinical and Ethical Considerations in the Treatment of Gender Dysphoric Children and Adolescents: When Doing Less Is Helping More. *Journal of Infant, Child, and Adolescent Psychotherapy*. Published online November 22, 2021:1-11. doi:10.1080/15289168.2021.1997344

[105] https://www.ushmm.org/information/exhibitions/online-exhibitions/special-focus/doctors-trial/nuremberg-code

the absolute risk of suicide among gender-dysphoric youth remains exceedingly rare, recently estimated at 0.03% over 10 years in the UK.[106] That the US is not doing similar quality research with clinic-referred populations, instead relying on alarmist statistics derived from online activist surveys, further emphasizes just what an outlier the US-based approach to gender dysphoric minors has become compared to the rest of the western world.

146. Unfortunately, no study to date has been able to demonstrate that actual suicides are reduced post-transition. Parents are wrongly and unethically told that transition is the only solution to their child's problems. The "transition or suicide" mantra proclaimed by gender ideology is coercive, untrue, and unethical. [107]

147. Ethical behavior demands that we are truthful with our patients. Dishonesty, deceit, and coercion are unethical. Problematically, in my experience, some proponents of medicalization of minors mislead children and their families that "gender-affirming care" leads to a "sex change." They assert that through the hormonal and surgical manipulations of one's physical body, the "true sex," which they claim is signified by their "gender identity" will be allowed to emerge. I have heard from youth who decided to detransition when they finally come to the realization that they will never become the opposite sex. It is hard for me to believe that professionals mislead children in such a fundamental way.

148. Children believe adults. This is especially true when adults with medical degrees assure them that they can change sex. At least some of these children will be bitterly disappointed later when they realize that they will be medically dependent for life. Cross-sex hormones

[106] Biggs M. Suicide by Clinic-Referred Transgender Adolescents in the United Kingdom. *Arch Sex Behav*. Published online January 18, 2022. doi:10.1007/s10508-022-02287-7

[107] https://www.wbez.org/stories/id-rather-have-a-living-son-than-a-dead-daughter/69b0e784-d9c1-44a3-a0f7-419864fe0d3c

will be needed for life to maintain the superficial appearance of the desired sex. They will never be able to procreate. Their sexual function destroyed, and reproductive capacity lost forever. And they will come to realize that their sex, which permeates every cell in their body, is immutable and unchangeable.

149. Mature adults with well-controlled mental health problems can consent to gender transition, provided they have received full and truthful disclosure of the complete range of benefits, risks and uncertainties associated with gender transition.

150. However, I am confident that children are not capable of either consenting or assenting to such a profound decision under any circumstances—and especially when they and their caregivers are effectively being misled by the medical community in fundamental ways.

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct. Executed on May 1, 2022.

Patrick Hunter

CURRICULUM VITAE

Patrick K. Hunter, MD, MSc

PERSONAL DATA

Place of Birth	Chicago, IL
Home Address	[redacted]
Telephone	[redacted]
Email	[redacted]

EDUCATIONAL DEGREES

May 1992	MD	University of Louisville Louisville, Kentucky
April 2020	MSc, Biomedical Ethics	University of Mary Bismarck, ND
May 1988	BA Zoology	Miami University Oxford, Ohio

POSTGRADUATE TRAINING

1992 to 1995	Internship and Residency Tripler Army Medical Center Department of Pediatrics Honolulu, Hawaii

PROFESSIONAL EXPERIENCE

January 2022-present	Pensacola Pediatrics Milton, FL
August 2015 to December 2021	Lake Nona Pediatrics, in Association with Nemours
August 2013 to July 2015	The Maui Medical Group Wailuku, HI Member, Board of Directors
June 2008 to June 2013	U.S. Department of Defense Tripler Army Medical Center and Naval Health Clinic Hawaii Honolulu, HI Academic General Pediatrician Chief, Mother-Baby Unit
July 1998 to June 2008	The Purcell Clinic Laurinburg, North Carolina Partner/Owner
July 1995 to June 1998	Staff Pediatrician & Chief of the Pediatric Clinic Captain, Medical Corps US Army Darnall Army Community Hospital Fort Hood, Texas

CURRICULUM VITAE

Patrick K. Hunter, MD, MSc

EDUCATIONAL APPOINTMENTS

July 2017 to present	Assistant Professor of Medicine University of Central Florida College of Medicine
March 2009 to June 2015	Assistant Clinical Professor Department of Pediatrics University of Hawaii John A. Burns School of Medicine
February 2012 to July 2013	Assistant Clinical Professor Department of Pediatrics Uniformed Services University of the Health Sciences Bethesda, Maryland
1998 – 2008	Study Investigator North Carolina Children and Adult Research Foundation

CLINICAL INTERESTS

Biomedical ethics
Judicious use of health care services
Immunizations
Asthma -- patient and parental education and motivation
Promotion of early childhood literacy
Newborn and Neonatal Care
Breastfeeding Promotion
Infectious Diseases
Well Child Care
Motivational Interviewing

HOSPITAL APPOINTMENTS

Nemours Children's Hospital Orlando, FL	2015 to 2021
Ethics Committee	
Maui Memorial Hospital Wailuku, HI	2013 to 2015
Tripler Army Medical Center Honolulu, HI	2008 - 2012
Scotland Memorial Hospital Laurinburg, NC	1998-2009
Medical Record Review Committee	2001-2002
Chairman, Department of Pediatrics	2001-2002, 2007-2008
Medical Executive Committee	2001-2005, 2007-2008
Medical Staff Secretary	2001-2002
Chief of Staff—Elect	2002-2003
Chief of the Medical Staff	**2003-2004**
Chair, Credentials Committee	**2004-2005**
Physician Effectiveness Committee	**2002-2008**

CURRICULUM VITAE

Patrick K. Hunter, MD, MSc

MEDICAL LICENSES

Hawaii
Florida

BOARD CERTIFICATION

American Board of Pediatrics	October 1995

COMMUNITY SERVICE

Scotland County Habitat for Humanity	
Board Member	2002-2003
Scotland Memorial Hospital	
Foundation Board Member	1999-2002
Scotland Memorial Hospital	
Board Member	2003-2005
Executive & Operating Committee Member	2003-2004
St. Andrews Presbyterian College	
Laurinburg Area Campaign Committee	2000 and 2007
St. Anthony Catholic Church	
Knights of Columbus	2008 to 2013
Pastoral Council	2010 to 2012
St. Thomas Free Clinic	2018 to 2021
Pediatrician	
St. John Fisher Catholic Church	2018 to 2021
Finance Committee	

ABSTRACTS, PAPERS, AND PRESENTATIONS

The Western Society of Pediatric Research Annual Meeting, February 1994
Pallister Hall syndrome in siblings, a case report and review of the literature Abstract and presentation

Smith AE, Vedder TG, Hunter PK, et al. The Use of Newborn Screening Pulse Oximetry to Detect Cyanotic Congenital Heart Disease: A Survey of Current Practice at Army, Navy, and Air Force Hospitals. *Military Medicine*. March 2011; 176(3) 343-346

Hunter PK. Political Issues Surrounding Gender Affirming Care of Transgender Youth. *JAMA Pediatrics*. December 2021; 176(3):322-323. doi:10.1001/jamapediatrics.2021.5348

DEFENDANT'S EXHIBIT 7

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER, *et al.*,	)	
Plaintiffs,	)	
v.	)	No. 2:22-cv-00184-LCB-SRW
KAY IVEY, in her official capacity as Governor of the State of Alabama, *et al.*,	)	
Defendants.	)	

DECLARATION OF DIANNA KENNY

My name is Dianna Kenny. I am over the age of 19, I am qualified to give this declaration, and, I have personal knowledge of the matters set forth herein.

I am a former Professor of Psychology at the University of Sydney. I now practice as a consulting psychologist and psychotherapist. My CV is attached to this declaration. Recent publications can be found at www.diannakenny.com.au and https://www.researchgate.net/profile/Dianna-Kenny. Some are also listed on my CV.

I was retained by the State of Alabama as an expert witness in the above-styled case. A copy of my expert report is attached to this declaration. It contains my opinions in this matter based upon my research and experience. I have reviewed the Complaint filed by the Plaintiffs and the declarations submitted by the Plaintiffs.

In the past four years, I have provided expert testimony in the following cases: 12, supplied on request.

I am compensated at the rate of $__400__ per hour for my work on this matter. My compensation is not dependent upon the substance of my opinions or the outcome of the case.

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct. Executed on ___1 May__, 2022.

Dianna Kenny

IN THE UNITED STATES DISTRICT COURT

FOR THE MIDDLE DISTRICT OF ALABAMA

NORTHERN DIVISION

JEFFREY WALKER, et al.,

Plaintiffs,

v.

STEVE MARSHALL, in his official capacity as Attorney General of the State of Alabama, BRIAN C.T. JONES, in his official capacity as District Attorney for Limestone County, and JESSICA VENTIERE, in her official capacity as District Attorney for Lee County,

Defendants.

Civil Action No. 2:22-cv-00167

DECLARATION OF DIANNA KENNY PHD IN SUPPORT OF

S.B. 184 (THE "FELONY HEALTH CARE BAN" OR THE "BAN")

TABLE OF CONTENTS

CHAPTER 1

SOCIAL CONTAGION

Abstract

In this chapter, I review the evidence for social contagion of gender dysphoria in adolescents. I begin with a review of the historical phenomenon of social contagion, demonstrating that it predated the digital age. I then review the nature of social contagion and the mechanisms by which certain phenomena are propagated through social networks. Social network analysis, the method applied to study contagions of all kinds, was first developed and used in public health as a way of determining the spread of diseases. For the spread of social phenomena among adolescents, three mechanisms - peer contagion, deviancy training and co-rumination in peer groups - have been identified as "spreaders." Four possible causes of peer effects – endogenous, exogenous, correlated and social media – all amplify the spread of information in a social network. Four areas of empirically established social contagion in adolescents - marijuana use, eating disorders, non-suicidal self-injury, suicide and emotion – are presented as a prelude to the discussion of how the same processes are at work in the social contagion of gender dysphoria and the wish to transition in adolescence. Specific mechanisms of transmission such as low gender typicality, peer victimization, ingroups, the trans-lobby, the role of social media in rapid onset gender dysphoria (ROGD) in are proposed. Preliminary statistical support for social contagion in gender dysphoria are presented.

INTRODUCTION: SOCIAL CONTAGION PREDATES THE DIGITAL AGE

> It is not famine, not earthquakes, not microbes, not cancer but man himself who is man's greatest danger to man, for the simple reason that there is no adequate protection against psychic epidemics, which are infinitely more devastating than the worst of natural catastrophes - Carl Jung

The term social contagion describes the "spread of phenomena (e.g., behaviours, beliefs and attitudes) across network ties" (Christakis & Fowler, 2013, p. 556). Social contagion has existed long before the advent of the digital age and social media. In 1774, Johann von Goethe (1990) published a novel, *The sorrows of young Werther*, in which an idealistic young man finds his actual life too difficult to reconcile with his poetic fantasies, including his

unrequited love for his friend's fiancée. He eventually becomes so depressed and hopeless by the perceived emptiness of his life, he commits suicide. Goethe was able to capture the nameless dread and endless longing of the human condition so well that his novel spawned a number of suicides, committed in the same way that Werther had killed himself, by shooting (Phillips, 1974). Such was the alarm created by this phenomenon, the book was banned in several European cities.

More than two hundred years later, in 1984, the suicide of a young Austrian businessman, who threw himself in front of a train, initiated a spate of similar suicides that averaged five per week for nearly a year. Sociologists argued that this alarming occurrence was amplified by media coverage that glamorised suicide by providing graphic images of the suicidal act and details of the young man's life. When media exposure of the event was curtailed and then stopped completely, the suicide rate dropped by 80 percent almost immediately. Although the influence of suggestion and imitation on suicide rates was dismissed by Durkheim (2005/ 1897), Phillips's (1974) work indicated that these factors do indeed play a significant role in the increase in suicides following a publicised suicide.

In 1841, a Scottish journalist, Charles Mackay (2012) wrote a book entitled *Extraordinary popular delusions and the madness of crowds.* In the preface to the first edition of the book, the aim of writing it is stated thus:

> …to collect the most remarkable instances of those *moral epidemics* … to show how easily the masses have been led astray, and how imitative and gregarious men are, even in their infatuations and crime (p. 1) …Popular delusions began so early, spread so widely, and have lasted so long, that instead of two or three volumes, fifty would scarcely suffice to detail their history... The present may be considered…a miscellany of delusions, a chapter only in the great and awful book of human folly (p. 3).

The preface to the second edition in 1852 continued this theme:

> Nations… like individuals, …have their whims and their peculiarities; their seasons of excitement and recklessness… whole communities suddenly fix their minds upon one object and go mad in its pursuit; …millions of people become simultaneously impressed with one delusion, and run after it, till their attention is caught by some new folly more captivating than the first. At an early age in the annals of Europe its

> population lost their wits about the sepulchre of Jesus and crowded in frenzied multitudes to the Holy Land; another age went mad for fear of the devil and offered up hundreds of thousands of victims to the delusion of witchcraft... the belief in omens and divination of the future… defy the progress of knowledge to eradicate them entirely from the popular mind… *Men… think in herds; …they go mad in herds, while they only recover their senses slowly, and one by one* [Author's italics] (p. 7).

With the arrival of COVID-19, the World Health Organization (WHO) warned that there would be an "infodemic"[1] of misinformation spawned by social contagion. This has in fact occurred, but the false beliefs have not taken centre stage and swept all science before it in the manner of transgender ideology. As Anderson (2018)[2] concluded:

> The [transgender] movement has to keep patching and shoring up its beliefs, policing the faithful, coercing the heretics, and punishing apostates, because as soon as its furious efforts flag for a moment or someone successfully stands up to it, the whole charade is exposed. That's what happens when your dogmas are so contrary to obvious, basic, everyday truths. A transgender future is not the "right side of history," yet activists have convinced the most powerful sectors of our society to acquiesce to their demands. While the claims they make are manifestly false, it will take real work to prevent the spread of these harmful ideas.

SOCIAL NETWORK EFFECTS UNDERLIE SOCIAL CONTAGIONS

Using very large datasets (e.g., Framingham Heart Study) that have collected longitudinal data on original participants (Original cohort), as well as their children (Offspring cohort) and their children's children (Third generation cohort) and including their spouses, siblings, friends and neighbours, Christakis and Fowler have shown that social network effects, known as clustering, remain strong and can extend to those up to three degrees of separation from the original cohort. Such effects have been demonstrated across a large range of factors by different researchers using differing datasets. Examples include overweight/obesity, sleep patterns, smoking, alcohol abuse, alcohol abstention, marijuana use, loneliness, happiness, depression, cooperation, and divorce among others. It can be argued that the spread of

[1] W.H.O. Fights a Pandemic Besides Coronavirus: An 'Infodemic' - The New York Times (nytimes.com)
[2] The Philosophical Contradictions of the Transgender Worldview - Public Discourse (thepublicdiscourse.com)

gender dysphoria and transgenderism is underpinned by these now well-established mechanisms of social contagion in other human behaviours.

Social network analysis, the method applied to study contagions of all kinds, was first developed and used in public health as a way of determining the spread of diseases (e.g., influenza, HIV/AIDS) that resulted in pandemics. It was subsequently applied to the challenges of introducing changes and innovations in the health system (Blanchet, 2013). Its applications have since expanded with the advent of computers, the internet, mobile and smart phones, and social media. Members of a network play different roles in the dissemination of innovations. A small number will adopt early (i.e., early adopters). Some of these will become opinion leaders who are central to the network who contaminate their "peers" (homophily) who in turn will influence those others at different levels of the network.

There are three types of social networks; (i) egocentric (networks assessing a single individual); (ii) sociocentric (social networks in a well-defined social space, such as a hospital or a school); and (iii) open system networks (e.g., globalised markets, social media). Each network consists of nodes (members), ties (connections between nodes), and measures of centrality, density and periphery or distance between the nodes. Networks with high centrality are the most effective in disseminating information or innovation. A key example is the transactivist lobby that has achieved spectacular success in a short time in changing health care, educational practices and legislation related to transgender individuals. Other characteristics of networks include cohesion (number of connections within a network) and shape (distribution of ties within the network) (Otte & Rousseau, 2002).

First, I examine the concept of social contagion and the mechanisms by which it influences behaviour and attitudes. Then I review four adolescent behaviours that have been empirically revealed to be subject to social contagion. I then demonstrate that the same principles of social contagion apply to the increase of young people who believe that they are transgender and are consequently seeking irreversible medical remedies to assuage their gender dysphoria. Finally, I explore the social contagion (i.e., clustering) of medical practice with respect to treatment of gender dysphoria, the precipitous legislation appearing in its support, and changes to policy and practice in education and sport, despite our collective failure to

date to fully understand the phenomenon of gender dysphoria and its rapid, epidemic-like spread in the Western world.

THE MECHANISMS OF SOCIAL CONTAGION

(i) Peer contagion

Peer contagion is a form of social contagion, defined as a process of reciprocal influence to engage in behaviours occurring in a peer dyad that may be life-enhancing (e.g., taking up a sport, studying for exams, health screening, resisting engaging in negative behaviours, altruism) or life-compromising (e.g., illegal substance use, truanting from school, aggression, bullying, obesity). Peer contagion has a powerful socializing effect on children beginning in the pre-school years. By early childhood, the time spent interacting with same-age playmates frequently exceeds time spent with parents (Ellis, Rogoff, & Cromer, 1981). Further, characteristics of peer interactions in schools (e.g., aggression, coercive behaviours, mocking peers) are carried over into the home environment (Patterson, Littman, & Bricker, 1967). By middle childhood, gender is the most important factor in the formation of peer associations, highlighting the significance of gender as the organizing principle of the norms and values associated with gender identity (Fagot & Rodgers, 1998).

(ii) Deviancy training as a mechanism of social contagion

Different mechanisms of transmission of peer influence have been identified. Deviancy training, in which deviant attitudes and behaviours are rewarded by the peer group have a significant effect on the development of antisocial attitudes and behaviours such as bullying, physical violence, weapon carrying, delinquency, juvenile offending, and substance abuse (Dishion, Nelson, Winter, & Bullock, 2004). Aggression in adolescence becomes more covert and deliberate and takes the form of exclusion, spreading rumours, and suborning relational damage among an adolescent's friendship network (Sijtsema, Veenstra, Lindenberg, & Salmivalli, 2009). Interestingly, adolescents associated with peers who engage in instrumental aggression became more instrumentally aggressive, while those associated with peers who engaged in relational aggression became more relationally aggressive, demonstrating the specificity of the effects of peer contagion via the deviancy training.

(iii) Co-rumination as a form of social contagion

Another form of peer contagion in adolescence is co-rumination, a process of repetitive discussion, rehearsal and speculation about a problematic issue within the peer dyad or peer group that underlies peer influence on internalizing problems such as depression, anxiety, self-harm, suicidal ideation and suicide (Schwartz-Mette & Rose, 2012). Co-rumination is more common among adolescent girls (Hankin, Stone, & Wright, 2010) although a similar phenomenon among boys has been observed. Being in a friendship that engages in perseverative discussions on deviant topics has been associated with increased problem behaviour over the course of adolescence. The longer these discussions, the greater the association with deviant behaviour in later adolescence (Dishion & Tipsord, 2011).

Peer contagion may undermine the effects of positive socializing forces such as schools, rehabilitation programs for young offenders, and treatment facilities for eating disorders among others. Collecting same-minded adolescents into group programs may be counter-productive because the peer influence impacts of a homogeneous peer group to maintain disordered behaviours may be greater than the program effects of the treatment facility (Dishion & Tipsord, 2011).

Young people are particularly vulnerable to peer contagion if they have experienced peer rejection, hostility and/or social isolation from the peer group (Light & Dishion, 2007). On the contrary, protective factors against peer contagion effects include secure attachment to parents, adequate adult supervision and oversight of the young person's activities, school attendance, and the capacity for self-regulation (T. W. Gardner, Dishion, & Connell, 2008).

(iv) Social contagion has a causal effect on behaviour uptake

Establishing a causal role for the effect of peer behaviour on adolescents is difficult because adolescents choose their peer networks; that is, they choose to associate with like-minded adolescents and those exhibiting similar attributes (homophily). This raises the question: Do adolescents choose their peers because they sanction and engage in similar behaviours or can peer social networks explain the uptake of (new) behaviours in individuals in the network? Sophisticated statistical models have been used to tease out the relative contributions of peer selection and peer influence. Correctly attributing the effects of these two factors has

important policy implications since most interventions for reducing risky behaviour among adolescents are implemented at a school level (Ali & Dwyer, 2010).

(v) The special case of social contagion via social media

In the world of social media, social contagion takes on a new, less complex, and narrower meaning:

> "Unlike the broadcasts of traditional media, which are passively consumed, social media depends on users to deliberately propagate the information they receive to their social contacts. This process, called social contagion, can amplify the spread of information in a social network" (Nathan & Kristina, 2014, p. 1).

For example, the social network 'Instagram' is one of the most popular platforms for adolescents and young people, with 44% reporting Instagram to be an important part of their daily lives (Feierabend et al. 2015). Analysis of content shows that it is a major vehicle for the sharing of mental health issues, including depression, eating disorders, and non-suicidal self-injury (NSSI) (Fischer et al. 2015).

Systematic reviews have identified both potential risks and benefits of online activity. On the one hand, it reduces social isolation and offers encouragement, camaraderie, and reduction of self-harm impulses. On the other, it enables, enhances, or triggers potential risks of 'copycat' behaviours such as NSSI, suicide, and eating disorders through normalization of pathological behaviours, or vicarious and social reinforcement of these behaviours (Brown, et al., 2017).

A number of studies have demonstrated the impact that social media can have on emotional contagion. For example, one study[3] demonstrated that interactions with others can alter our mood in the direction of the mood of the person with whom we are interacting. A number of mechanisms - for example, social influence, social selection, and shared external causation – can impact our changes in mood. The phenomenon is prevalent in bounded social networks such as touring orchestras where adolescent musicians have been observed to become more

[3] Block, P., & Burnett Heyes, S. (2020). Sharing the load: Contagion and tolerance of mood in social networks. *Emotion*. Advance online publication. doi: https://doi.org/10.1037/emo0000952

reciprocally similar in mood to their close associates on tour. The observed emotional contagion effects are greater for negative than positive moods.

In a study on Twitter posts[4], the distribution of positive and negative comments varied according to weekends and holidays. Figure 1 shows the trends.

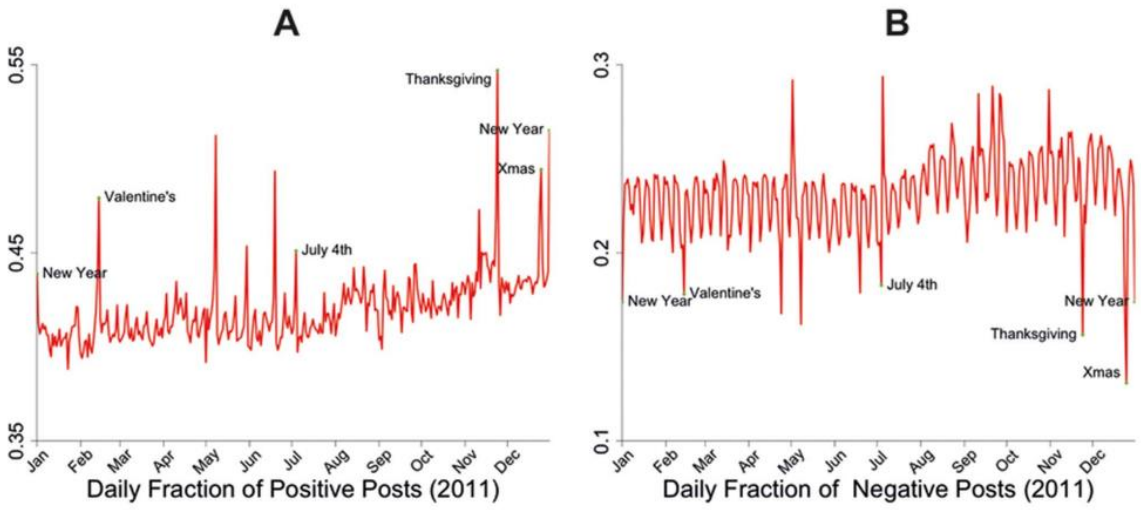

Figure 1

Pain behaviour has also been shown to be affected by the social mechanisms of observation, modelling, vicarious learning, social interaction and media reports. Both placebo and nocebo hyperalgesia have been recorded in patients who observed confederates modelling pain behaviour in response to social stimuli[5].

While many studies show how emotions spread between individuals in direct contact, a novel study demonstrated that online social networks produce emotional contagion in the same way[6]. Using data from millions of Facebook users, the researchers showed that rainfall directly influences the emotional content of their status messages, including messages of friends in other cities who were not experiencing rainfall. Results showed that …"for every person affected directly, rainfall altered the emotional expression of one to two other people,

[4] Golder SA, Macy MW (2011) Diurnal and seasonal mood vary with work, sleep, and daylength across diverse cultures. *Science* 333: 1878–81.

[5] Benedetti, F. (2013). Responding to nocebos through observation: social contagion of negative emotions. *Pain*, *154*(8), 1165.

[6] Coviello, L., Sohn, Y., Kramer, A. D., Marlow, C., Franceschetti, M., Christakis, N. A., & Fowler, J. H. (2014). Detecting emotional contagion in massive social networks. *PloS One*, *9*(3), e90315.

suggesting that online social networks may magnify the intensity of global emotional synchrony" (p. 1165).

EVIDENCE FOR SOCIAL CONTAGION AMONG ADOLESCENTS

In this section, I review the evidence for social contagion among adolescents for four key psychopathologies that arise in adolescence (eating disorders, marijuana use, non-suicidal self-injury, and suicide) and compare the mechanisms of social contagion in these well documented areas with evidence for social contagion in gender dysphoria.

(i) Anorexia nervosa

A number of researchers have identified the central role of social contagion in the development and propagation of anorexia nervosa in adolescent girls (Allison, Warin, & Bastiampillai, 2014). Adolescence is a time in which the focus on oneself becomes intense, and for some, critical and unrelenting. The developing female body constitutes one of the main objects of scrutiny. When this scrutiny is compounded by the collective inspection of all of one's body's flaws, the peer group becomes a powerful crucible for both the development and maintenance of disordered eating.

Intensification of peer influence in closed communities of like individuals, such as schools, inpatient wards, residential units (Huefner & Ringle, 2012), or therapy groups often results in the advocacy of the practices (e.g., self-starvation, compulsive exercise, deceitful practices around eating) associated with anorexia nervosa (Dishion & Tipsord, 2011).

If we add social media and online networks as further sources of influence, affected adolescents can effectively surround themselves exclusively with like minds, thereby normalising cognitive distortions around eating and body image and making recovery very difficult. These effects are further compounded by the high status of thinness in western culture, and an ubiquitous focus on nutrition and exercise. Originally thought to be caused by genetics and pathological family dynamics, this view was revised with the finding, using longitudinal study designs and social network analyses, that same-gender, mutual friends were most influential in the development of obesity in adulthood, with siblings and opposite-sex friends having no effect (Christakis & Fowler, 2007).

(ii) Marijuana use among adolescents

Substance use amongst adolescents is a major public health issue (Fletcher, Bonell, & Hargreaves, 2008), with a population study conducted by the Center for Disease Control and Prevention showing that 10 percent of youths reported using illegal substances before the age of 13, with marijuana the most frequently used substance (Chen, Storr, & Anthony, 2009). Peer influence has long been suspected as a stimulus that amplifies risky behaviours in the social network (Clark & Loheac, 2007; Lundborg, 2006).

Using the National Longitudinal Study of Adolescent Health (Add Health) (n=20,745) representing a sample of adolescents from grades 7-12 in 132 middle and high schools in 80 communities across the USA examined the influence of peer networks in the uptake and continued use of marijuana. The peer group was identified by the nomination of close friends and classmates within a grade were used to identify the broader social network from which friends were chosen (Ali et al., 2011).

Results showed that for every increase in marijuana use of 10 percent in adolescents in a close friend network increased the likelihood of marijuana use by two percent. An increase of 10% in usage in grade peers was associated with a 4.4 percent increase in individual use. Reporting a good relationship with one's parents, living in a two-parent household and being religious were protective against marijuana uptake. When peer selection and environmental confounders were held constant, increases in close friend and classmate usage by 10 percent both resulted in a five percent increase in uptake in individuals within those networks

(iii) Non suicidal self-injury (NSSI)

NSSI is defined as a deliberate self-inflicted attack on one's own body without suicidal intent. It excludes cultural practices such as ear piercing, tattooing, or circumcision, most of which are performed by others. NSSI is defined as socially contagious when at least two people in the same group inflict NSSI within a 24-hour time period. The social contagion of NSSI has been reported in a variety of 'closed' social networks such as in inpatient units, prisons, group homes, and special education schools, as well as in community samples of adolescents, young adults and college students (Jarvi, Jackson, Swenson, & Crawford, 2013).

Adolescence (onset between 12 and 14 years) and early adulthood are high-risk developmental periods for NSSI (Lloyd-Richardson, Perrine, Dierker et al., 2007). Between 14% and 21% of high-school aged adolescents report engaging in NSSI, with higher estimates (30%-40%) for adolescent psychiatric populations (Muehlenkamp, Hoff, Licht, Azure & Hasenzahl, 2008).

More recently, social media has been identified as an important conduit for social contagion of NSSI among young people. Platforms such as Instagram have high-frequency occurrences of pictures from adolescents who have self-harmed. When associations between characteristics of pictures (e.g., seriousness and type of the self-injury) and comments (e.g., supportive, empathic, negative, offers of help) and weekly and daily trends of posting were analyzed, patterns emerged suggesting social contagion. For example, the more serious injuries attracted more views and comments. Social reinforcement, imitation and modelling of NSSI through social media are the possible mechanisms whereby young people increase their risk of engaging in NSSI through digital means (Brown, Fischer, Goldwich, Keller, Young, & Plener, 2018; Fulcher, Dunbar, Orlando, Woodruff, & Santarossa, 2020).

(iv) Suicide

Although social ties are generally protective against loneliness, depression and suicide, social ties can be toxic and can amplify the risk of psychopathology in members of a social network (Christakis & Fowler, 2008). Exposure to the suicidal ideation or suicide attempts of significant others increases the risk of suicidality in other network members (Abrutyn & Mueller, 2014). Experiencing self-harm or suicide at close quarters may erode the emotionally regulating effects of normative moral precepts against such behaviour (Mueller, Abrutyn, & Stockton, 2015). When vulnerable individuals share “ecologically bounded spaces” (p. 205) like schools or the family home, this may increase suicide contagion if social relationships within those spaces are psychopathological. Our emotional connections to members of our social networks is the mechanism through which social learning and the development of normative behaviours and attitudes are built. However, negative emotions are more “contagious” and thus exert a greater impact on members (Turner, 2007).

Celebrity suicides also trigger spikes in suicide rates, with the greater visibility of the celebrity and prolonged coverage of the suicide triggering higher spikes and longer duration of

elevation of rates of suicide amongst fans (Fu & Chan, 2013; Stack, 2005). Durkheim (1951) highlighted the phenomenon of suicide outbreaks or "point clusters" defined as "temporally and geographically bounded clusters" such as gaols, regiments, monasteries, psychiatric wards, and First Nations reservations (Mueller et al., 2015, p. 206). Individuals in such networks share a collective identity that appears to heighten subsequent suicides following the suicide of the first decedent (Niedzwiedz, Haw, Hawton, & Platt, 2014).

Perhaps one of the most compelling studies on the social contagion of suicide is the study of celebrity suicides by Ha and Yang (2021). This study tracked the suicides 10 days before a well-publicised celebrity suicide and then the suicides 10 days after the suicide was reported in the media. Figure 2 presents these data graphically.

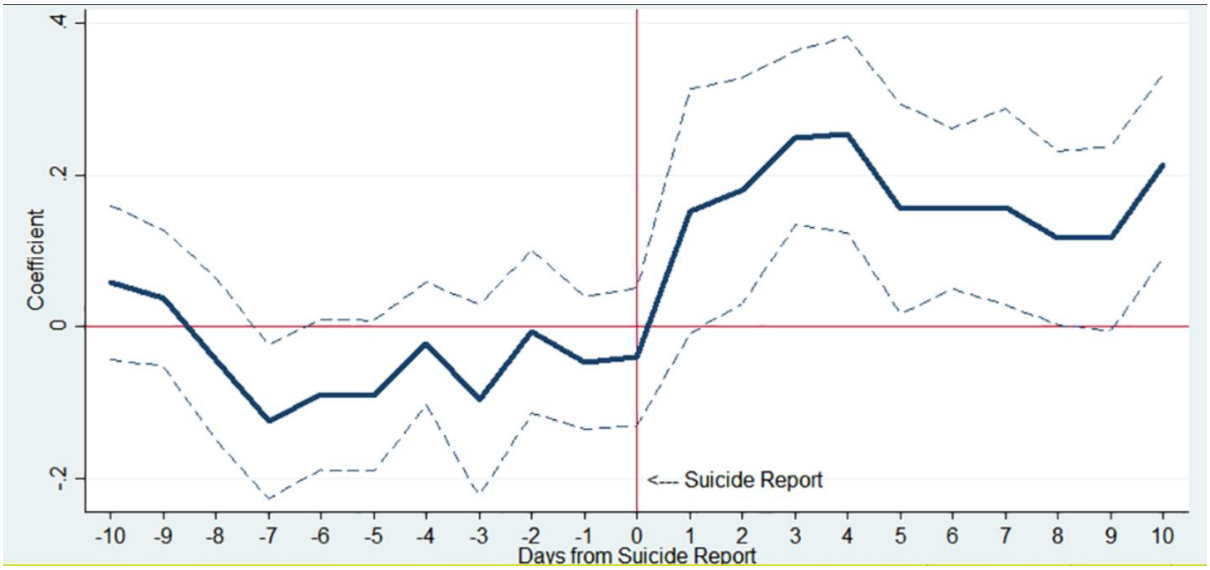

Figure 2[7] Suicide trends before and after reporting of a celebrity suicide

The sharp increase in suicides following celebrity suicide was mostly accounted for by suicides in the 10–29-year age group, the age group. Figure 3 shows the trends.

[7]The *y*-axis indicates an approximate percent change in public suicide by corresponding day

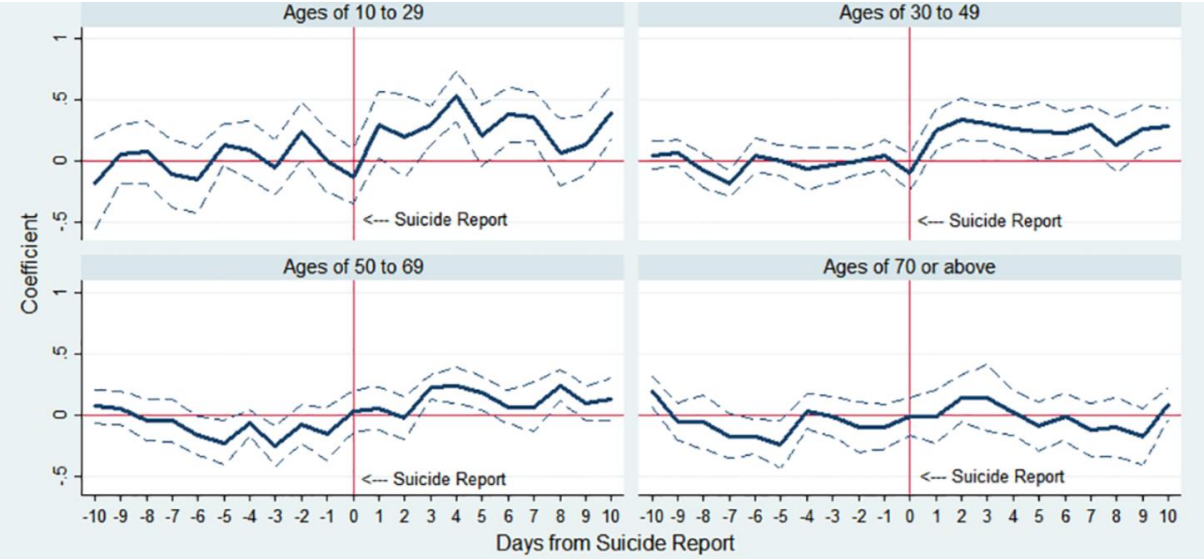

Figure 3 Suicide trends by age group

When the data are segmented by sex (Figure 4), the figures show that females are more susceptible to social contagion than males. The is exactly the same pattern of social contagion we are witnessing in gender dysphoria – young females aged between 10 and 29 years. Is this a coincidence?

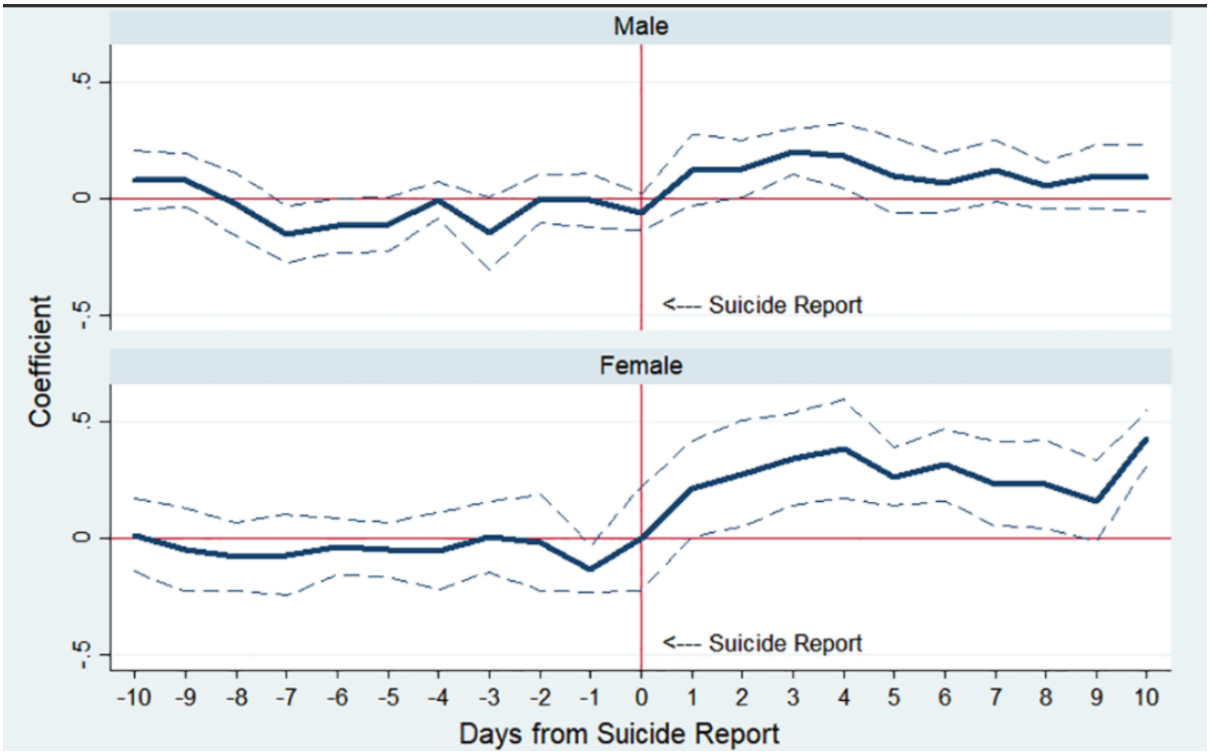

Figure 4 Suicide trends by sex

A well-documented example of a suicide "echo" cluster (an identical suicide cluster occurring within 10 years of a first cluster) occurred in two high schools in Palo Alto that, between them, had suicide rates four to five times higher than the national average. In 2009, three students committed suicide in a nine-month period by stepping in front of a commuter train. A fourth student committed suicide by hanging. In 2013 a mental health survey showed that 12 percent of students from these schools had seriously considered suicide in the previous 12 months. Thereafter, there was another spate of suicides, with three students taking their lives within three weeks of each other. A fourth committed suicide four months later by jumping off a tall building and a fifth followed shortly afterwards by walking in front of a train. Extreme perfectionism and pressure to excel at school, get into Stanford, make a lot of money, and be ostentatiously successful materially and intellectually were assessed to be far too great a burden for the more vulnerable students to withstand.

Using the same data set as the study examining marijuana use but following up four waves of these participants into adulthood, Wave IV assessed suicidality in young adults aged 24-32. This study showed that holding all other psychological risks constant, those young people having a role model who attempted suicide were more than twice as likely to report suicidal ideation in the following 12 months. Participants who had a friend or family member commit suicide were 3.5 times more likely to attempt suicide themselves compared with those who had no close associate attempt or commit suicide in the same 12-month timeframe. These effects were enduring. Young adults who reported an attempted suicide of a role model were more than twice as likely to report a suicide attempt six years after the role model's attempt compared with their otherwise similar peers. Attempting suicide in adolescence increased suicidal ideation and suicide attempts in young adulthood. Significant risk factors for this association included experiencing emotional abuse in childhood, a diagnosis of depression, and a significant other attempting suicide. Thus, suicide contagion appears to be a significant risk factor for suicide in young adulthood but contagion in this study did not require bounded social contexts.

SOCIAL CONTAGION OF GENDER DYSPHORIA

The UK has reported a 4,000% increase in the number of children presenting to gender clinics over the past 10 years. Similarly, Sweden has reported a 1,500% in the same time period.

Commentators on the burgeoning incidence of young people claiming that they are transgender assert that peer contagion may underlie this ominous trend. However, it has rarely been systematically studied either theoretically or empirically. Given the strong evidence of peer contagion in suicide, substance abuse and eating disorders, especially among adolescents, the role of peer contagion in gender dysphoria demands urgent attention.

If we examine the gender dysphoria epidemic in social network terms, we see several features operating. It is an open-system network with nodes and ties expanding across the oceans to the US, UK, Asia, Europe, Scandinavia, and Australia. Most countries are reporting sharp increases in the number of people seeking services and treatment for gender dysphoria. Many are ramping up services and setting up new gender clinics to cope with demand. This network is highly centralised with only one voice – the transactivist lobby - being heard above the desperate whispers of terrified parents and horrified academics, doctors, psychologists and psychotherapists. Opinion leaders operating at the centre of these networks are very influential. The level of density in a network has two effects – firstly, it enhances the circulation of information between members and secondly, it blocks the introduction of dissenting ideas and evidence (Iyengar, Van den Bulte, & Valente, 2011).

The field is too young to have attracted researchers to undertake social network analyses to assess peer contagion effects in gender dysphoria. Hence, formal empirical studies have not yet been conducted. However, there is evidence from several sources that peer contagion may be a relevant factor in the sharp increases in young people presenting with gender dysphoria.

(i) Low gender typicality, peer victimization, ingroups and the trans-lobby

Low gender typicality (i.e., perceived lack of fit within one's binary gender) has a significant impact on social acceptance within one's peer group (Sentse, Scholte, Salmivalli, & Voeten, 2007). It is strongly associated with adjustment difficulties, behavioural problems, lower self-esteem, and increased internalizing disorders (e.g., anxiety, depression) (Smith & Juvonen, 2017). As children progress to adolescence, peer as opposed to parental acceptance becomes paramount. Peers therefore take over the role of gender socializing agents from parents (Blakemore & Mills, 2014). Adolescent peers tend to be critical of behaviours, dress,

mannerisms and attitudes that are not gender typical as a way of policing and reinforcing gender norms and respond with criticism, ridicule, exclusion and even intimidation of non-conformers (Zosuls, Andrews, Martin, England, & Field, 2016). Research shows that the problems accruing to low gender typicality are mediated by peer victimization and that reducing peer victimization may ameliorate these difficulties (Smith & Juvonen, 2017). Conversely, peer acceptance mediated the self-worth of gender non-conforming 12- to 17-year-olds (Roberts, Rosario, Slopen, Calzo, & Austin, 2013). Gender non-conformity and gender atypicality have also been associated with higher physical and emotional abuse by caregivers (Roberts, Rosario, Corliss, Koenen, & Austin, 2012). Mental health is difficult to sustain in the face of caregiver abuse and peer bullying and victimization (Aspenlieder, Buchanan, McDougall, & Sippola, 2009). Indeed, gender non-conforming and gender atypical youth are at higher risk of depression, anxiety and suicidality in adulthood (Alanko et al., 2009).

It is tempting to speculate that these groups of young people, searching for homophily (i.e., like peers) started to exaggerate their points of difference from their gender-conforming peers rather than to hide and minimize them to avoid being bullied and excluded. In so doing, they left the "outgroup" of nonconformers and formed an ingroup of extreme gender-nonconformers, transcending the gender barrier altogether and declaring themselves transgender. Suddenly, the discomfort and fear of not being gender typical becomes a virtue and rather than fearing the disapprobation of their peers, their open revolt in declaring themselves transgender is valorised by a politically powerful transactivist lobby. One would expect that gender atypical children who feel both internal and external pressure to be gender conforming would experience greater discomfort (Carver, Yunger, & Perry, 2003) and therefore be more susceptible to the message of trans activism.

Ingroups behave in stereotypical ways with respect to outgroups – they favour ingroup characteristics, assigning more positive attributes to its members and derogating outgroups in order to enhance the status of their ingroup (Leyens et al., 2000). It is not surprising, then, that members of the transgender ingroup exaggerate the characteristics of the "trans" gender they take on – becoming more "feminine" or "masculine" than heteronormative groups of cismen and ciswomen. Transactivist groups have proliferated and consolidated in a short time frame by exploiting the characteristics of ingroups and outgroups. For example, social

projection (i.e., the belief that other members of the group are similar to oneself) has been a powerful integrating process that simultaneously creates protection for its own members and distance from outgroup members, using the formula, "if you are not with us, you are against us" – those disagreeing with the ideology of the trans-lobby are labelled "transphobic" and publicly denounced.

(ii) Rapid onset gender dysphoria (ROGD) and the role of social media

The upsurge in rapid onset gender dysphoria (ROGD) tends to occur mostly in girls at around the age of 14 years, which is an age identified by developmental psychologists to be particularly susceptible to peer influence (Steinberg & Monahan, 2007). For example, a study of peer contagion for risky behaviours found that exposure to risk-taking peers doubled the amount of risky behaviour in middle adolescents, increased it by 50% in older adolescents and young adults, and had no impact on adults (M. Gardner & Steinberg, 2005). This group of young people were likely to belong to peer groups in which one or more of their friends had become gender dysphoric or transgender identified. Their coming-out announcement to parents also tended to be preceded by recent increases in their daughters' social media and internet usage. It is only a small step to understanding the social contagion of ROGD in this age group.

Lisa Littman (2018) canvassed the perceptions of parents who had children who displayed ROGD during or just after puberty. There were 256 respondents, of whom 83% had daughters, with a mean age of 15.2 years when they declared themselves transgender,41% of whom had previously expressed a non-heterosexual sexual orientation, and 62.5% of whom had received a diagnosis for a mental health disorder (e.g., anxiety, depression) or a neurodevelopmental disability (e.g., autism spectrum disorder). Thirty-seven percent (37%) of these young people belonged to peer groups with other members identifying as transgender. Parents also reported a decline in their child's mental health (47%) and relationship with parents (57%) after declaring themselves transgender. Thereafter, they preferred transgender friends, websites, and information coming from the transgender lobby.

An indicative case study was written up in an article for *The Atlantic* by Jesse Singal (2018), in which a 14-year-old girl decided she must be trans because she was uncomfortable with her body even after she restricted her food intake, was finding puberty uncomfortable, had

difficulty making friends, was feeling depressed and was lacking in self-confidence. Against this backdrop of woes, she came across MilesChronicles[8], the website of an omnipotent and histrionic transboy, now a young transman. Watching this video resulted in Claire pouring all her sadness and unease about herself into the "realisation" that she was really a "guy." Miles made transitioning appear easy and simple, was effusive in his praise of his new self and supportive of others to follow suit. This is a very common scenario reported by parents of teenage girls with ROGD.

Such websites, all easily accessible to vulnerable adolescents, can have a very persuasive effect on viewers. Recent studies show that contagion is enhanced when the influencer is perceived to have high credibility and reduced when the influencer is perceived to have low credibility. A similar effect is observed if the influencer belongs to an out-group or an in-group (Andrews & Rapp, 2014). Miles is the quintessential trans pinup icon with a "You can be just like me if you transition!" message.

Following YouTube posts and social media with respect to the transgender debate over the past few years, I have noticed that posts that depict young people struggling with their gender identity or questioning their decision to take puberty blocking agents and cross-sex hormones, or to undergo what is euphemistically called sex reassignment surgery are rapidly taken down so that only a homogenous message that matches the strident messaging of the transactivist lobby is on display in the ether.

A recent Swedish study[9] tracked referrals and attendances at gender clinics of young people following major media events related to transgender health care in 2019. One event was positive, and two media events [i.e., the airing of "The Trans Train and the Teenage Girls,"[10] a 2-part documentary series broadcast on April 3, 2019 (event 2), and October 9, 2019 (event 3)] determined as negative portrayed gender transition as dangerous and damaging. In the three months following one of the negative media events, referrals decreased by 25% overall – there was a 32% reduction in female referrals - and by 25% for young people aged 13-18

[8] MilesChronicles - YouTube

[9] Indremo, M., Jodensvi, A. C., Arinell, H., Isaksson, J., & Papadopoulos, F. C. (2022). Association of media coverage on transgender health with referrals to child and adolescent gender identity clinics in Sweden. *JAMA network open*, *5*(2), e2146531-e2146531.

[10] . Mission: Investigate. The trans train and the teenage girls. Tranståget och tonårsflickorna. Video in Swedish. Swedish Public Service Television Co. April 3, 2019. Accessed December 28, 2021. https://www.svtplay.se/video/ 21717158/uppdrag-granskning/uppdrag-granskning-sasong-20-avsnitt-12

years. On the contrary, increased positive media coverage of trans issues resulted in an increase in referrals to gender clinics[11].

Nonetheless, a statement released in August 2021 by the Coalition for the Advancement & Application of Psychological Science (CAAPS)[12] called for the elimination of the use of Rapid-Onset Gender Dysphoria (ROGD), "given the lack of rigorous empirical support for its existence," although this evidence abounds (see next section on empirical evidence). Deplorably, CAAPS did not see fit to question the exponential increase in the adolescent trans phenomenon, both in declarations and referrals to gender clinics across the globe[13] nor how these new referrals differed substantially in profile from previously recorded demographics of transgender young people along dimensions of age of onset, sex ratio, comorbid mental health issues[14] and clustering.

EMPIRICAL EVIDENCE

In recent decades, there has been an unmistakably sharp increase in the population estimates of young people identifying as transgender. A retrospective analysis[15] (Figure 5) of the pattern of referrals to gender clinics from 1976 to 2011 is instructive in demonstrating the shifting

[11] Pang KC, de Graaf NM, Chew D, et al. Association of media coverage of transgender and gender diverse issues with rates of referral of transgender children and adolescents to specialist gender clinics in the UK and Australia. JAMA Netw Open. 2020;3(7):e2011161. doi:10.1001/jamanetworkopen.2020.11161

[12] https://www.caaps.co/rogd-statement

[13]de Graaf, N. M., Giovanardi, G., Zitz, C., & Carmichael, P. (2018). Sex ratio in children and adolescent referred to the Gender Identity Development Services in the UK (2009–2016) [Letter to the Editor]. *Archives of Sexual Behavior, 47,* 1301–1304;

Frisén, L., Söder, O., & Rydelius, P. A. (2017). [Dramatic increase of gender dysphoria in youth]. Lakartidningen. Retrieved from http://lakartidningen.se/Klinik-och-vetenskap/Klinisk-oversikt/2017/02/Kraftig-okning-av-konsdysfori-bland-barn-och-unga/.

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Littman, L. (2018). Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria. *PLoS ONE, 13*(8), e0202330.

[15] Wood, H., Sasaki, S., Bradley, S. J., Singh, D., Fantus, S., Owen-Anderson, A., ... & Zucker, K. J. (2013). Patterns of referral to a gender identity service for children and adolescents (1976–2011): age, sex ratio, and sexual orientation. *Journal of Sex & Marital Therapy*, *39*(1), 1-6.

patterns of presentations of young people to gender clinics. The sample comprised 577 children aged 3-12 years and 253 adolescents aged 13-20 years. Prior to around 2000, the child referrals greatly exceeded referrals of adolescents. After that time, there was a steep and significant increase in adolescents. Also of interest is that the overall sex ratio of male to female children was 4.5:1 (boys:girls). For three-year-olds the ratio was 33:1 (boys:girls). The ratio dropped to 3.4:1 in the last cohort of children (2008-2011). The adolescent sex ratios were at parity but by 2008-2011 girls exceeded boys.

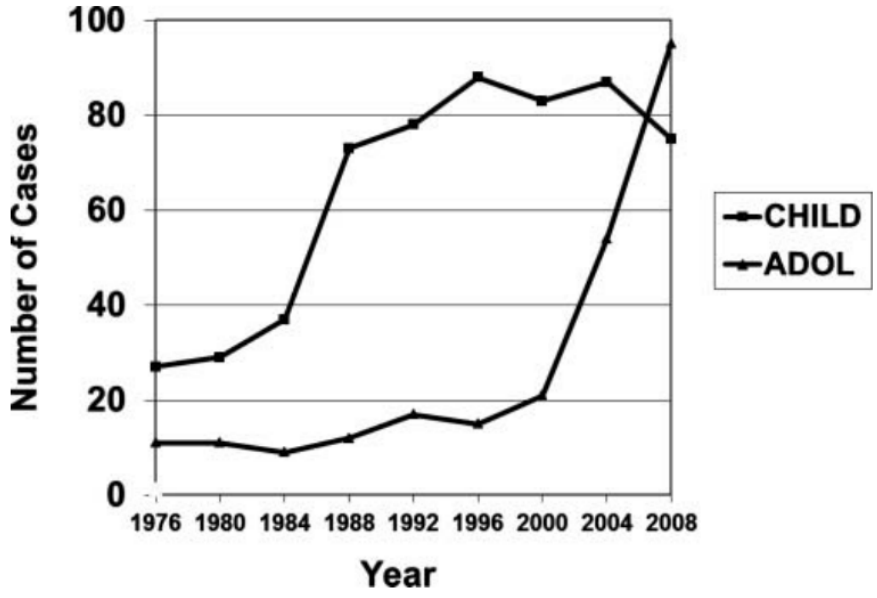

Figure 5 Number of children and adolescents referred to gender clinics 1976-2011)

For the adolescents in this study, data on sexual orientation were available for 248 participants. Using standardized measures[16] to assess heteroerotic and homoerotic sexual orientation in fantasy, 76% of the girls were classified as homosexual compared with 57% of boys. These figures vastly exceed population estimates of homosexuality and begs the question as to whether many young people presenting to gender clinics are confused about their sexual orientation, experience socialized and/or internalized homophobia or do not understand the difference between gender identity and sexual orientation.

[16] Zucker, K. J., Bradley, S. J., Owen-Anderson, A., Kibblewhite, S. J., Wood, H., Singh, D., & Choi, K. (2012). Demographics, behavior problems, and psychosexual characteristics of adolescents with gender identity disorder or transvestic fetishism. *Journal of Sex & Marital Therapy*, *38*, 151–189.

Another study, a meta-regression of population-based probability samples provides compelling evidence of this trend, where estimates have more than doubled in the space of eight years from 2007 to 2015 (See Figure 6).

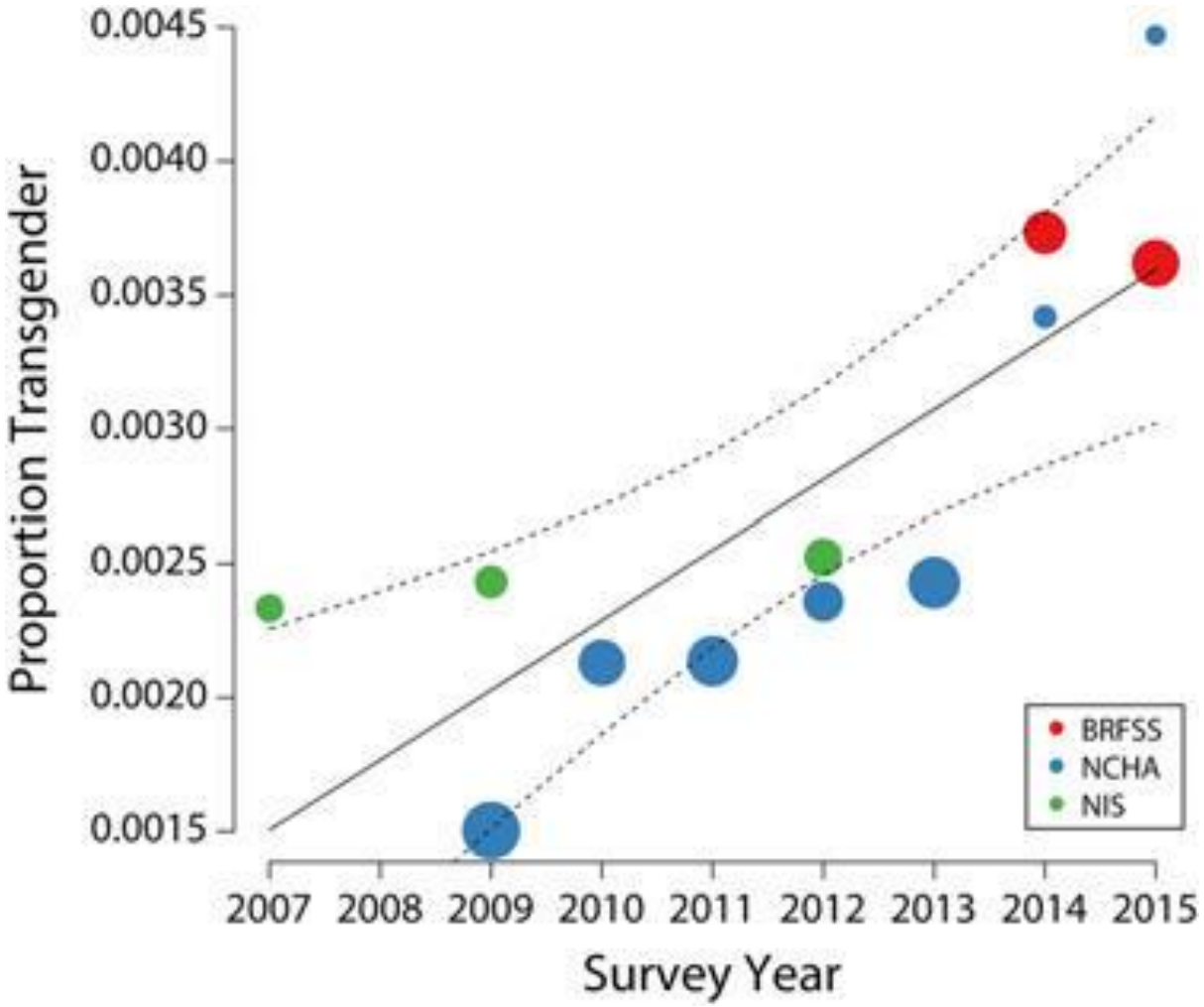

Figure 6[17] [Source: Meerwijk & Sevelius (2017)]

Similarly, upward trajectories of enrolments in GD clinics have been observed in the UK and Australia. Figure 7 summarizes the trends.

[17] Meerwijk, E. L., & Sevelius, J. M. (2017). Transgender population size in the United States: a meta-regression of population-based probability samples. *American Journal of Public Health, 107*(2), e1-e8. https://ajph.aphapublications.org/doi/pdfplus/10.2105/AJPH.2016.303578

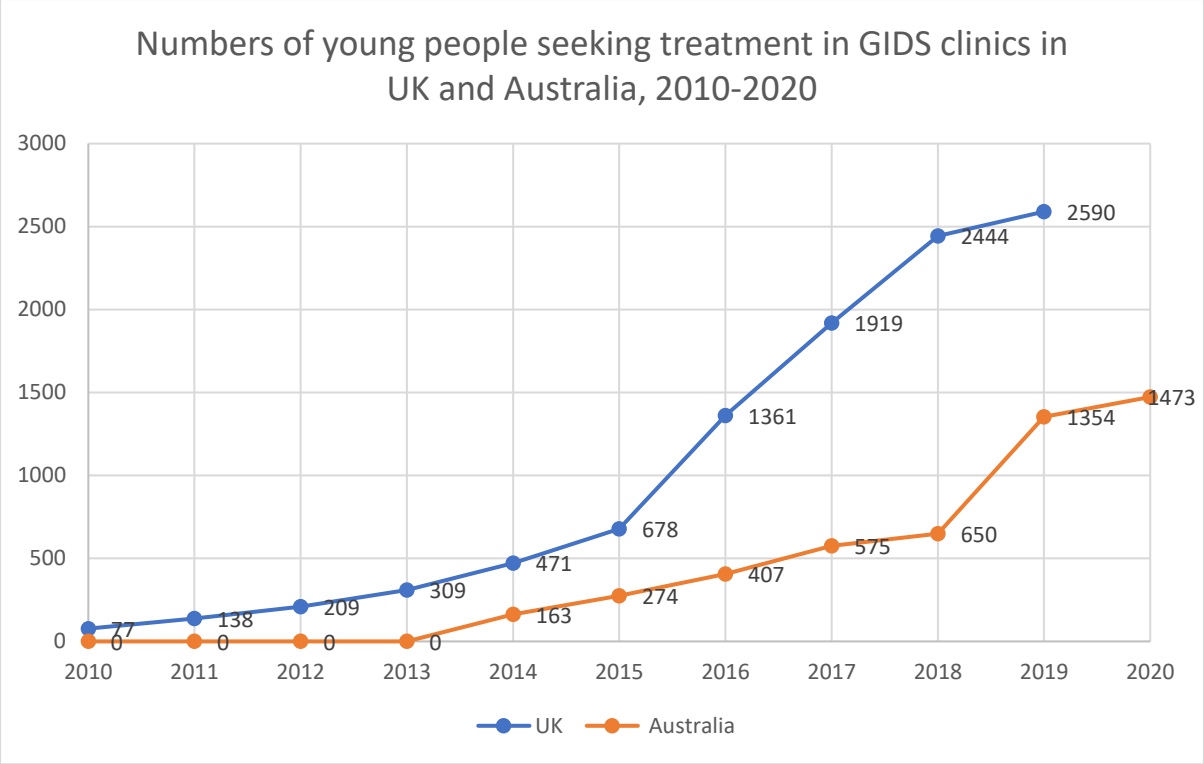

Figure 7

Source: Kenny, D.T. (2021). Australian data provided by the gender clinics under freedom of information applications

Perusal of the UK graph indicates a doubling of the number of referrals in 2015-2016 compared with the previous year. There is a continuous, but less steep increase until 2017, which is followed by a slowing of referral growth rates between the two years 2017-2018 and 2018-2019.

In each of these samples, these numbers would comprise two groups of young people, a core group of "actual" cases and the additional cases created by social contagion. Within the actual cases, there would be the group who declared themselves and a group of latently gender dysphoric young people who have not felt able to declare themselves until recently because of greater community acceptance and support from the transgender lobby and social media. This latter group of "actual" cases and the ROGD group have both been affected by social contagion.

Further analysis is required to determine the nature of the clustering of these increased numbers. In school-aged children, one would expect to see multiple cases in particular high schools. If gender dysphoria referrals occurred independently of each other, one would

expect to see referrals per high school follow a Poisson distribution, in which the variance is equal to the mean. A clustering effect would be hypothesised if the variance were greater than the mean. The strongest indicator of social contagion would occur if the ROGD young people showed strong clustering effects. Evidence that this may in fact be the case is provided by the distribution of new referrals by age and sex in the GIDS sample (Tables 2 and 3), where new referrals in the 12–16-year group far exceeds those in younger and older age groups.

Table 2 Age at referral to GIDS, UK in 2018-20

Age at referral	Number of referrals
3 and 4	10
5	21
6	21
7	42
8	34
9	43
10	59
11	78
12	135
13	331
14	511
15	529
16	474
17	88
18	30

Source: NHS (2019)

Age groups segmented by sex show much larger proportions of females seeking gender transition – for 13-year-olds, girls accounted for 86% of referrals, for 14-year-olds, girls accounted for 82% of referrals and for 15-year-olds girls accounted for 76% of referrals.

Table 3 GIDS figures from England by sex at birth

Age	2019-20, England only		
	Assigned sex at birth		
	AFAB	AMAB	Not Known
3 and 4	<5	<5	0
5	5	12	0
6	7	9	0
7	13	16	<5
8	17	24	<5
9	24	21	<5
10	22	32	0
11	52	23	6
12	127	37	5
13	270	45	11
14	404	90	16
15	470	152	31
16	350	162	24
17	101	67	10
18+	30	28	<5

Data from Australia (Figure 8) also show an upward trajectory in the number of children enrolled in gender clinics in the five states of Australia that offer a gender service over the period 2014-2020.

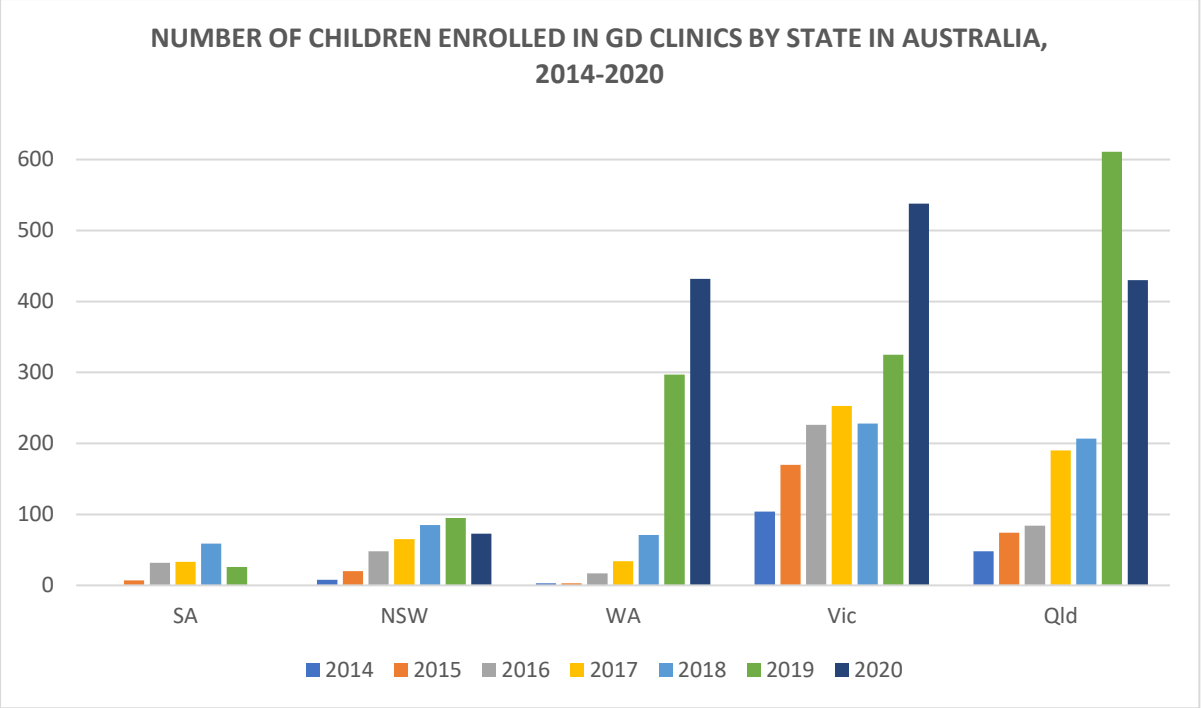

Figure 8

Source: Kenny, D.T. (2021). Data provided by the gender clinics under freedom of information applications

The noteworthy feature of this graph is that three states (WA, Queensland and Victoria) show similar increases over the five-year study period (2014-2020), although Queensland showed a downturn in 2020. While figures in NSW increased, the magnitude of absolute numbers was significantly lower than for the other states. Overall, Victoria had the largest numbers. It is also a state where the trans lobby has been particularly vocal, where the concept of the "safe schools" policy was conceived and implemented, and where the gender clinic at the Royal Children's Hospital, Melbourne has assumed the mantle of trailblazer in the gender transition enterprise in Australia.

Figures from the Nordic countries[18] show very similar patterns as those described above. See for example, Figure 9 below.

[18] Kaltiala, R., Bergman, H., Carmichael, P., de Graaf, N. M., Egebjerg Rischel, K., Frisen, L., ... & Waehre, A. (2020). Time trends in referrals to child and adolescent gender identity services: a study in four Nordic countries and in the UK. *Nordic Journal of Psychiatry*, *74*(1), 40-44.

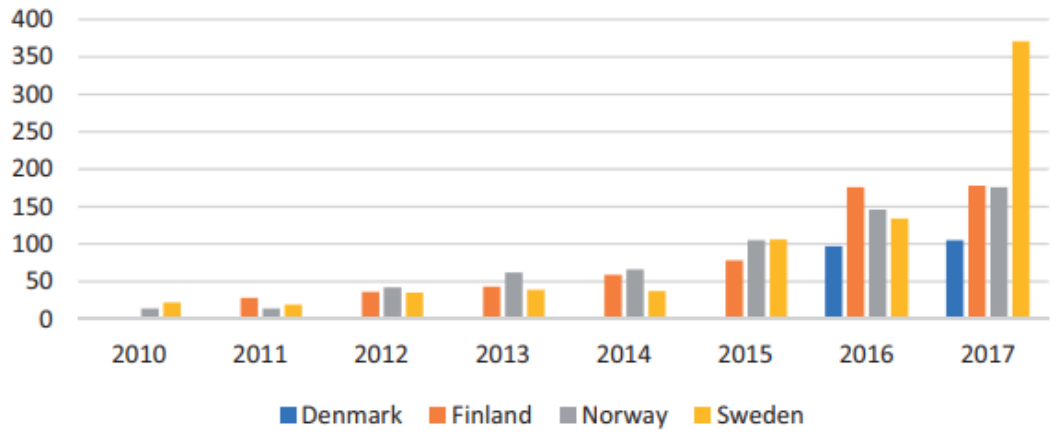

Figure 1. Referrals to child and adolescent gender identity services 2010–2017 in four Nordic countries.

Figure 9

Table 4[82] shows the dramatic increases in just a six-year time frame between 2011 and 2017 in the four Nordic countries and the UK (for comparison).

Table 1. Population adjusted numbers of referrals to gender identity services for minors in four Nordic countries and the UK in 2011 and 2017.

	2011	2017
Denmark[a]	–	9.0/100,000 (1/11,000)[c]
Finland	2.63/100,000 (1/38,071)[b]	16.7/100,000 (1/10,155)
Norway	1.24/100,000 (1/80,643)	15.6/100,000 (1/6414)
Sweden	0.90/100,000 (1/111,663)	17.4/100,000 (1/5719)
UK	1.25/100,000 (1/79,588)	17.5/100,000 (1/5078)

These population adjusted rates are orders of magnitude higher than those observed in transgender adult populations[19]. Rapid changes in any relevant biological factors that could possibly account for these trends across global populations appears both unlikely and implausible.

Figure 10[20] shows the total number of young people taking puberty blockers and cross-sex hormones over the seven-year study period across Australia.

[19] Zucker KJ. (2017). Epidemiology of gender dysphoria and transgender identity. *Sex Health,* 14(5):404–411.

[20] NSW supplied "0" in each data cell for each of the seven years. A follow-up inquiry to Sydney Children's Hospital Network (Ref No: SCHN18/7854, 6/8/19) indicated "Sydney Children's Hospitals Network (SCHN) does not provide cross sex hormones at The Children's Hospital at Westmead. [O]ccasionally SCHN sees a patient in a cross-over transition phase who has had stage two treatment initiated by an adult physician, as The Children's Hospital at Westmead pharmacy is still providing the patient's treatment in that cross-over phase. However,

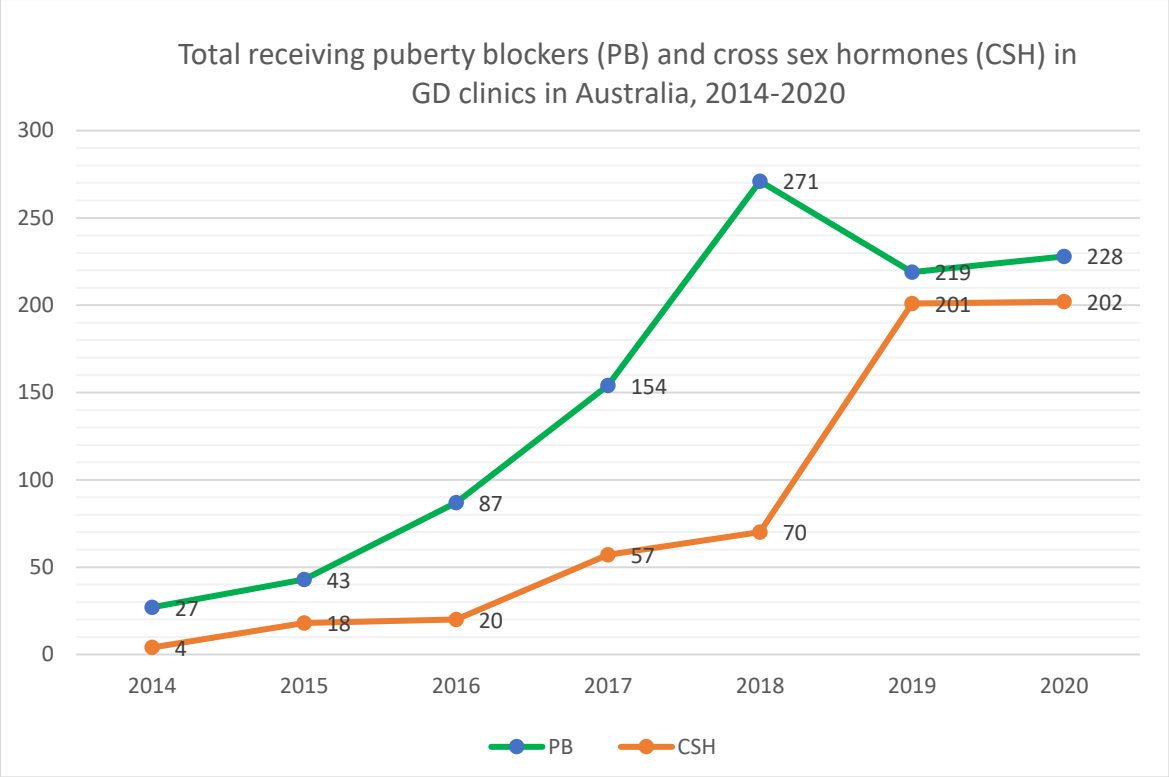

Figure 10

Source: Kenny, D.T. (2021). Data provided by the gender clinics under freedom of information applications

Finally, in case we are left in any doubt about why these numbers have been rapidly increasing over the past 10-15 years, Figure 11 shows the increase in the number of gender clinics across the USA in the past 15 years, from 2007 to 2022.

their primary care at this stage is under the adult physician who prescribes the stage two therapy. The zero-response provided in the GIPA Notice of Decision is correct but that there may be instances in which children are receiving active stage 2 treatment elsewhere while still attending The Children's Hospital at Westmead clinic".

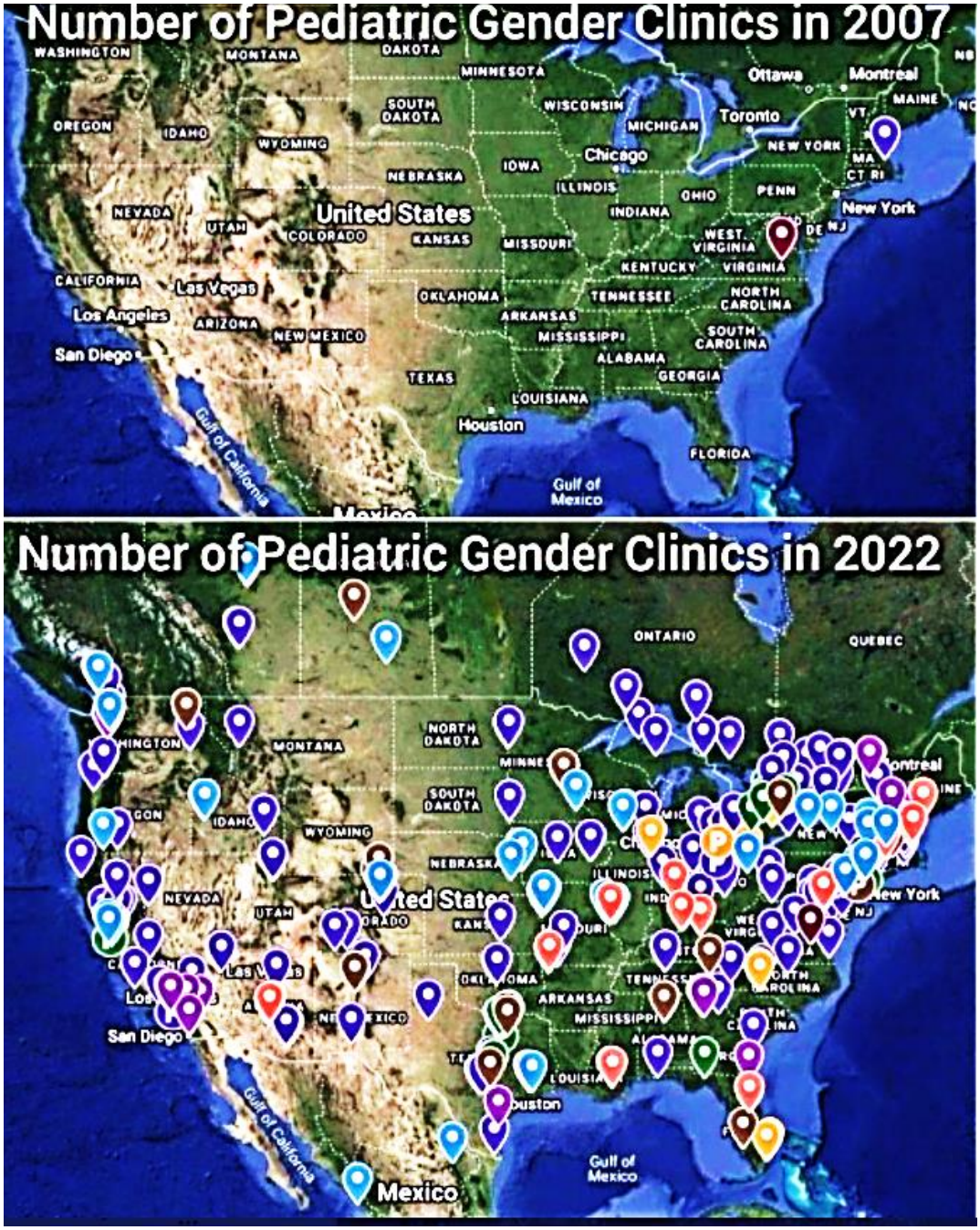

Figure 11 Number of gender clinics in USA and Canada in 2007 and 2022.

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CHAPTER 2

THERAPY FOR TRANSGENDER DECLARING ADOLESCENTS

Abstract

In this chapter, I present a detailed account of exploratory psychotherapy with an adolescent and a number of case studies of young people whom I have treated for gender dysphoria. Through respectful engagement, building of the therapeutic relationship and establishment of rapport and safety, these young people gradually reveal their developmental struggles and strivings, their complex and conflicted interpersonal relationships and growing understanding of their own intrapsychic process that will hopefully equip them to make informed decisions about their lives when they reach the age of majority. To deny young people the opportunity to engage in exploratory psychotherapy when they declare a transgender identity would risk exposing them to iatrogenic harm, which they may come to deeply regret. First, I present a detailed case study demonstrating how family, developmental history and social influences intersect in the formation of a transgender identity. I then present summaries of other cases to demonstrate how factors such as developmental psychopathologies and struggles with sexual orientation problematize young people's endeavours to understand themselves.

INTRODUCTION

The Cass Review[21] into the GIDS (Gender Identity Development Services) in the UK concluded:

> Primary and secondary care clinicians have reported to the Review that they are nervous about seeing children and young people with gender-related distress because of lack of evidence and guidance about appropriate management, and the toxicity of the societal debates. Some clinicians also reported feeling unable to undertake the process of assessment and differential diagnosis that would be the norm in their clinical practice because they perceived that there is an expectation of an unquestioning affirmative approach. They felt that this was at odds with a more open and holistic evaluation of the factors underpinning the young person's presentation, and consideration of the full range of possible support and treatment options.

[21] https://www.bmj.com/content/376/bmj.o629

The report also acknowledges that received medical wisdom about the treatment of young people with gender dysphoria is inappropriate and inapplicable to the young ROGD people currently presenting to gender services, in particular adolescent females who are now accepted to be influenced by the forces of social contagion. These include those with mental health issues, various forms of neurodiversity, and those from dysfunctional and disrupted families.

In a sample of 56 children appearing before the Family Court in Australia for permission to proceed to cross sex hormones, 25 of 39 cases in which family constellation could be discerned lived in single parent families or foster care, with only 14 from two parent families. In this same group of 56 children, 50% had a diagnosed psychological disorder, including six with autism spectrum disorder (ASD), major depression, anxiety, oppositional defiance disorder (ODD), ADHD, or intellectual disability. A recent study has shown a higher prevalence of gender dysphoria in those with ASD[22].

In a sample of 105 gender dysphoric adolescents and using the Diagnostic Interview Schedule for Children (DISC), anxiety disorders were found in 21%, mood disorders in 12.4%, and disruptive disorders in 11.4% of the adolescents. Males had greater psychopathology compared with females, including comorbid diagnoses[23].

Case studies from the public domain

In the early stages of attempting to understand young people identifying as transgender, I studied a large number of publicly available posts that young people had shared on the internet. Close reading of these scripts assisted my own theorizing about the psychodynamics of the transgendering process. Here are some examples:

Alex

Alex (a biological female), aged 12, petitioned the Family Court of Australia to permit her to transition. The Court made orders allowing the commencement of puberty-suppressing

[22] van der Miesen, A. I. R., Hurley, H., Bal, A. M., & de Vries, A. L. C. (2018). Prevalence of the wish to be of the opposite gender in adolescents and adults with autism spectrum disorder. *Archives of Sexual Behavior*. doi: 10.1007/s10508-018-1218-3

[23] de Vries, A.L.C, Doreleijers, T. A. H., Steensma, T. D., & Cohen-Kettenis, P. T. (2011). Psychiatric comorbidity in gender dysphoric adolescents. *Journal of Child Psychology and Psychiatry, 52*(11), 1195-1202. doi:10.1111/j.1469-7610.2011.02426.x

hormone medication because of the intense distress Alex felt at her emergent feminine body. At 17, the Court granted permission for a double mastectomy. Psychiatric evidence indicated a traumatic childhood, in which Alex's mother rejected her completely. However, she had a close and idealised relationship with her father, who wanted her to be a boy and who treated her as such, even teaching her to urinate in the standing position. He died suddenly when Alex was six. Psychiatric evaluation revealed significant early trauma and concluded that "Alex's cross-gender identification appears to have emerged in the context of an idealised, physically close relationship with her father, rejection and abandonment by her mother, and her father's desire for her to be a male … Her investment as male simultaneously expresses anger towards her mother and maintains closeness with her dead father... in the context of her incomplete mourning for him"[24].

Ariel

Ariel, transfemale, aged 13, who had commenced puberty blockers, insisted on being called by the name of a different Disney princess every day, until she settled on the name, Ariel:

> I remember… when everyone was talking about having babies and it really makes me upset. I don't want to tell them to stop talking about it… but it hurts my feelings when they're talking about it… I am like a girl, but can I have the pain of labour? For a lot of people, it is hard for them to understand, but I don't want to burden them with that. Sometimes I just walk away and sometimes I try to get into the conversation, but it's hard". Her remarkably perceptive friend then says, "You can get so close to being a girl but you can't get to that exact point. Is that what upsets you?" Ariel says "Yeah, that's exactly how I feel, the thing with having a baby, I can never be fully there. It is a natural thing that happens. I buy a bra but it's not to hold in my boobs – it is an illusion. It felt like an act, so I feel lost sometimes[25].

Ariel articulates her lived experience of impersonating a girl rather than becoming one or being one. None of the culturally feminine ideals and products with which she surrounds

[24] Kissane, K. (2009). Young people, big decisions. Retrieved 21 May 2018, from https://www.smh.com.au/national/young-people-big-decisions-20090504-arxc.html

[25] (https://www.youtube.com/watch?v=sTfQ44HFu6k

herself can fully convince her that she is female. She acknowledges that it is an "illusion", "an act", and she feels "lost" that a true gender identity eludes her.

A transmale (unnamed)

A transmale, aged 13, had this to say about the role of the internet in his "coming out as trans":

> The internet is the best place for trans people, it is the best place you can go to if you are scared about talking to anyone. TUMBLR Oh, My God! TUMBLR! Youtube too. That's how I found out that I was trans – it was from a youtube video[26]…

This young person appeared to have no caring, empathic adult with whom to share his identity/gender confusion and turned to the internet to seek out like minds, that is, to find his "true" in-group. Seeking and finding membership in a valued in-group enhances self-esteem and feelings of belonging and affiliation (Buck, Plant, Ratcliff, Zielaskowski, & Boerner, 2013). Feeling alienated and marginalised in the "real" world, the virtual world of the internet appears to provide a substitute community missing in the child's real world. However, there is no opportunity to reality-test in such a process, and this young person may have commenced down a dangerous path in order to experience social inclusion. One can also characterize this process as social contagion, since it is likely that the transgender in-group comprise members who are also seeking inclusion and validation in an in-group. For another example of this process[27], in which a young boy says that the internet is "hugely important" particularly when parents are disapproving.

John

John, age 16, transmale,

> For as long as I can remember, I always felt male. I did come out to my parents as lesbian, sometime around seventh grade. I thought, "Oh well, I seem to wear boys' clothes all the time, I feel masculine, and I realise that I like girls, so then I thought, "OK, I must be a lesbian. That was tough. My dad, he wouldn't have any part of it. He said, "This is not a world that you are going to be a part of." Then, when I got to my

[26] https://www.youtube.com/watch?v=sTfQ44HFu6k
[27] https://www.youtube.com/watch?v=eYOuqgoxAik

> freshman year, I identified as trans, so I came out to them again as a transmale. I always had a hard time making friends. I was a very strange kid. I would just feel bad because every day I went to school, I felt like everybody wanted me to go; nobody wanted me there. One of the girls said, "Man, you are an ugly dyke. You are a lesbian." I went from shaky, to unstable, to almost impossible. I started drifting off to a very violent place in my head. I had thoughts of harming my family. It got so bad, I felt like a threat to my family, and to myself. One night, I went down to my mom and said that I wanted her to take me to a hospital; I wanted to get locked up.

This transcript demonstrates the confusion experienced by some young people with gender dysphoria as to their sexual orientation and gender identity, with some believing they are transgender when they are in fact homosexual/lesbian. Existing theories of transgender also conflate these two dimensions, based as they are on a "coming out" model developed for people with lesbian/gay orientations. There has also been a tendency to conflate gender identity with sexual orientation in seeking causal explanations[28].

From these and my own cases, I developed the following intake assessment.

INTAKE ASSESSMENT

A very careful intake assessment of every young person presenting with gender concerns needs to be undertaken. I have developed the following:

i. **Family constellation**, family conflict /dysfunction, marital and sibling dynamics

ii. **Trauma,** physical, emotional, and/or sexual abuse, attachment disorders

iii. **Psychological evaluation** – ADD/ADHD, ASD, learning disability, self-harm, suicidality, suicide attempts, anxiety, depression, incipient BPD, and psychosis

iv. History of **body dysmorphia**, eating disorders

[28] Katz-Wise, S. L., Budge, S. L., Fugate, E., Flanagan, K., Touloumtzis, C., Rood, B., . . . Leibowitz, S. (2017). Transactional pathways of transgender identity development in transgender and gender-nonconforming youth and caregiver perspectives from the Trans Youth Family Study. *International Journal of Transgenderism, 18*(3), 243-263.

v. **School life experiences** e.g., attitude towards school, peer rejection, bullying, truanting, academic performance, post school aspirations

vi. **Cognitive immaturity, concrete thinking, cognitive rigidity, and cognitive distortions**, lack of understanding or misunderstanding of gender ideology and capacity to critically review it (given the illogical and scientifically unsound basis of the ideology)

vii. Perceptions and misperceptions of **gender roles**

viii. **Degree to which there is understanding of the gravity and irreversibility of medical/surgical transition**; what gender affirmation treatment entails, and the consequences of treatment (e.g., infertility, sexual dysfunction, complications of cross-sex hormones and surgery, lifelong patienthood, relationship complexity).

ix. **Sexual experience** history – sexual relationships, sexual abuse experiences, sexual knowledge, sexual anxiety

x. Emerging awareness of **ego dystonic sexual orientation** - > internalized homophobia

xi. **Social contagion** (influence of social milieu e.g., schools, gender clinics, internet, online transgender communities)

xii. **Systemic function of ROGD** e.g., defiance of parents, finding an "in group," being "seen", denying the development of their sexed bodies, fear of adulthood, fear of sexual relationships.

Psychodynamic Formulation

Identity is not hard-wired – it develops in a social world where the young person experiences attachments, trauma, abuse, or misperceives the meaning of experiences because of cognitive immaturity or concrete thinking. Clinicians need to explore identifications (I want to be like…) and dis-identifications (I do not want to be like…) within the family, the peer group, and the social milieu.

The vulnerable (traumatized) part of the self is hated so it is subsumed into the omnipotent self which is the part that suppresses doubts and anxiety and presses for transition. If the traumatized self pushes for recognition of psychic pain, the young person may resort to self-harm and suicidal ideation which is a form of acting out of their self-

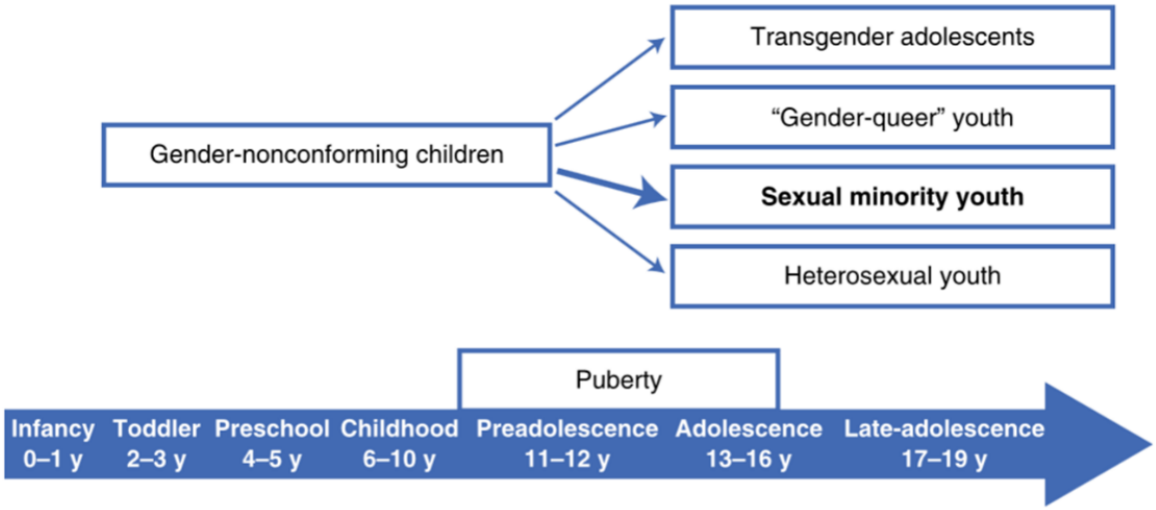
hatred against their bodies. Affirming clinicians collude with the patient's own attacks on the traumatized self by "traumatizing" their young patients' bodies with cross-sex hormones and mutilating surgery. In the hope that transition will restore the young person to an ideal state, medics become omnipotent creators of this ideal state. When this fails, the patient sinks into further self-hatred which is enacted through self-harming and suicidal states.

The majority of GD young people have had very limited life experience. For example, they

i. have had no sexual experience (other than crushes from a distance, hand holding and kissing)
ii. disdain genital sex as "gross"
iii. are indifferent to loss of sexual function and fertility, claiming that they never want to have children
iv. are confused about the nature of "trans" relationships e.g., a self-declared non-binary male (natal sex = male) in a relationship with a transgender declaring natal female (i.e., a trans man) told their parents they were in a gay male relationship. Similarly, two natal females, both transmen, rejected the suggestion that they were a lesbian couple and stated that they were a gay male couple.

It is imperative to keep the developmental path open into adulthood because frontal lobe maturation continues to occur into the early 20s. Further, there are several final trajectories for gender-nonconforming children. The trajectory of gender-nonconforming children varies greatly, and therefore, not all gender-nonconforming children will report persisting gender dysphoria once pubertal changes begin to develop. Prospective studies show that the majority of gender-nonconforming children will report being a sexual minority at some point later in life. An individual child's trajectory may not be known until later in life and it is imperative that this not be disturbed by iatrogenic interference[29].

[29] Leibowitz, S. F., & Telingator, C. (2012). Assessing gender identity concerns in children and adolescents: evaluation, treatments, and outcomes. *Current Psychiatry Reports, 14(2), 111-120*



Psychological trauma from the past forms part of one's psychic structure in the present. The expression of these traumas is socio-culturally embedded, that is, social contagion permits particular forms of "acting out" of these traumas. Envy and rivalry are an integral part of human condition; unconscious envy is a factor in trans identification. GD adolescents need assistance to explore their defences and internal psychic conflicts and to manage their psychic pain before irreparably altering their bodies. "The body is used to act out something that cannot be accepted or processed by the mind." (Evans & Evans, 2021, Ch 2, p. 28). Clinicians should not collude with the phantasy that the "embodied" self can be altered or removed.

Sexual development poses a threat to young people as it signifies approaching adulthood, the demands of which they feel ill equipped to manage. ROGD may be conceptualized as a "trauma" or a response to the reality of puberty that one now has a sexed body. Rigid adherence to peer norms temporarily assuages vulnerabilities because the young person has found others like him/her who are acting out in the same way. The desire for transition could be:

i. related to a grievance against the parents and a struggle for autonomy/individuation
ii. part of a process of identification and disidentification with parents and siblings
iii. related to an idea that one can create an ideal self
iv. protective against feelings of inadequacy, anxiety, jealousy, and disappointment
v. a triumph over feelings of vulnerability
vi. a repudiation of the sexed body and adulthood

DEVELOPMENTAL TRAJECTORIES OF YOUNG PEOPLE DECLARING THEMSELVES TRANSGENDER

Alicia

Alicia was a 14-year-old ROGD adolescent at the time of coming out as trans and starting therapy. She advised her parents that she was a trans male, whereupon they sought therapy for her. Alicia comes from an intact family and is an only child. She has a good relationship with her mother with whom she shares intimate thoughts and feelings and a positive, companionate relationship with her father with whom she shares enjoyable activities. Neither parent is prepared to affirm her, although they have told her that she is loved and wanted. She has been formally diagnosed on the Autism Spectrum, Level 2. Alicia has experienced school refusal, suicidal ideation, depression, peer relationship difficulties, and identity confusion. At the time of writing, Alicia had been in therapy once a week for 18 months. During this time, she had returned to school, recovered from her depression, ceased her suicidal ideation, and started to think about her future.

Developmental history

Alicia's parents had no concerns about her gender development in early childhood. There was one occasion when Alicia was 7 or 8 when told her mother that she wanted to be a boy. She had early puberty at age 10 in grade 4 and this was very unsettling for Alicia, who expressed discomfort with her developing breasts and hips. She wanted to cover up more and changed her clothing preferences.

Alicia was bullied and excluded from peer groups. She moved in and out of peer groups but was frozen out by bullies. She befriended different girls but found out that they did not regard her as a friend – they just allowed her to "hang out" with them. She was "broken hearted".

Alicia was diagnosed ASD in grade 6. Alicia wanted to get her long hair cut off. She started wearing boys' clothes. She was unhappy with her female genitalia. She started questioning her gender and became hyper focused on the internet – into YouTube, Discord, etc. She told her mother she didn't understand why everyone didn't question their gender. Mother closed off access to Reddit and Tumblr.

At the time of referral, Alicia had an online boyfriend (15) who is gay. She has not admitted to him that she is a girl. She thinks she is in a gay relationship. Mother thinks that she has told him that she is intersex and has male genitalia and that she is trans. Her mood improved once this relationship began. They play Minecraft online together, chat about life. Alicia feels guilty about lying to him about her gender.

In year 7 (the first year of high school) a male student liked her, but she didn't pick up the cues. Another boy tried to get someone to have sex with her. He cornered her in the bushes and invited other boys to "fuck" her. It all got reported to school management, boy was suspended, but Alicia she was severely traumatised. She became suicidal and could not get the incident out of her mind, could not go to that space in the school grounds. One day, she climbed the stairs in a school building with the intention of jumping off, but boy(friend) came and distracted her to go to the library. The school got someone to accompany her to classes to keep her safe. She started to school refuse.

Mother said that suicide became Alicia's "go to" to solve her problems, but she is not unduly concerned about her safety. Her main concern is the GD. Mother sees her as her daughter, cannot use the alternative name or pronouns.

Mother thinks her husband is also on the autism spectrum. He loves Alicia but cannot talk comfortably with her. She rarely goes to him with problems.

First month of therapy

Session 1

> I have spent three years trying to figure out my gender identity and why I have gender dysphoria (GD). This year, I have found out and feel comfortable. I have told my parents, but they are not taking me seriously. They have barred me from doing stuff that might help me – they don't understand how I feel about my gender. My friends use my preferred name and pronouns (he/him), but my parents refuse.
>
> My relationship with my parents is good except for the gender issues. We are strained over that – I feel isolated around them. I feel I can't go to them. They give me reasons as to why I shouldn't be trans. I am being encouraged not to explore how I feel because

of what my Mum has read. I want to tell them that I feel mistreated by them for not respecting my chosen name and pronouns.

Most of my classmates are not accepting either; they make jokes about trans people, so I am hesitant about using my chosen name and pronouns at school.

I have online friends I feel close to. Two of them know that I am trans and are accepting. Others don't know but I go by my trans name and pronouns online because it relieves my distress. They are struggling with stuff as well.

I started wondering about my gender when I was 10 which is when I started puberty. I felt something was "off" about myself. I tried to understand it by experimenting with different identities and what felt right for me. I explored them all, but nothing felt right, I couldn't stick to one thing. I was all over the place. I knew about trans people while I was trying to figure myself out. At the beginning of 2020, I finally found an identity that I was looking for but then had trouble expressing that and finding acceptance. At one point, I considered myself non-binary (NB), gender fluid (GF), agender. I landed on non-binary because I don't identify as male or female; GF fluctuates between the poles of male and female. But NB didn't feel right either, thinking of myself as other than male or female. GF felt like something that I had to actively think about all the time. "What do I feel like right now – male or female?" Then I decided that trans felt best for me – it felt like I could recognize who I am – I really wasn't comfortable with being female. Saying that I am trans feels right in the sense that I now know who I am.

As a female, I experienced GD, didn't like my female pronouns, within my peer group at school, I felt very disconnected from girls in my classes, slowly gravitated towards having a male peer group, with whom I felt more comfortable. They don't acknowledge my trans status except when they are making jokes about trans people. At school, I still go by my birth name and female pronouns. My male peer group see me as the only girl in their friend group. One of them reads me as more masculine, sometimes uses male pronouns then corrects himself. Secretly, I don't want him to correct himself but none of them know that I am trans.

Some students in class make awful jokes about trans people, making fun of NB people. In a science class we had to classify salts and gases. Some of them related this to trans categories. I had to sit there pretending that I didn't care about what they were saying. I was on the verge of breaking down, so I left to go to the bathroom. I was crying for the last ten minutes of period in bathroom. They were jabs at me personally. They figured I was part of the LGBTQ community.

Second month of therapy

The only thing that I want at the moment is to transition socially without going through more struggles and to feel more comfortable with myself. I also want to get a binder to feel more comfortable. Mum says no - she says she wants me to be comfortable in my own skin but I can't without doing anything. I wear sports bras and baggy clothing, but sports bras don't help much. My height is a problem because I am short, I am insecure with that. I also have bottom dysphoria – I am distressed at not having a penis. I have to wear loose pants to stop myself from being more aware of it. Having a penis would make me feel more comfortable and more complete.

I am attracted to guys. I have a boyfriend. He knows that I am trans and he genders me correctly. My parents know that I have a boyfriend. He is 15, a year older than me.

I feel vulnerable and distressed at home and school. I would like my parents to be more accepting so that I can come to them with the issues that I am having. I would like to socially transition just in the house, I would feel more comfortable, just around my parents. There wouldn't be too much change. I have a lot of body hair - Mum says that I should shave my legs and armpits, but I prefer not to.

Six months into therapy

I have had some moments doubting my gender identity, sometimes I feel confused that I am faking it and doing it for attention. It comes and goes. It's quite distressing, I want to tell Mum and Dad that I am having doubts and need some comforting words. It is hard to let them know that I am not trans anymore because when I am doubting it is very hard to stay grounded. It feels like a big swamping feeling that I am overwhelmed by, and it is hard to reach out for comfort to them. I am scared that they might take my doubting as a good thing. Mum is OK with other stuff but not for my

gender dysphoria; we are at opposite ends. We can't see eye to eye. There is a lack of understanding about how I am feeling. I talked to her before about my breast dysphoria. I said to her, "I don't like my breasts." My mother then said, "Well, I don't like having fat legs."

Conversation with mother:

What is worthy of note is that Alicia started taking her bra off to sleep while we were on holidays at the beginning of December, and she has kept doing that. She had refused to do that for about a year. Also, she would always hide her breasts with her arms when in the bathroom, going to the bathroom without clothes on, or whatever, but is no longer doing that since sleeping without the bra. She even unzipped her sun shirt while in the pool, which has not happened for a few years. She had swimmers underneath, but normally would never expose herself that much. Four or five days ago, she was upset, but didn't tell me until after, but said it was to do with gender dysphoria and doubting herself. I didn't want to push her, but I took that to mean she doubted she was trans, and that's what was upsetting her - the thought of not being trans.

12 months into therapy

My thinking has changed about the gender issues over time - I feel once again that I am not sure who I am regarding gender. I want to block out everyone else's opinion because it is a life changing issue. Questioning has the potential to be life changing. I am at a point where I feel I have to go through it alone, to avoid multiple opinions. There is no check list that definitively says what you are. I have to step back from everyone and dive deep down into myself to try to know who I am. It is a very tricky experience to try to explain. I feel like I know how I stand, how I perceive myself in terms of gender but there is no way I can know for sure. I might feel one way now and will be treated in a certain way but then I might change my mind.

Alicia's current summation, 18 months into therapy

I have decided that I am a nonbinary male, but I am not necessarily male. My gender is neutral – overall, I am in the middle of thinking about it on a spectrum. I feel that I have now landed on something that feels right; it is the best descriptor for me. I

> previously considered myself trans FtM but now that doesn't fit. I have made peace with it. I have made peace with the fact that I have been born with a female body. I might not like it, but it is my body and the best I can do is try to feel at home one way or the other in it. When I think about medical transition - I will leave that alone until I am 18 and responsible for my own choices. Hopefully, I would have a firm grasp on who I am by then. Medical treatment is risky for people who are going through puberty, and I am too old now to have puberty blockers, so I have decided to get to the end of this, I mean puberty, being a teenager. I don't want to make irresponsible decisions when I am not mature enough to do so. I think I will eventually start testosterone, but not too rapidly. I want more masculine features/characteristics, but I prefer to appear androgynous, more male leaning androgyny. I want to minimize my overtly feminine features that get to me. I expect to shave but not have a bushy beard, maybe minimal hair on my face. I have never grown any facial hair. I don't like having wide hips or a curvy body. I want bulkier arms and bigger hands. My body is "petite" - I don't like that. I am short and insecure about my height. I am 157 cms - that is short compared to my classmates. I am embarrassed that I am so short compared with my classmates. I feel inferior having to look up to them. In my friend group, I am the oldest but also the shortest. I want more respect.

I asked Alicia whether she will get more respect if she looks more androgynous. She replied:

> It is a grey area for me. In terms of feeling respected, I want to feel like myself, like a proper person. Sometimes I am shambling around as some thing and not as any sort of defined me. I really don't like the fact that I have a fanny. I am tolerating the breasts more than the fanny. Having a fanny doesn't feel right or proper. It feels like empty space. It doesn't feel like a part of my body. My ideal body would not include a fanny. I would rather have a willy.

I explained how testosterone would and would not change her body. I told her that it would produce facial hair and a deeper voice but would not increase her height or grow a penis. She was somewhat shocked to hear about these limits of testosterone. She then said, “In that case, I will leave the big decisions until I am 18”.

These statements from this young ASD person highlight how young people's sense of gender changes over time and how dangerous it is for gender clinics to accept their first pronouncements of how they perceive themselves. It also brings into sharp focus the misunderstandings and confusion that can arise. Without careful discussion in a safe space, such misconceptions may never be detected or corrected, and the young person may be left with their erroneous beliefs, the basis upon which they make irreversible decisions about their bodies. It is also noteworthy that a significant proportion (~51%) of young people with ASD express anxiety related to gender while not expressing unhappiness with their biological sex (60%) or a desire to change their biological sex (70%)[30]. It is therefore imperative that anxiety about gender not be used as the determinant for medical interventions in ASD populations.

Jared[31]

Below is a two-year history summarizing the gender identity and sexual orientation trajectory of an adolescent male. Apart from his gender questioning, Jared was an otherwise psychologically healthy young person from an intact family. He loved BMX and scouts, was doing well at school, had friends, both male and female, and two older siblings, including a 23-year-old brother who proved a very useful ally and role model in Jared's treatment.

At the age of 14, Jared came out to his parents as GAY. He soon changed that declaration to BISEXUAL when he experienced a powerful crush on a female classmate. After she rejected him, he came out as TRANS and demanded puberty blockade and cross sex hormones.

In therapy, his demands for transition were strident and incessant. He constantly asked me when I was going to tell his parents that he was competent to give consent and could therefore proceed with his transition.

He shaved his legs, arms, and body hair, grew his hair long, and started to wear eye makeup and nail polish. He ordered female clothing from the internet and wore it secretly in his room. When his parents confiscated these clothing items, his female friends from school lent him

[30] Adesman, A., Brunissen, L., & Kiely, B. (2020). Characterization of Gender-Diverse Expressions and Identities among Youth with Autism Spectrum Disorders. *Pediatrics*, *146*(1_MeetingAbstract), 302-303.
[31] A very similar case has been posted online https://genderclinicnews.substack.com/p/florida-warns-doctors-off-gender?r=130uly&s=w&utm_campaign=post&utm_medium=web

their clothes to wear until I advised his parents to put a stop to this. Teachers at his school started calling him by his preferred name and pronouns until I advised his parents not to allow this.

He became increasingly hostile towards me because I was not advising his parents to allow him to transition. His parents had told him that they were not prepared to act on his desire to transition until they were advised by me that this was the medically and psychologically sound course of action. I told Jared that such decisions required great care and exploration and that we needed to understand more about his motivation for wanting to transition and what it meant in his life. I explained that I needed to be sure that he understood all the ramifications of such treatment and the fact that some aspects were irreversible. He insisted like so many young transgender declaring adolescents that he didn't care about having sex or children so none of that mattered.

Several months after therapy commenced, while still vehemently protesting his trans-female identity, he wrote a letter to his parents apologising for misleading them. He said he now realised that he was not a trans-female but a DEMIGIRL (denoting partial non-binary, partial female gender identity).

He changed this orientation shortly thereafter to DEMIBOY (denoting partial non-binary, partial male gender identity). He stopped trying to deceive his parents with regards to wearing makeup and nail polish and secretly stashed his female clothing obtained illicitly through the internet (with packages delivered to his friends' houses so that his parents did not suspect) into the recycle bin.

Three months later, he again wrote to his parents, telling them that he was only joking about the whole thing and that they were the only people who had taken it seriously.

I advised his parents to eat humble pie to give their son the opportunity to exit the gender maze without losing face.

The next day, shortly after his 16th birthday, he asked his parents to take him for a haircut and to take him shopping for new clothes. He directed them to a barber and a male clothing store. He quietly advised his parents that he now realised that was STRAIGHT.

SOCIALIZED AND INTERNALIZED HOMOPHOBIA

An adolescent realises that s/he is same sex attracted. Finding this unacceptable, due to parental and/or internalized homophobia, the adolescent reasons as follows: Being same sex attracted is bad and shameful. My parents will reject me if I am gay. If I am a boy attracted to other boys, I must be a girl and therefore need to transition so that my attraction to boys becomes heterosexual.

Hossein

Sociocultural issues and parental homophobia

Hossein was aged 15 years when his parents contacted me about their many concerns for their son. He is the elder of two children; he has a nine-year-old sister. The family migrated to Australia from a Balkan country when Hossein was five. They became panicked when Hossein declared that he was transgender and wished to transition immediately.

Hossein was difficult to engage except when talking about his gender dysphoria and pressing his case for transition. He said that his parents were waiting for my assessment before they agreed to any medical treatment. He asked several times each session when I would finish my assessment and advise his parents that he could start taking oestrogen. He was otherwise hard to engage and was sometimes irritated, sleepy, and uncooperative.

Hossein expressed concern about his schoolwork. He had aspirations to study aerospace engineering but was finding senior school maths and physics difficult. He also reported serious attentional problems. I advised his parents to obtain psychometric assessments of his ability, attention, and social skills in order to gain a baseline of his current functioning. Hossein was found to have average intelligence, which was not concordant with his parents' view of him, or his own view, that he was "gifted." I attempted to do some reality testing regarding parental expectations for his academic performance.

Hossein also scored in the clinical range for both attention deficit disorder and autism spectrum disorder. I indicated to his parents that these conditions were priorities for treatment and that the school needed to be informed about the results of psychometric testing in order to better support Hossein at school.

When I explored Hossein's perception of his sexuality and sexual orientation, Hossein disclosed the following:

> I see myself as bisexual. I have feelings for guys and girls, more like a pan-thing. I have had a boyfriend who identifies as male and pan since last year. We get together just the two of us - we visit each other's houses. I guess I would be OK with being gay. For me, it fluctuates.

Of his mother, Hossein said:

> Mum knows I have this friend. She doesn't know that he is my boyfriend. I don't think Mum will take it well because she asked me if I still liked girls. She wouldn't take kindly to knowing I have a boyfriend.

Of his father, Hossein said:

> Dad is trying to suppress his queer phobia, but he says bad things about LGBTQ. He is anti it all; he got angry with me for refuting what he was saying. Dad said gay is about anal sex and that is gross. Then Mum told him to shut up and I went to my room and cried. Dad is anti queer for sure, he tries to suppress it because he still loves me. I felt very disappointed in Dad when he expressed these sentiments. He will be very freaked out if he thinks I am queer, gay, or trans.

This is a [….] family who speak [….] at home. [….] culture is homophobic. In a family meeting, I tentatively prepared his parents for the possibility that Hossein's sexuality may eventually resolve as homosexual and that if that were the case, they would need to resolve their own antipathy to homosexuality in order to support their son.

Declaring oneself transgender in this sociocultural milieu is an attempt to resolve the difficult dilemma of a […] boy being gay. Sadly, transgender identity is preferred to a homosexual orientation in certain Balkan countries and the Middle East.

Hossein was insistent at various times that he was transgender and was impatient to commence his social transition and to obtain prescriptions for cross sex hormones. He was dismissive of the life changing effects of these drugs on his body, was indifferent to the loss of sexual function, and declared that he was not interested in preserving his sperm for later reproduction because he had no intention of having children. Hossein was cognitively rigid

and evinced concrete thinking when discussing his potential transition. He had researched the "facts" about MtF transition but could not discuss them in a nuanced way or accept the possibility that he may be disturbed by side effects or uncertainties about his course of action. He did not wish to proceed with surgery at this time.

In view of Hossein's recently diagnosed ADD, ASD, and uncertainty about his gender identity and sexual orientation, I drew the conclusion that Hossein was not Gillick competent and should not be supported to transition at this time, either socially (i.e., changing his name and pronouns) or through cross sex hormones.

The priority for Hossein was to address his ADD and to get support for his ASD. I referred him to a child and adolescent psychiatrist for a medication review for his ADD and depression. The psychiatrist prescribed methylphenidate and antidepressants. I ceased therapy with Hossein as he refused to engage further because I had not supported his transition and had several further sessions with his parents to assist them to address their homophobia and grief that their only son was, in all likelihood, gay.

Roisin

Internalised homophobia

Roisin is a 15-year-old adolescent attending an exclusive girls' school. She came out as trans to her mother at the age of 14. It seemed like rather a half-hearted coming out. Roisin had not chosen a new name or pronouns and did not seem particularly interested in exploring her new identity. The only change was that she asked her mother to buy her the alternative school uniform, which consisted of trousers and a shirt instead of a pinafore. This did not trouble mother too much as a significant number of the students had opted for this style of uniform.

Roisin's presentation was more consistent with body dysmorphia than gender dysphoria. Roisin complained that her hips were too wide, that her thighs were too big and that her face was the wrong shape although she could not be specific about what it was about her normal, symmetrically placed features that were so wrong. Roisin suffered from severe acne for which she was prescribed medication. When her skin cleared up and she appeared in the full bloom of good health, she confided to me that she was not that happy that her skin looked so good. When I inquired why, she replied that now that the focus was taken away from her acne, all

the other "hideous" features of her countenance were in the full glare of the spotlight, and she could not tolerate looking at herself in the mirror or having her photo taken.

Roisin is gifted and had been performing well at school, but teachers had commented recently that she was distracted, disconnected, often "spaced out" and not "with it" in class. She appeared sleepy and often put her head on the desk. In response to a question about how she was sleeping, Roisin responded:

> I am having nightmares about events in my life and about what could go wrong. They are most often about peer interactions. I worry about potential issues related to my peers judging me, exposing me as gay. I wake up in a panic about who is talking about me. There are a few girls in my class who won't shut up about LGBTQ issues. They are really obnoxious and loud, and I always feel as if they are referring to me when they talk about lesbians in a disparaging way. I have thought about asking them not to keep talking about LGBTQ issues all the time, but if I do that, I will be accused of being homophobic. I might risk being ostracized by other girls as well.

Soon after she reported her nightmares, Roisin disclosed that she had been self-harming for about a year.

> Sometimes, I come home from school defeated, nothing in particular has necessarily happened, it is just the constant stress of the environment. I tried sitting with the feeling, but it didn't pass, so I got the reed on my clarinet and scraped and cut my waist and hip. It is still red and angry, it was painful, but it is healing. Other times I use scissors and cut the top of my thighs. I only cut where it is not obvious, and no-one will see it.

About nine months into therapy, Roisin confided that she had a powerful crush on a girl at school but would never act on it for fear of rejection by the girl in question, and peer vilification in general. She was very troubled by the intensity of her feelings and asked me whether she was gay.

I had a very open and scientifically oriented discussion with Roisin about female sexual orientation. I explained that sexual orientation in females appears more likely to change over time. I discussed hypotheses regarding the greater sexual orientation fluidity in females

compared with males that are underscored by biologically based sex differences in foetal hormone exposure and socio-political forces that constrain sexual self-concept, expression, and opportunities differently in women and men. I indicated that while she currently felt strongly same sex attracted, her feelings may well change over time. I explained that many adolescents experienced same sex attractions but mostly reached adulthood as heterosexual. I normalized her feelings and explained that she was not inferior, diseased, or immoral if she were, in fact, gay. Roisin was greatly relieved by our several discussions on female sexual orientation and decided that she would like to share this with her mother.

I coached mother about appropriate responding and reinforced what I had already discussed with Roisin in her sessions. Mother was relieved that Roisin no longer thought of herself as trans and was not at all troubled that she may be lesbian. She said:

> Being gay is biologically based and does not involve self-mutilation or lifelong patienthood at the behest of the medical profession. There are a number of gay people in our extended family, and all are accepted without question. We do not have a problem with it at all.

The disclosure went well, and Roisin was greatly comforted by her parents' easy acceptance of her declaration. However, she is troubled by possible responses from her peer group should they find out (she has no intention of disclosing to them). She continues to struggle with other aspects of her mental health, including a treatment resistant clinical depression for which she has been medicated unsuccessfully.

Professor Dianna Theadora KENNY Mob: [redacted]

E: [redacted]

ABN [redacted]

Professor of Psychology (rtd)

Consultant Psychologist and Psychotherapist

Registered psychologist (No. 0005390)

AHPRA number PSY0001136350, specialist endorsements: developmental, educational and counselling psychology

Medicare Provider No 2876971T

Marriage and Family Therapist (Relationships Australia)

Nationally Accredited Mediator (Australian Dispute Resolution Association)

Family Dispute Resolution Practitioner **(**No. R1005291**)** (NSW College of Law)

ABBREVIATED CURRICULUM VITAE

Current	2019 -	Principal, DK Consulting (Psychology, psychotherapy, family dispute resolution, and medico-legal services)
Previous appointments	2013-2019	Hon Professor of Psychology, The University of Sydney
	2006-2013	Professor of Psychology, The University of Sydney
	1988-2006	A/Professor, Senior Lecturer, Lecturer in Psychology, The University of Sydney
	1986-1987	Psychologist in private practice
	1986-1987	Lecturer in School Counselling, School of Counselling and Disabilities Studies, The University of Western Sydney
	1983-1985	Regional Specialist Counsellor for Emotionally Disturbed Children, Liverpool region, Division of Guidance and Special Education, NSW Department of Education
	1978-1983	District School Counsellor, NSW Department of Education
	1976-77	Teacher, Haberfield Demonstration School, Haberfield, NSW

University Qualifications

1988	Doctor of Philosophy (PhD) (Developmental and Educational Psychology), Macquarie University (School of Behavioural Sciences)
1980	Master of Arts (School Counselling), [M.A. (Sch. Couns.)], Macquarie University (School of Behavioural Sciences)
1974	Bachelor of Arts (Honours - Psychology) [B.A. (Hons)] The University of Sydney

Other Qualifications

2016	Postgraduate Diploma in Family Dispute Resolution (PG Dip FDR) (NSW College of Law)
2015	Nationally accredited mediation training – Resolution Institute
1986	Diploma in Clinical Hypnotherapy (DCH), Australian Society of Clinical Hypnotherapists

1982	Certificate in Marriage and Family Therapy, Marriage Guidance Council, N.S.W. (now Relationships Australia).
1977	Associate Diploma in piano, Trinity College of Music, London (ATCL)
1975	Diploma in Education, (DipEd) Sydney Teachers' College

Registrations and Accreditations

Psychology Board of Australia (No.0005390)

Australian Health Practitioner Regulation Agency (PSY0001136350)

Approved Medicare provider (No 2876971T)

Nationally accredited Mediator (LEADR, Australian Dispute Centre)

Family Dispute Resolution Practitioner (NSW College of Law)(Registered with Attorney General Department) (No. R1005291)

Membership of professional societies

Member, Australian Psychological Society: Specialist Accreditations

Academic Member, College of Developmental and Educational Psychologists

Fellow, APS College of Counselling Psychologists

Member, American Psychological Society

Member, Society for Psychotherapy Research

Member, International Association of Relational Psychoanalytic Psychotherapy

Elected Member, New York Academy of Sciences

Member, Australian Dispute Resolution Association

International affiliate, American Psychological Association

Consultancies relevant to psychology and the law, transgender issues in children and adolescents (informed consent, assessment and suitability, family conflict, comorbid conditions), child sexual abuse, sex offending, and sexual misconduct

Expert report writer, Human Rights Law Alliance

Expert report writer, Amicus Briefs for cases occurring in Canada and USA

Expert reviewer/report writer, Office of the Director of Public Prosecutions, Armidale, Gosford, Lismore, Parramatta, Penrith, Sydney, Tamworth, Wollongong

Expert reviewer /report writer, Crown Solicitors' Office, Sydney

Expert reviewer/report writer, Victorian Government Solicitor's Office (VGSO)

Expert reviewer/report writer, Joint Investigative Response Team (JIRT), NSW Police – Blacktown, Chatswood, Coffs Harbour, Manly, Penrith, Tamworth

Expert reviewer/report writer, Health Care Complaints Commission (HCCC) – NSW, Victoria, and Western Australia

Expert developmental psychologist, various Barristers chambers

Assessment psychologist, Aboriginal Legal Service

Research consultant, *NSW Department of Juvenile Justice*

Research consultant, *Justice Health NSW*

Research consultant, *Youth Justice Coalition* (pro bono)

Research consultant, *Public Interest Advocacy Centre* (pro bono)

Consultant investigative psychologist (of alleged child sexual abuse), *St Joseph's College, Hunter's Hill*

Consultant psychologist, *Tribunal of the Catholic Church*

Expert reviewer for Joint Investigative Response Team, NSW Police

- Provide advice and court reports on cases related to child sexual assault, including reports of historical child sexual abuse
- Appraise the quality and plausibility of disclosures made by complainants in cases of current and historical sexual abuse
- Provide literature reviews and advice on the status of recovered memories, the reliability of childhood memory, and memory processes over time and factors that can alter or affect memories
- Provide advice on language development, children's use of and understanding of sexual language
- Provide expert advice on other matters related to criminal offending against children.
- Provide expert advice on the nature of psychopathologies arising from child sexual abuse

Expert developmental psychologist for various Barristers chambers, Crown Solicitor, and Office of the Director of Public Prosecutions

- Provision of expert reports on matters pertaining to child development
    - credibility and reliability assessments of disclosures of child sexual abuse
    - Reasons for delay of disclosures of child sexual abuse
    - memory and language development as it pertains to child sexual abuse disclosures
    - evaluation of "recovered memories"
    - Long term impacts of child sexual abuse
    - Capacity for consent

Court referred clients

- In cases of parental alienation, assess the quality and veracity of accusations of emotional, physical and sexual abuse of children in divorcing couples undergoing family court proceedings for custody and access of the children of the marriage, and report these findings to the court.
- Assess parenting capacity in separating and divorcing parents to ascertain child safety and capacity of parents to undertake shared parental responsibility.
- Where mandated by the court, provide assessment, counselling and therapy for accused fathers and report on the alleged risks to their children while in their care.

Expert reviewer for the Health Care Complaints Commission

- Investigate complaints against psychologists for malpractice and misconduct, including sexual misconduct, and other conduct that falls below the standard expected of the profession.
- Undertake review and critical appraisal of treatments offered by psychologists and whether those treatments have been collusive, coached, suggestive or in other ways biased with respect to issues of child sexual abuse, including historical sexual abuse.

- Evaluate psychologists' psychological practice, evidence-base for therapeutic interventions, and competence in implementing psychological therapies.

- Undertake file review of documents (letters, submissions, complaints, statements, accounts of therapy, therapy case notes) from complainants and defendants, report writing, participation in conclaves, and court appearances.

Consultant Psychologist to the Tribunal of the Catholic Church

- Assessment of marriages for annulment
- Assessment of claims of sexual abuse within marriage and non-consummation of marriage, among other relationship issues.

Research on sexual offending in young sex offenders

- Extensive research undertaken on sexual offending examining life histories and precursors to sexual offending, young offenders' experience of sexual abuse, and other forms of maltreatment for the NSW Department of Juvenile Justice.

Ministerial and other Appointments in Psychology and the Law

2013 Board Member, Daystar Foundation (a foundation for the provision of vocational training and employment to 'at risk' young people)

2003-2009 Chair, Ministerial Steering Committee, NSW Department of Juvenile Justice Collaborative Research Unit

2003-2009 Member, Ministerial Steering Committee on Sexual Offending, New South Wales Department of Corrective Services

2002 A/Chair, Ministerial Reference Group on Sexual Offending, New South Wales Department of Corrective Services

2001 Member, Ministerial Reference Group on Sexual Offending, New South Wales Department of Corrective Services

2003 COCQOG (Commonwealth Cost and Quality of Government): External Reviewer of Psychological Services and Specialist Programs, NSW Department of Juvenile Justice

1996-2002 Deputy Chair, Ministerial Steering Committee, NSW Department of Juvenile Justice Collaborative Research Unit

1997-2003 Chair, Research and Ethics Subcommittee, NSW Department of Juvenile Justice Collaborative Research Unit

Expertise

I divide my expertise into five key areas –

(a) Gender dysphoria (GD) in children and adolescents including a clinical practice working with young people with GD and their parents/families and schools. I bring my decades of experience working with children and families to my practice in working with young people with GD (key areas b, c, d, and e are all relevant to my clinical practice in gender dysphoria).

(b) Child development – including children's social, emotional and cognitive development, assessment of children's attachment to primary care givers, peer relationships, cognitive abilities including intelligence, memory and language; assessment of developmental psychopathologies and behavioural disorders and provision of therapy for same.

(c) Matters pertaining to child sexual abuse, including the disclosure of child sexual abuse, the impact of sexual abuse on children, historical child sexual abuse and its reporting, and issues of repressed or false memory, grooming by paedophiles, and counter-intuitive behaviour.

(d) Matters pertaining to school performance and achievement, psychometric assessment of intelligence, assessment in literacy and numeracy and specific learning disabilities.

(e) Family dispute resolution (I am an FDRP registered with the Attorney General's Department) in which role I asses alleged offences of one parent against another and/or their children in the context of family court proceedings. I report on issues such as access, parental alienation, and child stress in the context of contested divorce and custody disputes.

(a) Gender dysphoria in children and adolescents

I have a busy clinical practice specializing in the treatment of gender dysphoric children and young people, their parents and families. I have contributed invited submissions to government here in Australia and overseas on matters relevant to education policy on transgender declaring children and adolescents and acceptable therapies with which to treat them. I have published in the area and provided expert reports on disputes regarding treatment of gender dysphoric young people whose cases reach the Family Court.

Key publications (Books, edited books, book chapters, journal articles)

Kenny, D.T. (2020). *Gender dysphoria in children and young people: Collected papers on the psychology, sociology and ethics of gender transitioning*. Germany: Scholars Press.

This book critiques gender dysphoria in young people and its current treatments that include gender affirmation therapy involving puberty blocking agents, cross sex hormones and sex reassignment surgery. I examine the safety of these treatments, evidence of efficacy, capacity of children and young people to give consent to life altering treatments, the social impacts of transgender individuals, particularly in women's sport, and the social contagion of gender dysphoria.

D'Angelo, R., Syrulnik, E., Ayad, S., Marchiano, L., **Kenny, D. T.,** & Clarke, P. (2021). One size does not fit all: In support of psychotherapy for gender dysphoria. *Archives of Sexual Behavior*, *50*(1), 7-16.

Holloway, G., **Kenny, D.T.,** Deves, K., …Parkinson, P., Morris, P., & Halasz, G. (2021). Australian perspectives on transgendering children and adolescents: Implications for policy and practice. Hobart: Author.

Kenny, D.T. (2021). *Opposing the teaching of gender fluidity ideology: The Education Legislation Amendment (Parental Rights) Bill 2020* (pp. 13-22). In Holloway, G., **Kenny, D.T.,** Deves, K., …Parkinson, P., Morris, P., & Halasz, G. (2021). Australian perspectives on transgendering children and adolescents: Implications for policy and practice. Hobart: Author.

Kenny, D.T. (2021). *The social contagion of gender dysphoria: a theoretical and empirical proposition* (pp. 56-70). In Holloway, G., **Kenny, D.T.,** Deves, K., …Parkinson, P., Morris, P., & Halasz, G. (2021). Australian perspectives on transgendering children and adolescents: Implications for policy and practice. Hobart: Author.

Submissions to government inquiries

Kenny, D.T. (2021). Submission to the NSW Parliamentary Inquiry: Education Legislation Amendment (Parental Rights) Bill 2020.

https://www.parliament.nsw.gov.au/lcdocs/submissions/70648/0005%20Professor%20Dianna%20Kenny.pdf and

https://www.parliament.nsw.gov.au/lcdocs/inquiries/2610/Report%20No%2044%20-%20PC%203%20-%20Education%20Legislation%20Amendment%20(Parental%20Rights)%20Bill%202020.pdf

Kenny, D.T. (2020). Gender development and the transgendering of children. In H. Brunskell-Evans and M. Moore. *The fabrication of the transgender child*. Cambridge: Cambridge Scholars Press.

Kenny, D.T. (2020). Submission and invited presentation to the Queensland government Inquiry into the proposed *Health Legislation Amendment Bill 2019* to outlaw conversion therapy.
https://diannakenny.com.au/images/pdfs/Submission_to_the_Queensland_Inquiry_into_Outlawing_Conversion_Therapy.pdf and
https://documents.parliament.qld.gov.au/tableOffice/TabledPapers/2020/5620T328.pdf

Kenny, D.T. (July 2020). Submission to the ACT government into proposed amendments to outlaw conversion therapy.

Clinical guidelines

Morris, P. …. **Kenny, D.T**….. (May, 2021). *Managing Gender Dysphoria/Incongruence in Young People: A Guide for Health Practitioners.* National Association of Practising Psychiatrists. https://napp.org.au/2021/05/managing-gender-dysphoria-incongruence-in-young-people-a-guide-for-health-practitioners/

Presentations

Kenny, D.T. (2021). *Transgendering our young people: Faulty science, psychic epidemic.* Invited lecture to the Faculty of Medicine, Notre Dame University, Sydney, Australia.

Kenny, D.T. (2020). *Affirmation only: Where's the evidence.* Invited presentation to the Catholic Medical and Bioethical Conference, 30 May.

Kenny, D.T. (2020). *Is gender dysphoria socially contagious?* Invited presentation to the NSW Parliament Forum on gender dysphoria in our young people, 18 February.

Kenny, D.T. (2020). *Transgender "ideology" and the "trans-gendering" of young people.* Invited presentation to the Northern Area Mental Health Network, NSW Department of Health, 12 February.

Kenny, D.T. (2019). *Children and young people seeking and obtaining treatment for gender dysphoria in Australia: Trends by state over time (2014-2018).* Paper presented at the Forum on transgender children and adolescents at the Parliament of NSW, 2 July, 2019.

Children and young people seeking and obtaining treatment for gender dysphoria in Australia: Trends by state over time (2014-2018) - Professor Dianna Kenny

Kenny, D.T. (2019). Female sport participation and gender affirmation: A collision course for medical ethics. Invited presentation Melbourne consortium of parents of transgender declaring children. 12-13 October.

Female sport participation and gender affirmation: A collision course for medical ethics - Professor Dianna Kenny

For other significant contributions to the gender dysphoria debate, go to https://www.diannakenny.com.au/

(b) Child and adolescent development

(i) I commenced my professional life as a primary school teacher, then became a school counsellor, and specialist counsellor for emotionally disturbed children with the NSW Department of Education. I held these positions for 10 years before joining The University of Sydney, where I rose to the rank of Professor of Psychology in 2006.

(ii) I hold a PhD in developmental and educational psychology, a master's degree in School Counselling, an honours degree in psychology and postgraduate diplomas in education and family dispute resolution.

(iii) I am a recognised expert in child development. I have designed and lectured in a range of courses at undergraduate and postgraduate levels pertaining to child development including: Developmental psychology; developmental psychopathology; infant and child study (with a focus on language and cognitive development); attachment theory; the psychological and cognitive assessment of children; and the developmental foundations of stress and coping.

(iv) I have major publications in the area of child development.

(v) I have provided reports on children to the courts and police, including on issues in child development such as language and cognitive development, childhood memory and its reliability, and adverse experiences that impair normal development such as attachment trauma and environmental risks to safety and security.

(vi) I am able to provide comprehensive literature reviews on most subjects related to child development.

Key publications:

Kenny, D.T. (2013). *Bringing up baby: The psychoanalytic infant comes of age.* London: Karnac.

This book examines the development of children, from birth to adolescence. It provides a detailed analysis of all modes of development including cognitive and social development, language development, the development of memory, the role of secure attachments in emotional development and the contribution of developmental neuroscience to our understanding of infant and child development.

Kenny, D.T. (2007). *Lifespan development: Theories and research.* The University of Sydney: Author.

This comprehensive manual describes how people develop and change throughout the lifespan, critically evaluates how cultural, historical, and economic factors influence development, presents the major psychosocial, emotional, and cognitive developmental theories, discusses the major controversies in developmental psychology, integrates different theoretical perspectives on development, and applies developmental theory to healthcare practice. It includes a critical review of the methods and research approaches (including genetic, comparative, cross cultural, ethological, and ecological) in developmental psychology and research designs (including cross-sectional, cohort and longitudinal, time lag and sequential).

Schofield, P., Mason, R., Nelson, P.K., **Kenny, D. T.,** & Butler, T. (2018). Traumatic brain injury is highly associated with self-reported childhood trauma within a juvenile offender cohort. *Brain Injury,* DOI: 10.1080/02699052.2018.1552020.

Kenny, D.T. (2016). The adolescent brain: Implications for assessing young offenders' legal competence. *Judicial Officers' Bulletin* (Judicial Commission of NSW), April, 28, 3, 23-27.

Kenny, D.T., Blacker, S. & Allerton, M. (2014). *Reculer pour mieux sauter*: A review of attachment and other developmental processes inherent in identified risk factors for juvenile delinquency and juvenile offending. *LAWS,* 3, 439–468; doi:10.3390/laws3030439.

Kenny, D.T., & Nelson, P.K. (2008). *Young offenders on community orders: Health, welfare, and criminogenic needs*. Sydney, Australia: Sydney University Press. ISBN 978-0-9804117-0-6.

Kenny, D.T. (2001). Cognitive-developmental theory. In Carol Jones (Ed). *Readers' Guide to the Social Sciences Volume 1, pp. 230-231.* London, United Kingdom: Fitzroy Dearborn Publishers.

Kenny, D.T. (2001). Nature and nurture. In Carol Jones (Ed). *Readers' Guide to the Social Sciences Volume 1, pp 1105-1106.* London, United Kingdom: Fitzroy Dearborn Publishers.

Kenny, D.T. (2000). Psychological foundations of stress and coping: A developmental perspective. In Kenny, D.T., Carlson, J. G. McGuigan, F. J. & Sheppard J. L. (Eds.). *Stress and health: Research and clinical applications*. Ryde, NSW: Gordon Breach Science/Harwood Academic Publishers (pp. 73-104).

Kenny, D.T. & Waters, B. (1995). Current issues in adolescent mental health. In D.T. Kenny and R.F.S. Job (Eds). *Australia's Adolescents: A Health Psychology Perspective.* Armidale: University of New England Press (pp 68-88).

Kenny, D.T. & Job, R.F.S. (Eds.) (1995). *Australia's adolescents: A health psychology perspective* (272 pages). Armidale: University of New England Press ISBN 1 875821 24 4.

(c) Child sexual abuse (CSA)

I provide expert reports on child complainants and alleged adult sex offenders to Joint Investigative Response Teams and Child Abuse Teams within the NSW Police. I have current experience:

(i) in counselling CSA victims.

(ii) providing structural and psychological analysis of CSA victim statements. I have developed specific expertise in the assessment of child testimony in sexual abuse cases.

(iii) reviewing video recordings of police interviews with alleged victims of CSA and providing commentary on the pertinent psychological issues.

(iv) providing expert statements and reviews of literature on matters pertaining to child development in general and CSA in particular, for the ODPP, Police, JIRT, barristers, and court.

(v) acting as an expert witness in cases of child sexual abuse, historical child sexual abuse, and paedophilia.

(vi) I have given evidence in court and have been cross-examined.

(vii) I have extensive knowledge of the child abuse literature and have written a book on the subject (see below).

(viii) I am able to provide comprehensive literature reviews on most subjects related to child sexual abuse.

(ix) I have publications – book, journal articles, monographs – on sex offending and have served on ministerial committees within the NSW Department of Juvenile Justice and the NSW Department of Corrective Services.

Key publications:

Kenny, D.T. (2018). *Children, sexuality, and child sexual abuse*. East Sussex, UK: Routledge**.**

This book has become a seminal text in the field because of its wide-ranging coverage and attention to all the recent research in the field, including the *Royal Commission into Institutional Responses to Child Sexual Abuse*. It covers all the key topics in child sexual abuse, including the nature of disclosures, both immediate and delayed, and their reliability; normal memory development and distortions of memory that can occur from a range of environmental influences including leading and suggestive interviewing; impacts of child sexual abuse, including short- and long-term consequences; assessment and forensic analysis of witness statements, and psychological analysis of CSA victim statements.

Kenny, D.T. (1997). Opinion, policy and practice in child sexual abuse: Implications for detection and reporting. In M. James (Ed.). *Paedophilia: Policy and prevention.* Research and Public Policy Series No 12: Australian Institute of Criminology, Sydney, Australia. ISSN 1326-6004. (pp 14-31).

In addition, last year I wrote a major report on paedophilia for the Child Abuse Squad, Ballina, addressing the question as to whether an individual in possession of child abuse material is a paedophile. This question had not been explicitly dealt with in the literature. Accordingly, I undertook major research on the subject and produced a report that the presiding judge allowed to be admitted into evidence to demonstrate tendency. The solicitor for the ODPP advised me that my report "may create a precedent for use in future similar matters."

(d) Juvenile offending and juvenile sex offending

For a number of years, I chaired or was a member of several committees within the NSW Department of Juvenile Justice and the New South Wales Department of Corrective Services, including Chair, Ministerial Steering Committee, NSW Department of Juvenile Justice Collaborative Research Unit, Chair, Research and Ethics Subcommittee, NSW Department of Juvenile Justice Collaborative Research Unit, Chair, Ministerial Steering Committee on Sexual Offending, New South Wales Department of Corrective Services, A/Chair and Member, Ministerial Reference Group on Sexual Offending, New South Wales Department of Corrective Services.

Kenny, D.T., Seidler, K., Keogh, T., & Blasczynski, A., (2000). Offence and clinical characteristics of Australian juvenile sex offenders. *Psychiatry, Psychology, and the Law, 7*, 2, 212-227.

Kenny, D.T., Keogh, T., & Seidler, K. (2001). Predictors of recidivism in Australian juvenile sex offenders. *Sexual Abuse: A Journal of Research and Treatment, 13*, 2, 131-148.

Kenny, D.T., & Nelson, P.K. (2008). *Young offenders on community orders: Health, welfare and criminogenic needs*. Sydney, Australia: Sydney University Press. ISBN 978-0-9804117-0-6.

Kenny, D.T. & Lennings, C. J. & Nelson, P. (2008). Mental health of young offenders serving orders in the community: Implications for rehabilitation. In Daniel W. Phillips III (Edited). *Mental Health Issues in the Criminal Justice System*. New York: Haworth Press.

Kenny, D.T. (2014). Mental health concerns and behavioural problems in young offenders in the criminal justice system. *Judicial Officers' Bulletin (Judicial Commission of NSW)*, 26 (4), 29-33.

Kenny, D.T. (2013). Violent young offenders in the criminal justice system. *Judicial Officers' Bulletin (Judicial Commission of NSW),* 25 (3), 19-24.

Kenny, D.T. (2015). Juvenile sex offenders in the criminal justice system. *Judicial Officers' Bulletin,* (Judicial Commission of NSW*), 27 (*4), 31-34.

(e) Educational psychology

During my earlier professional life, I worked as a school counsellor and specialist counsellor for emotionally disturbed children within the Division of Guidance and Special Education, NSW Department of Education. I was responsible for assessing children whose psychological difficulties were such that they could not be managed within the mainstream classroom. I undertook detailed assessments of their educational, social, and cognitive development in order to provide appropriate school placements for children who had significant trauma histories and intellectual disabilities.

Key publications:

Kenny, D.T. (2016). The adolescent brain: Implications for assessing young offenders' legal competence. *Judicial Officers' Bulletin* (Judicial Commission of NSW*), 28* (3), 23-27.

Kenny, D.T. (2012). Young offenders with an intellectual disability in the criminal justice system: Prevalence, profile, policy, planning and programming. *Judicial Officers' Bulletin (Judicial Commission of NSW),* 24, 5, 35-42.

Jensen, P. Stevens, S., & **Kenny, D.T.** (2012). Effects of yoga breathing on the behaviour and attention of boys with ADHD. *Journal of Child and Family Studies,* 2, 4, 667-681. DOI 10.1007/s10826-011-9519-3.

Kenny, D.T. & Frize, M. (2010). Intellectual disability, Aboriginal status and risk of re-offending in

young offenders on community orders. Special Edition, *Indigenous Law Bulletin,* 7, 18, 14-19

Kenny, D.T., & Faunce, G. (2004). Effects of academic coaching on elementary and secondary school students. *Journal of Educational Research, 98*, 2, 115-126.

Kenny, D.T. (1992). Can teachers be tests? A comparison of teacher ratings and test assessments of early reading performance. In H. Motoaki, J. Misumi, J. B. Wilport (Eds). *Social, Educational and Clinical Psychology*, Vol 3, pp 177-178. London: Lawrence Erlbaum Associates.

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(f) Family Therapy and Family Dispute Resolution

I assist parents to reach parenting agreements with respect to shared parental responsibility of their children following separation and divorce. I also undertake mediation with respect to property settlements. I undertook an 18-month training program with Relationships Australia in marriage and family therapy, in which capacity I work with families to resolve conflict, attachment ruptures, relationship stresses, and behavioural difficulties.

Having dual qualifications in both family therapy and family dispute resolution places me in an ideal position to assess families in custody disputes in relation to parenting capacity, shared parental responsibility and allegations of emotional, physical and sexual abuse. In these capacities I have provided parenting capacity reports to both family law solicitors and barristers, the Family Court and the Children's Court.

Key publication:

Kwok, E. & **Kenny, D.T.** (2015). The application of collaborative practice to misattributed paternity disputes. *Australasian Dispute Resolution Journal*, 26, 127- 136.

Other Major Consultancies, Invited Commissioned Reports and Invited Submissions to Government Inquiries

Kenny, D.T. (April, 2011). The NSW Law Reform Commission (NSW LRC). Consultation Paper 11. *Young people with cognitive and mental health impairments in the criminal justice system*, Roundtable.

Kenny, D.T. (2009). Submission on bullying to the NSW Legislative Council General Purpose Standing Committee No 2.

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Kenny, D.T. & Hunter, J. (2003). *Review of psychological services and specialist programs in the NSW*

Department of Juvenile Justice. Commonwealth Cost and Quality of Government (Internal Audit Bureau). (170 pages).

Kenny, D.T. (1996). *The effects of television/movie/video violence on the behaviour of children and adolescents*. Invited submission from the Australian Family Association (NSW Branch) to the Federal Government's Committee of Ministers on the 'Portrayal of Violence.'

Professional contributions in Psychology and the Law

Journal Reviewer

1. Frontiers in Psychology
2. Journal of Child Sexual Abuse
3. Sexual Abuse: A Journal of Research and Treatment
4. Psychology and the Law
5. International Journal of Offender Therapy and Comparative Criminology
6. Clinical Psychology Review
7. Journal of Sexual Abuse and Treatment
8. Behavioral and Brain Functions
9. Archives of Clinical Psychiatry
10. Australian Psychologist

Other invited presentations (selected)

Kenny, D.T. (2017). *Institutional Child Sexual Abuse*. Invited paper to the Local Court of NSW Annual Conference (2-7 August), Sydney, Australia.

Kenny, D.T. (2013). Young offenders in the juvenile justice system: A story of violence, intellectual disability, substance abuse, alienation and social disadvantage. Invited paper to *The Children's Court Magistrates' Section 16 meeting* (2 November). Sydney, Australia.

Kenny, D.T. (2011). Risks and needs of indigenous offenders: physical and mental health. Invited paper to A weekend conference for judicial officers and Aboriginal community members, *Judicial Commission of NSW* (10-11 September). Sydney, Australia.

Kenny, D.T. (2009). Intellectual disability and Indigenous status are predictors of recidivism in young offenders. Invited paper to the *Australian Institute of Criminology Conference* (1 September), Parramatta, Australia.

Kenny, D.T. (2009). Young offenders: the importance of compensatory attachments and the role of teachers. Keynote paper to the *NSW Department of Education Principals' Conference* (April), Sydney, Australia.

Kenny, D.T. (2007). Juvenile sex offenders: Theory into practice. Invited paper to the *Australian and New Zealand Association for the Treatment of Sex Abuse* (21 June). Blacktown, Sydney.

Kenny, D.T. (2007). Cognitive and educational problems of young offenders. *School Education Directors of Education Twilight Seminars* (26 June). Sydney, Australia.

Kenny, D.T. (2006). Physical and mental needs of young offenders. *Disability Strategic Group*, NSW Department of Juvenile Justice (August). Sydney, Australia.

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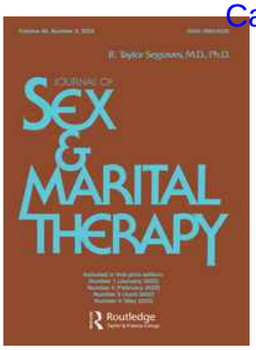
Kenny, D.T., Keogh, T., & Seidler, K. (2001). Developmental and clinical characteristics of juvenile sex offenders: Predictors of recidivism and implications for treatment. *Inaugural Australian Forensic Psychology Conference* (February). Sydney, Australia.

Kenny, D.T. (1999). *Recidivism prediction model for juvenile sex offenders.* Invited presentation to the Minister for Juvenile Justice, Carmel Tebbutt MLC, and the Collaborative Research Unit, NSW Department of Juvenile Justice.



Journal of Sex & Marital Therapy

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/usmt20

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To cite this article: Stephen B. Levine, E. Abbruzzese & Julia M. Mason (2022): Reconsidering Informed Consent for Trans-Identified Children, Adolescents, and Young Adults, Journal of Sex & Marital Therapy, DOI: 10.1080/0092623X.2022.2046221

To link to this article: https://doi.org/10.1080/0092623X.2022.2046221

JOURNAL OF SEX & MARITAL THERAPY
https://doi.org/10.1080/0092623X.2022.2046221

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REVIEW

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Reconsidering Informed Consent for Trans-Identified Children, Adolescents, and Young Adults

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ABSTRACT

In less than a decade, the western world has witnessed an unprecedented rise in the numbers of children and adolescents seeking gender transition. Despite the precedent of years of gender-affirmative care, the social, medical and surgical interventions are still based on very low-quality evidence. The many risks of these interventions, including medicalizing a temporary adolescent identity, have come into a clearer focus through an awareness of detransitioners. The risks of gender-affirmative care are ethically managed through a properly conducted informed consent process. Its elements—deliberate sharing of the hoped-for benefits, known risks and long-term outcomes, and alternative treatments—must be delivered in a manner that promotes comprehension. The process is limited by: erroneous professional assumptions; poor quality of the initial evaluations; and inaccurate and incomplete information shared with patients and their parents. We discuss data on suicide and present the limitations of the Dutch studies that have been the basis for interventions. Beliefs about gender-affirmative care need to be separated from the established facts. A proper informed consent processes can both prepare parents and patients for the difficult choices that they must make and can ease professionals' ethical tensions. Even when properly accomplished, however, some clinical circumstances exist that remain quite uncertain.

KEYWORDS

Informed consent; ethics; gender dysphoria; gender identity; detransition

Introduction

Reconsideration of the meanings, purposes, indications, and processes of informed consent for transgender-identified youth is urgently needed. Parents of gender atypical children are considering social transition as early as preschool or grade school. Parents of preteens and teens are considering supporting their children's wishes to present in a new gender, take puberty blockers, cross-sex hormones, and plan for surgical alterations. College-aged youth are declaring new identities for the first time and obtaining hormones and surgery without their parents' knowledge.

When uncertain parents of children and teens consult their primary care providers, they are usually referred to specialty gender services. Parents and referring clinicians assume that specialists with "gender expertise" will undertake a thorough evaluation. However, the evaluations preceding the recommendation for gender transition are often surprisingly brief (Anderson & Edwards-Leeper, 2021) and typically lead to a recommendation for hormones and surgery, known as *gender-affirmative* treatment.

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Despite the widely recognized deficiencies in the evidence supporting gender-affirmative interventions (National Institute for Health & Care Excellence, 2020a; 2020b), the process of obtaining informed consent from patients and their families has no established standard. There is no consensus about the requisite elements of evaluations, nor is there unanimity about how informed consent processes should be conducted (Byne et al., 2012). These two matters are inconsistent from practitioner to practitioner, clinic to clinic, and country to country.

Social transition, hormonal interventions, and surgery have profound implications for the course of the lives of young patients and their families. It is incumbent upon professionals that these consequences be thoroughly, patiently clarified over time prior to undertaking any element of transition. The informed consent process does not preclude transition; it merely educates the family about the state of the science underpinning the decision to transition. Social transition, hormones, and surgeries are unproven in a strict scientific sense, and as such, to be ethical, require a thorough and fully informed consent process.

Ethical Concerns About Inadequate Informed Consent

The concept of informed consent in medicine has roots in both ethical theory and law. The ethical foundation is centered in the principles of beneficence, justice, and respect for autonomy, while the legal issues have to do with questions of malpractice (Katz et al., 2016).

Patients consenting to treatment must meet age-based and decisional capacity requirements (Katz et al., 2016). Minors less than the age of consent participate in decision-making by providing *assent*—an agreement with the intervention. The limited maturational cognitive capacities of minors are the key reason why parents serve as the ethical and legal surrogates for medical decision-making, tasked with signing an informed consent document (Grootens-Wiegers, Hein, van den Broek, & de Vries, 2017).

The informed consent process consists of three main elements: a disclosure of information about the nature of the condition and the proposed treatment and its alternatives; an assessment of patient and caregiver understanding of the information and capacity for medical decision-making; and obtaining the signatures that signify informed consent has been obtained (Katz et al., 2016). The current expectation that clinicians and institutions are required to thoroughly inform their patients about the benefits, risks, and uncertainties of a particular treatment, as well as about alternatives, has a long legal history in the United States (Lynch, Joffe, & Feldman, 2018).

Ethical concerns about inadequate informed consent for trans-identified youth have several potentially problematic sources, including *erroneous assumptions* held by professionals; *poor quality of the evaluation process*; and *incomplete and inaccurate information* that the patients and family members are given.

These concerns are amplified by the *dramatic growth* in demand for youth gender transition witnessed in the last several years that has led to a perfunctory informed consent process. A rushed process does not allow for a proper discussion of not only the benefits, but the profound risks and uncertainties associated with gender transition, especially when gender transition is undertaken before mature adulthood.

a. *Dramatic growth in demand for services threatens true informed consent*

Gender identity variations were thought to be extremely rare a generation ago. While the incidence in youth had not been officially estimated, in adults it was 2-14 per 100,000 (American Psychiatric Association, 2013, p. 454). However, around 2006, the incidence among youth began to rise, with a dramatic increase observed in 2015 (Aitken et al., 2015, de Graaf, Giovanardi, Zitz, & Carmichael, 2018). Currently, 2-9% of U.S. high school students now identify as transgender, while in colleges, 3% of males and 5% of females identify as gender-diverse (American College Health Association, 2021; Johns et al., 2019; Kidd et al., 2021).

Whereas previously most of the affected individuals identified as the opposite sex, there is now a growing trend toward identifying as *nonbinary*: neither male nor female or both male and female (Chew et al., 2020). A recent study reported that the majority of transgender-identifying youth (63%) now have a non-binary identity (Green, DeChants, Price, & Davis, 2021). Although the incidence of natal males asserting a trans identity in adolescence has significantly increased, the dramatic increase is driven primarily by the increase in natal females requesting services (Zucker, 2017). Many suffer from significant comorbid mental health disorders, have neurocognitive difficulties such as ADHD or autism or have a history of trauma (Becerra-Culqui et al., 2018; Kozlowska, McClure, et al., 2021).

The increase in rates of transgender identification is reflected in the numbers of youth seeking help from medical professionals. For example, according to data reported by the Tavistock gender clinic in the UK, in 2009, there were 51 requests for services (de Graaf et al., 2018); in 2019-2020, 2728 referrals were recorded—a 53-fold increase in just over a decade (Tavistock & Portman NHS Foundation Trust, 2020). The growing number of urban transgender health centers that have arisen in recent years (HRC, n.d.) reflects the increased demand for gender-related medical care among young people in North America Australia, and Europe.

This unprecedented increase has created pressure on institutions and practitioners to rapidly evaluate these youth and make recommendations about treatment. To respond to growing demand, an innovative *informed consent model of care* has been developed. Under this model, mental health evaluations are not required, and hormones can be provided after just one visit following the collection of a patient's or guardian's consent signature (Schulz, 2018). The provision of transition services under this model of care is available not just to those over 18, but for younger patients as well (Planned Parenthood League of Massachusetts, n.d.).

Although following the informed consent model of care for hormones and surgeries for youth may diminish clinicians' ethical or moral unease (Vrouenraets et al., 2020), we believe this model is the antithesis of true informed consent, as it jeopardizes the ethical foundation of patient autonomy. Autonomy is not respected when patients consenting to the treatment do not have an accurate understanding of the risks, benefits, and alternatives.

b. *Assumptions held by professionals influence the integrity of the informed consent process*

Gender dysphoric children and teens can intensely occupy the belief that their lives will be immensely improved by transition. Clinicians who have embraced the gender-affirmative model of care operate on the assumption that children and teens know best what they need to be happy and productive (Ehrensaft, 2017). These professionals, responding to the youths' passionate pleas, see their role as validating the young person's fervent wishes for hormones and surgery and clearing the path for gender transition. In doing so, they privilege the ethical principle of respect for patient autonomy (Clark & Virani, 2021) over their obligations for beneficence and non-maleficence.

Many of the gender-affirmative clinicians subscribe to the theory of *minority stress* – the supposition that the frequently co-occurring psychiatric symptoms of gender dysphoric individuals are a result of prejudice and discrimination brought about by gender non-conformity (Rood et al., 2016; Zucker, 2019), and that gender transition will ameliorate these symptoms. Some even claim that gender-affirmative care will successfully treat not only depression and anxiety but will also resolve neurocognitive deficits frequently present in gender dysphoric individuals (Turban, 2018; Turban, King, Carswell, & Keuroghlian, 2020; Turban & van Schalkwyk, 2018). These latter assertions have proven controversial even among the proponents of gender-affirmative interventions (Strang et al., 2018; van der Miesen, Cohen-Kettenis, & de Vries, 2018). The minority stress theory as the sole explanatory mechanism for co-occurring mental health illness has also been questioned in light of the evidence that psychiatric symptoms frequently pre-date the onset of gender dysphoria (Bechard, VanderLaan, Wood, Wasserman, & Zucker, 2017; Kaltiala-Heino, Sumia, Työläjärvi, & Lindberg, 2015; Kozlowska, Chudleigh, McClure, Maguire,

& Ambler, 2021). Other clinicians recognize the limits of gender-affirmative care and are aware that youth with underlying psychiatric issues are likely to continue to struggle post-transition (Kaltiala, Heino, Työläjärvi, & Suomalainen, 2020), but, unaware of alternative approaches such as gender-exploratory psychotherapy or watchful waiting (Bonfatto & Crasnow, 2018; Churcher Clarke & Spiliadis, 2019; Spiliadis, 2019), these well-meaning professionals continue to treat youth with gender-affirmative interventions despite lingering doubts.

It is common for gender-affirmative specialists to erroneously believe that gender-affirmative interventions are a *standard of care* (Malone, D'Angelo, Beck, Mason, & Evans, 2021; Malone, Hruz, Mason, Beck, et al:, 2021). Despite the increasingly widespread professional beliefs in the safety and efficacy of pediatric gender transition, and the endorsement of this treatment pathway by a number of professional medical societies, the best available evidence suggests that the benefits of gender-affirmative interventions are of very low certainty (Clayton et al., 2021; National Institute for Health & Care Excellence, 2020a; 2020b) and must be carefully weighed against the health risks to fertility, bone, and cardiovascular health (Alzahrani et al., 2019; Biggs, 2021; Getahun et al., 2018; Hembree et al., 2017; Nota et al., 2019). Recently, emphasis has also been placed on psychosocial risks and as yet unknown medical risks (Malone, D'Angelo, et al., 2021).

Five scientific observations question and refute the assumption that an individual's experience of incongruence of sex and gender identity is best addressed by supporting the newly assumed gender identity with psychosocial and medical interventions.

1. The most foundational aspect of the diagnoses of "gender dysphoria" (DSM-5) and "gender incongruence" (ICD-11), requisite for the provision of medical treatment, is in flux, as professionals disagree on whether the presence of distress is a key diagnostic criterion, as stated in the DSM-5, or is irrelevant, as is the case according to the latest ICD-11 criteria (American Psychiatric Association, 2013; World Health Organization, 2019). Further, these diagnoses have never been properly field-tested (de Vries et al., 2021).
2. There are no randomized controlled studies demonstrating the superiority of various affirmative interventions compared to alternatives. There isn't even agreement about which outcome measures would be ideal in such studies.
3. There are few long-term follow-up studies of various interventions using predetermined outcome measures at designated intervals. Studies that have been conducted are, at best, inconsistent. Higher quality studies with longer-follow-up fail to demonstrate durable positive impacts on mental health (Bränström & Pachankis, 2020a; 2020b).
4. Rates of post-transition desistance, increased mental suffering, increased incidence of physical illness, educational failure, vocational inconstancy, and social isolation have not been established.
5. Numerous cross-sectional and prospective studies of transgender adults consistently demonstrate a high prevalence of serious mental health and social problems as well as suicide (Asscheman et al., 2011; Dhejne et al., 2011). Controversies about how to deal with trans-identified youth must consider the well described vulnerabilities of transgender adults.

It is equally important to realize that to date, research about alternative approaches, such as psychotherapy or watchful waiting, shares the scientific limitations of the research of more invasive interventions: there are no control groups, nor is there systematic follow-up at predetermined intervals with predetermined means of measurement (Bonfatto & Crasnow, 2018; Churcher Clarke & Spiliadis, 2019; Spiliadis, 2019). Parents and patients need to be informed of this as well.

Perhaps the single most problematic assumption held by some gender clinicians is that the young patients have simply been "born in the wrong body." This assumption seemingly frees clinicians from having to contend with the ethical dilemmas of recommending body-altering

interventions that are based on very low-quality evidence. Despite the principle of development that biology, psychosocial factors, and culture generate behavior, these clinicians may believe that atypical genders are created by biology. This reductionistic approach has been criticized repeatedly (Kendler, 2019).

While the origins of childhood or adolescent onset of gender incongruence have not yet been fully elucidated, brain studies of increasing technical sophistication have yet to demonstrate a distinct structure or pattern that accounts for an atypical gender identity, after statistically controlling for sexual orientation and exposure to exogenous hormones (Frigerio, Ballerini, & Valdés Hernández, 2021). Twin studies also demonstrate that while biology plays a role in one's experience of "gender incongruence," it is far from deterministic (Diamond, 2013).

A growing number of clinicians and researchers are noting that the dramatic rise of teens declaring a trans identity appears to be, at least in part, a result of peer influence (Anderson, 2022; Hutchinson, Midgen, & Spiliadis, 2020 Littman, 2018; Littman, 2020; Zucker, 2019). Some have noted yet another influx of trans-identified youth emerging during the COVID lockdowns, and have hypothesized that increased isolation coupled with heavy internet exposure may be responsible (Anderson, 2022). While the research into the phenomenon of social influence as a contributor to trans identification of youth is still in its infancy, the possibility that clinicians are providing treatments with permanent consequences to address what may be transient identities in youth poses a serious ethical dilemma.

c. *Poor evaluations*

There is a growing recognition that rapid evaluations which disregard factors contributing to the development of gender dysphoria in youth are problematic. In November 2021, two leaders of the World Professional Organization for Transgender Health (WPATH) warned the medical community that the "The mental health establishment is failing trans kids" (Anderson & Edwards-Leeper, 2021). Frequently, evaluations provided by gender clinicians may only ascertain the diagnosis of *gender dysphoria* (DSM-5) or its ICD-11 counterpart *gender incongruence*, and screen for conspicuous mental illness prior to recommending hormones and surgeries. These limited, abbreviated evaluations overlook, and as a result fail to address, the relevant issue of the forces that may have influenced the young person's current gender identity.

Confirming the young person's self-diagnosis of gender dysphoria or gender incongruence is easy. Clarifying the developmental forces that have influenced it and determining an appropriate intervention are not. Contextualizing these forces involves an understanding of child and adolescent developmental processes, childhood adversity, co-existing physical and cognitive disadvantages, unfortunate parental or family circumstances (Levine, 2021), as well as the role of social influence (Anderson, 2022; Anderson & Edwards-Leeper, 2021; Littman, 2018; 2021).

The poor quality of mental health evaluations has been a point of significant discontent for a growing number of parents of gender dysphoric youth. Increasingly, parents have formed dozens of support groups in North America, Europe, Australia and New Zealand, united in their objections to the idea that the best or the only treatment for their gender dysphoric children is affirmation (Genspect, 2021). These distressed parents, recognizing that their son or daughter may eventually decide to present to others as a trans person, want a psychotherapeutic investigation to understand what contributed to the development of this identity and an exploration of noninvasive treatment options. Frequently, they cannot find anyone in their community who does not recommend immediate affirmation.

The American Academy of Pediatrics' Committee of Bioethics recognizes that "parents…are better situated than others to understand the unique needs of their children and to make appropriate, caring decisions regarding their children's health care" (Katz et al., 2016). The plight of the families unable to find specialists capable of conducting thorough evaluations draws attention to the widespread acceptance of medical interventions for gender-dysphoric youth as the first line of treatment. The problem is that such care has been established through precedent rather

than through scientific demonstrations of its efficacy. We contend that parents and patients have a right to know this, and that it is the professionals' responsibility and obligation to inform them of the state of knowledge in this arena of care.

d. *Incorrect information shared*

In sharing the information with patients and families, two key areas of uncertainty must be emphasized. The first one is the uncertain permanence of a child's or an adolescent's gender identity (Littman, 2021; Ristori & Steensma, 2016; Singh, Bradley, & Zucker, 2021; Vandenbussche, 2021; Zucker, 2017). The second is the uncertain long-term physical and psychological health outcomes of gender transition (National Institute for Health & Care Excellence, 2020a; 2020b). Unfortunately, gender specialists are frequently unfamiliar with, or discount the significance of, the research in support of these two concepts. As a result, the informed consent process rarely adequately discloses this information to patients and their families.

Problematically, it is common for gender clinicians to emphasize the risk of suicide if a young person's wish to transition gender is not immediately fulfilled. There is a significant amount of misinformation surrounding the question of suicidality of trans-identified youth (Biggs, 2022). Providers of gender-affirmative care should be careful not to unwittingly propagate misinformation regarding suicide to parents and youths. They should also be reminded that any conversations about suicide should be handled with great care, due to its socially contagious nature (Bridge et al., 2020; HHS, 2021).

i. High Rate of desistance/natural resolution of gender dysphoria in children is not disclosed

There have been eleven research studies to date indicating a high rate of resolution of gender incongruence in children by late adolescence or young adulthood without medical interventions (Cantor, 2020; Ristori & Steensma, 2016; Singh et al., 2021). An attempt has been made to discount the applicability of this research, suggesting that the studies were based on merely gender non-conforming, rather than truly gender-dysphoric, children (Temple Newhook et al., 2018). However, a reanalysis of the data prompted by this critique confirmed the initial finding: Among children meeting the diagnostic criteria for "Gender Identity Disorder" in DSM-IV (currently "Gender Dysphoria in DSM-5), 67% were no longer gender dysphoric as adults; the rate of natural resolution for gender dysphoria was 93% for children whose gender dysphoria was significant but subthreshold for the DSM diagnosis (Zucker, et al., 2018). It should be noted that high resolution of childhood-onset gender dysphoria had been recorded before the practice of social transition of young children was endorsed by the American Academy of Pediatrics (Rafferty et al., 2018). It is possible that social transition will predispose a young person to persistence of transgender identity long-term (Zucker, 2020).

The information regarding the resolution of gender dysphoria among those with adolescent-onset gender dysphoria, which is currently the predominant presentation, is less clear. A growing body of evidence suggests that for many teens and young adults, a post-pubertal onset of transgender identification can be a transient phase of identity exploration, rather than a permanent identity, as evidenced by a growing number of young detransitioners (Entwistle, 2020; Littman, 2021; Vandenbussche, 2021). Previously, the rate of detransition and regret was reported to be very low, although these estimates suffered from significant limitations and were likely undercounting true regret (D'Angelo, 2018). However, in the last several years since gender-affirmative care has become popularized, the rate of detransition appears to be accelerating.

According to a recent study from a UK adult gender clinic, 6.9% of those treated with gender-affirmative interventions detransitioned within only 16 months of starting treatment, and another 3.4% had a pattern of care suggestive of detransition, yielding a rate of probable detransition in excess of 10%. Another 21.7% of patients disengaged from the clinic without completing

their treatment plan (Hall, Mitchell, & Sachdeva, 2021). While some of these individuals later reengaged with the gender service, the authors concluded, "detransitioning might be more frequent than previously reported." Another study from a UK primary care practice found that 12.2% of those who had started hormonal treatments either detransitioned or documented regret, while the total of 20% stopped the treatments for a wider range of reasons. The mean age of their presentation with gender dysphoria was 20, and the patients had been taking gender-affirming hormones for the average 5 years (17 months-10 years) prior to discontinuing.

Comparing these much higher rates of treatment discontinuation and detransition to the significantly lower rates reported by the older studies, the researchers noted: "Thus, the detransition rate found in this population is novel and questions may be raised about the phenomenon of overdiagnosis, overtreatment, or iatrogenic harm as found in other medical fields" (Boyd, Hackett, & Bewley, 2022 p.15). Indeed, given that regret may take up to 8-11 years to materialize (Dhejne, Öberg, Arver, & Landén, 2014; Wiepjes et al., 2018), many more detransitioners are likely to emerge in the coming years. Detransitioner research is still in its infancy, but two recently published studies examining detransitioner experiences report that detransitioners from the recently-transitioning cohorts feel they had been rushed to medical gender-affirmative interventions with irreversible effects, often without the benefit of appropriate, or in some instances any, psychologic exploration (Littman, 2021; Vandenbussche, 2021).

Clinicians should also disclose to patients and parents that there is no test which can accurately predict who will persist in their transgender identification upon reaching mature adulthood (Ristori & Steensma, 2016). Families should be made aware that a period of strong cross-sex identification in childhood is commonly associated with future homosexuality (Korte et al., 2008). Research in desistance confirms that the majority of youth whose gender dysphoria resolves naturally do indeed grow up to be gay, lesbian, or bisexual adults (Cantor, 2020, Appendix; Singh et al., 2021).

ii. Implications of very low-quality evidence that underlies the practice of pediatric gender transition are not explained

The quality of evidence underlying the practice of pediatric gender transition is widely recognized to be of very low quality (Hembree et al., 2017). In 2020, the most comprehensive systematic review of evidence to date, commissioned by the UK National Health System (NHS) and conducted by the National Institute for Health and Care Excellence (NICE), concluded that the evidence for both puberty blocking and cross-sex hormones is of very low certainty (National Institute for Health & Care Excellence, 2020a; 2020b).

According to the NICE review of evidence for puberty blockers, the studies "are all small, uncontrolled observational studies, which are subject to bias and confounding, and are of very low certainty as assessed using modified GRADE [Grading of Recommendations, Assessment, Development and Evaluations]. All the included studies reported physical and mental health comorbidities and concomitant treatments very poorly" (National Institute for Health & Care Excellence, 2020a, p.13). NICE reached similar conclusions regarding the quality of the evidence for cross-sex hormones (National Institute for Health & Care Excellence, 2020b).

Problematically, the implications of administering a treatment with irreversible, life-changing consequences based on evidence that has an official designation of "very low certainty" according to modified GRADE is rarely discussed with the patients and the families. GRADE is the most widely adopted tool for grading the quality of evidence and for making treatment recommendations worldwide. GRADE has four levels of evidence, also known as certainty in evidence or quality of evidence: very low, low, moderate, and high (BMJ Best Practice, 2021). When evidence is assessed to be "very low certainty," there is a high likelihood that the patients will not experience the effects of the proposed interventions (Balshem et al., 2011).

In the context of providing puberty blockers and cross-sex hormones, the designation of "very low certainty" signals that the body of evidence asserting the benefits of these interventions is

highly unreliable. In contrast, several negative effects are quite certain. For example, puberty blockade followed by cross-sex hormones leads to infertility and sterility (Laidlaw, Van Meter, Hruz, Van Mol, & Malone, 2019). Surgeries to remove breasts or sex organs are irreversible. Other health risks, including risks to bone and cardiovascular health, are not fully understood and are uncertain, but the emerging evidence is alarming (Alzahrani et al., 2019; Biggs, 2021).

iii. The question of suicide is inappropriately handled

Suicide among trans-identified youth is significantly elevated compared to the general population of youth (Biggs, 2022; de Graaf et al., 2020). However, the "transition or die" narrative, whereby parents are told that their only choice is between a "live trans daughter or a dead son" (or vice-versa), is both factually inaccurate and ethically fraught. Disseminating such alarmist messages hurts the majority of trans-identified youth who are not at risk for suicide. It also hurts the minority who are at risk, and who, as a result of such misinformation, may forgo evidence-based suicide prevention intervention in the false hopes that transition will prevent suicide.

The notion that trans-identified youth are at alarmingly high risk of suicide usually stems from biased online samples that rely on self-report (D'Angelo et al., 2020; James et al., 2016; The Trevor Project, 2021), and frequently conflates suicidal thoughts and non-suicidal self-harm with serious suicide attempts and completed suicides. Until recently, little was known about the actual rate of suicide of trans-identified youth. However, a recent analysis of data from the biggest pediatric gender clinic in the world, the UK's Tavistock, found the rate of completed youth suicides to be 0.03% over a 10-year period, which translates into the annual rate of 13 per 100,000 (Biggs, 2022). While this rate is significantly elevated compared to the general population of teens, it is far from the epidemic of trans suicides portrayed by the media.

The "transition or die" narrative regards suicidal risk in trans-identified youth as a different phenomenon than suicidal risk among other youth. Making them an exception falsely promises the parents that immediate transition will remove the risk of suicidal self-harm. Trans patients themselves complain about the so-called "trans broken arm syndrome" – a frustrating pattern whereby physicians "blame" all the problems the patients are experiencing on their trans status, and a result, fail to perceive and respond to other sources of distress (Paine, 2021). Clinicians caring for trans-identified youth should be reminded that suicide risk in all patients is a multi-factorial phenomenon (Mars et al., 2019). To treat trans youths' suicidality as an exception is to deny them evidence-based care.

A recent study of three major youth clinics concluded that suicidality of trans-identifying teens is only somewhat elevated compared to that of youth referred for mental health issues unrelated to gender identity struggles (de Graaf et al., 2020). Another study found that transgender-identifying teens have relatively similar rates of suicidality compared to teens who are gay, lesbian and bisexual (Toomey, Syvertsen, & Shramko, 2018). Depression, eating disorders, autism spectrum conditions, and other mental health conditions commonly found in transgender-identifying youth (Kaltiala-Heino, Bergman, Työläjärvi, & Frisen, 2018; Kozlowska, McClure, et al., 2021; Morandini, Kelly, de Graaf, Carmichael, & Dar-Nimrod, 2021) are all known to independently contribute to the probability of suicide (Biggs, 2022; Simon & VonKorff, 1998; Smith, Zuromski, & Dodd, 2018).

The "transition or suicide" narrative falsely implies that transition will prevent suicides. Clinicians working with trans-identified youth should be aware that although in the short-term, gender-affirmative interventions can lead to improvements in some measures of suicidality (Kaltiala et al., 2020), neither hormones nor surgeries have been showed to reduce suicidality in the long-term (Bränström & Pachankis, 2020a; 2020b). Alarmingly, a longitudinal study from Sweden that covered more than a 30-year span found that adults who underwent surgical transition were 19 times more likely than their age-matched peers to die by suicide overall, with female-to-male participants' risk 40 times the expected rate (Dhejne et al., 2011, Table S1).

Another key longitudinal study from the Netherlands concluded that suicides occur at a similar rate at all stages of transition, from pretreatment assessment to post-transition follow-up (Wiepjes et al., 2020). The data from the Tavistock clinic also did not show a statistically significant difference between completed suicides in the "waitlist" vs. the "treated" groups (Biggs, 2022). Luckily, in both groups, completed suicides were rare events (which may have been responsible for the lack of statistical significance). Thus, we consider the "transition or die" narrative to be misinformed and ethically wrong.

In our experience in working with trans-identified youth, an adolescent's suicidality can sometimes arise as a response to parental distress, resistance, skepticism, or wish to investigate the forces shaping the new gender identity before social transition and hormone therapy. When mental health professionals or other healthcare providers fail to recognize the legitimacy of parental concerns, or label the parents as transphobic, this only tends to intensify intrafamilial tension. Clinicians would be well-advised that gender transition is not an appropriate response to suicidal intent or threat, as it ignores the larger mental health and social context of the young patient's life—the entire family is often in crisis. Trans-identified adolescents should be screened for self-harm and suicidality, and if suicidal behaviors are present, an appropriate evidence-based suicide prevention plan should be put in place (de Graaf et al., 2020).

The Dutch Study: the questionable basis for the gender affirmative model of care for youth

Few practitioners of gender-affirmative interventions, and even fewer patients and families, realize that the foundation of the practice of medically transitioning minors stems from a single Dutch proof of concept study, the outcomes of which were documented in two studies (de Vries, Steensma, Doreleijers, Cohen, & Kettenis, 2011; de Vries et al., 2014). The former (de Vries et al., 2011) reported on cases who underwent puberty blockade, while the latter (de Vries et al., 2014) reported on a subset of the cases who completed surgeries.

The Dutch study subjects' high level of psychological functioning at 1.5 years after surgery, which was the study end point, was an impressive feat. However, both of the studies suffer from a high risk of bias due to their study design, which is effectively a non-randomized case series—one of the lowest levels of evidence (Mathes & Pieper, 2017; National Institute for Health & Care Excellence, 2020a). In addition, the studies suffer from limited applicability to the populations of adolescents presenting today (de Vries, 2020). The interventions described in the study are currently being applied to adolescents who were not cross-gender identified prior to puberty, who have significant mental health problems, as well as those who have non-binary identities—all of these presentations were explicitly disqualified from the Dutch protocol. Despite these limitations, the Dutch clinical experiment has become the basis for the practice of medical transition of minors worldwide and serves as the basis for the recommendations outlined in the 2017 Endocrine Society guidelines (Hembree et al., 2017).

We contend that the Dutch studies have been misunderstood and misrepresented as providing evidence of the safety and efficacy of these interventions for all youth. It is important that both the strengths and the weaknesses of these two studies are understood, as to date, the Dutch experience presents the best available evidence behind the practice of pediatric gender transition.

Rationale for pediatric transition

Prior to the 1990s, gender transitions were typically initiated in mature adults (Dhejne et al., 2011). However, it was noted that particularly for natal male patients, hormonal and surgical interventions failed to achieve satisfactory results, and patients had a "never disappearing masculine appearance" (Delemarre-van de Waal & Cohen-Kettenis, 2006). The lack of adequate cosmetic outcomes was thought to contribute to the frequently disappointing outcomes of medical

gender transition, with persistently high rates of mental illness and suicidality post-transition (Delemarre-van de Waal & Cohen-Kettenis, 2006; Dhejne et al., 2011; Ross & Need, 1989).

In the mid 1990s, a team of Dutch researchers hypothesized that by carefully selecting a subset of gender dysphoric children who would likely be transgender-identified for the rest of their lives, and by medically intervening before puberty left an irreversible mark on their bodies, the cosmetic outcomes would be improved—and as a result, mental health outcomes might be improved (Gooren & Delemarre-van de Waal, 1996).

Mixed study findings

In 2014, the Dutch research team published a key longitudinal study of mental health outcomes of 55 youths who completed medical and surgical transition (de Vries et al., 2014). The 2014 paper (sometimes referred to as the "Dutch study") reported that for youth with severe gender dysphoria that started in early childhood and persisted into mid-adolescence, a sequence of puberty blockers, cross-sex hormones, and breast and genital surgeries (including a mandatory removal of the ovaries, uterus and testes), with ongoing extensive psychological support, was associated with positive mental health and overall function 1.5 years post-surgery.

While the Dutch reported resolution of gender dysphoria post-surgery in study subjects, the reported psychological improvements were quite modest (de Vries et al., 2014). Of the 30 psychological measurements reported, nearly half showed no statistically significant improvements, while the changes in the other half were marginally clinically significant at best (Malone, D'Angelo, et al., 2021). The scores in anxiety, depression, and anger did not improve. The change in the Children's Global Assessment Scale, which measures overall function, was one of the most impressive changes—however it too remained in the same range before and after treatment (de Vries et al., 2014).

Problematic discordance between reduced gender dysphoria and lack of meaningful improvements in psychological measures

The discordance between the marked reduction in gender dysphoria, as measured by the UGDS (Utrecht Gender Dysphoria Scale), and the lack of meaningful changes in psychological function using standard measures, warrants further examination. There are three plausible explanations for this lack of agreement. Any one of these three explanations calls into question the widely assumed notion that the medical interventions significantly improve mental health or lessen or eradicate gender dysphoria.

One possible explanation is that gender dysphoria as measured by UGDS, and psychological function, as measured by most standard instruments, are not correlated. This contradicts the primary rationale for providing gender-affirmative treatments for youth (which is to improve psychological health and functioning), and if true, ethically threatens these medical interventions. The other plausible explanation stems from the high psychological function of all the subjects at baseline; the subjects were selected because they were free from significant mental health problems (de Vries et al., 2014). As a result, there was little opportunity to meaningfully improve. This explanation highlights a key limitation in applying the study's results to the majority of today's gender dysphoric youth, who often present with a high burden of mental illness (Becerra-Culqui et al., 2018; Kozlowska, McClure, et al., 2021). The study cannot be used as evidence that these procedures have been proven to improve depression, anxiety, and suicidality.

A third possible explanation for the discordance between only minor changes in psychological outcomes but a significant drop in gender dysphoria comes from a close examination of the UGDS scale itself and how it was used by the Dutch researchers. This 12-item scale, designed by the Dutch to assess the severity of gender dysphoria and to identify candidates for hormones

and surgeries, consists of "male" (UGDS-aM) and "female" (UGDS-aF) versions (Iliadis et al., 2020). At baseline and after puberty suppression, biological females were given the "female" scale, while males were given the "male" scale. However, post-surgery, the scales were flipped: biological females were assessed using the "male" scale, while biological males were assessed on the "female" scale (de Vries et al., 2014). We maintain that this handling of the scales may have at best obscured, and at worst, severely compromised the ability to meaningfully track how gender dysphoria was affected throughout the treatment.

Consider this example. At baseline, a gender dysphoric biological female would rate items from the "female" scale such as: "I prefer to behave like a boy" (item 1); "I feel unhappy because I have to behave like a girl" (item 6) and "I wish I had been born a boy" (item 12). Positive answers to these questions would have contributed to a high baseline gender dysphoria score. After the final surgery, however, this same patient would be asked to rate items from the "male" scale, including the following: "My life would be meaningless if I had to live as a boy" (item 1); "I hate myself because I am a boy" (item 6) and "It would be better not to live than to live as a boy" (item 12). A gender dysphoric female would not endorse these statements (at any stage of the intervention), which would lead to a lower gender dysphoria score.

Thus, the detected drop in the gender dysphoria scores for biological males and females may have had less to do with the success of the interventions, and more to do with switching the scale from the "female" to the "male" version (and vice-versa) between the baseline and post-surgical period. This, too, may explain why no changes in gender dysphoria were noted between baseline and the puberty blockade phase, and were only recorded after the final surgery, when the scale was switched.

It must be considered that had the researchers administered the "flipped" scale earlier, at the completion of the puberty blocker stage, UGDS scale could have registered the reduction in gender dysphoria. Likewise, however, one must consider the possibility that had *both sets of scales* been administered to the same individual at baseline, a "reduction" in gender dysphoria could have been registered upon switching of the scale, *well before any interventions began*. The question here is whether the diminishment of quantitative measures of gender dysphoria is largely an artifact of what scale was used.

It must be noted that the UGDS measure has been demonstrated only to effectively differentiate between clinically referred gender dysphoric individuals, non-clinically referred controls, and participants with disorders of sexual development, and was not designed to detect changes in gender dysphoria during treatment (Steensma, McGuire, Kreukels, et al. 2013). The presence of items such as "I dislike having erections" (item 11, UGDS-aM), which would have to be rated by birth-females, and "I hate menstruating because it makes me feel like a girl (item 10, UGDS-aF), which would be presented to birth-males, neither of which could be meaningfully rated by either at any stage of the interventions, further illustrates that UGDS has questionable validity for the purpose of detecting meaningful changes in gender dysphoria as a result of medical and surgical treatment.

The updated UGDS scale (UGDS-GS), developed by the Dutch after the publication of their seminal study, has eliminated the two-sex version of the scale in favor of a single battery of questions applicable to both sexes (McGuire et al., 2020). This change may lead to a more reliable measurement of treatment-associated changes in future research. Other gender dysphoria scales also exist (Hakeem, Črnčec, Asghari-Fard, Harte, & Eapen, 2016; Iliadis et al., 2020) and may or may not be better suited for the purposes of measuring the impact of medical interventions on underlying gender distress. Gender dysphoria, of course, may also prove to be a more complex concept than can be measured by any scale.

Other limitations

The two Dutch studies were conducted without a control group (de Vries et al., 2011; de Vires et al., 2014). Nor could the researchers control for mental health interventions, which all the

subjects received in addition to hormones and surgery. The Dutch only evaluated mental health outcomes and did not assess physical health effects of hormones and surgery. The sample size was small: the final study reported the outcomes of only 55 children, and as few as 32 were evaluated on key measures of psychological outcomes.

It is important to realize that the Dutch sample was carefully selected, which introduced a source of bias, and also challenges the study's applicability. From the 196 adolescents initially referred, 111 were considered eligible to start puberty blockers, and of this group, only the 70 most mature and mentally stable who proceeded to cross-sex hormones were included in the study (de Vries et al., 2011). Of note, 97% of the selected cases were attracted to members of their natal sex at baseline. All were cross-sex identified, with no cases of non-binary identities. The final study only followed 55, rather than the original 70 cases, further excluding from reporting the outcomes of subjects who had experienced adverse events, including: one death from surgery-related complications and three cases of complications such as obesity and diabetes that rendered subjects ineligible for surgery. Three more subjects refused to be contacted or dropped out of care, which may mask adverse outcomes (de Vries et al., 2014).

There is no knowledge of the fate of 126 patients who did not participate in the Dutch study. Longer term outcomes of the subjects who did participate are lacking. We are aware of only one case of long-term follow-up for a female-to-male patient treated by the Dutch team in the 1990s. The case study describing the subject's functioning at the age of 33 found that the patient did not regret gender transition. However, he reported struggling with significant shame related to the appearance of his genitals and to his inability to sexually function; had problems maintaining long-term relationships; and experienced depressive symptoms (Cohen-Kettenis, Schagen, Steensma, de Vries, & Delemarre-van de Waal, 2011). Notably, these problems had not yet emerged when the same patient was assessed at the age of 20, when he reported high levels of satisfaction in general, and was "very satisfied with the results [of the metoidioplasty]" in particular (Cohen-Kettenis & van Goozen, 1998, p.248). Since the last round of psychological outcomes of the individuals in the Dutch study was obtained when the subjects were around 21 years of age (de Vries et al., 2014), it raises questions how they will fair in during the decade when new developmental tasks, such as, career development, forming long-term intimate relationships and friendships, or starting families come into focus.

As to the unknown outcomes of the patients rejected by the Dutch protocol, one study did report on 14 adolescents who sought gender reassignment in the same clinic, but were disqualified from treatment due to "psychological or environmental problems" (Smith, Van Goozen, & Cohen-Kettenis, 2001, p. 473). The study found that at follow-up 1-7 years after the original application, 11 of the 14 no longer wished to transition, and 2 others only slightly regretted not transitioning (Malone, D'Angelo, et al., 2021; Smith et al., 2001). This further underscores the importance of conducting research utilizing control groups and following the subjects for an extended period.

A recent attempt to replicate the results of the first Dutch study (de Vries et al., 2011) found no demonstrable psychological benefit from puberty blockade, but did find that the treatment adversely affected bone development (Carmichael et al., 2021). The final Dutch study (de Vries et al., 2014) has never been attempted to be replicated with or without a control group.

The scaling of the Dutch Protocol beyond original indications

The medical and surgical sequence of Dutch protocol has been aggressively scaled worldwide without the careful evaluations and vetting practiced by the Dutch. The protocol's original investigators have recently expressed concern that the interventions they described have been widely adopted on four continents without several of the protocol's essential discriminatory features (de Vries, 2020).

The extensive multi-year multidisciplinary evaluations of the children have been abbreviated or simply bypassed. The medical sequence is routinely used for children with post-pubertal onset of transgender identities complicated by mental health comorbidities (Kaltiala-Heino et al., 2018), and not just for those high-functioning adolescents with persistent early life cross-identifications, as was required by the Dutch protocol (de Vries & Cohen-Kettenis, 2012). Further, it has become increasingly common to socially transition children before puberty (Olson, Durwood, DeMeules, & McLaughlin, 2016), even though this was explicitly discouraged by the Dutch protocol at the time (de Vries & Cohen-Kettenis, 2012).

In addition, medical transition is frequently initiated much earlier than recommended by the original protocol (de Vries & Cohen-Kettenis, 2012). The authors of the protocol were aware that most children would have a spontaneous realignment of their gender identity with sex by going through early- to mid-stages of puberty (Cohen-Kettenis, Delemarre-van de Waal, & Gooren, 2008). The average age of initiating puberty blockade in the Dutch study was around 15. In contrast, currently the age limit has been lowered to the age of Tanner stage II, which can occur as early as 8-9 years (Hembree et al., 2017). Irreversible cross-sex hormones, initiated in the Dutch study at the average age of nearly 17, are currently commonly prescribed to 14-year-olds, and this lower age threshold has been recommended by draft recommendation by WPATH Standards of Care 8, the final version of which is due to be released in early 2022. The fact that children are transitioned before their identity is tested against the biological reality and before natural resolution of gender dysphoria has had a chance to occur is a major deviation from the original Dutch protocol. Systematic follow-up, reassessments, and tracking and publishing of outcomes are not performed.

As the lead Dutch researchers have begun to call for more research into the novel presentation of gender dysphoria in youth (de Vries, 2020; Voorzij, 2021) and question the wisdom of applying the hormonal and surgical treatment protocols to the newly presenting cases, many recently educated gender specialists mistakenly believe that the Dutch protocol proved the concept that its sequence helps all gender-dysphoric youth. Although aware of the Dutch study's importance, they seem to be unaware of its agreed upon limitations, and the Dutch clinicians' own discomfort that most new trans-identified adolescents presenting for care today significantly differ from the population the Dutch had originally studied. These facts, of course, underscore the need for a robust informed consent process.

The recommendations for informed consent process for children, adolescents, and young adults

Consent for all stages of gender transition should be explicit, not implied

Noninvasive medical care or care that carries little risk of harm does not require a signed informed consent document; rather, consent is implied through the act of a patient presenting for care. For example, when a parent brings in a child for a skin laceration or abscess, consent for sutures or simple incision and drainage is implied. Similarly, when a child presents with pneumonia and is hospitalized, consent for chest x-ray, IV fluids, and antibiotics is also implied. It is assumed that patients or their guardians agree to the interventions and understand the benefits and risks. When risks are greater, such as prior to surgery, chemotherapy, or another invasive procedure, an informed consent document is signed. Such situations require an explicit, or express informed consent.

In the context of interventions for gender dysphoria or gender incongruence, the uncertainties associated with puberty blocking, cross-sex hormones, and gender-affirmative surgeries are well-recognized (Manrique et al., 2018; National Institute for Health & Care Excellence, 2020a; 2020b; Wilson et al., 2018). In these cases, consent should be explicit rather than implied because of the complexity, uncertainty, and risks involved.

Informed consent for social transition represents a gray area. Evidence suggests that social transition is associated with the persistence of gender dysphoria (Hembree et al.,

2017; Steensma, McGuire, Kreukels, Beekman, & Cohen-Kettenis, 2013). This suggests that social gender transition is a form of a psychological intervention with potential lasting effects (Zucker, 2020). While the causality has not been proven, the possibility of iatrogenesis and the resulting exposure to the risks of future medical and surgical gender dysphoria treatments, qualifies social gender transition for explicit, rather than implied, consent.

Full unbiased disclosure of benefits, risks and alternatives is requisite

When mental health professionals are involved in evaluations and recommendations, the informed consent process begins either as part of an extended evaluation or is integrated in a psychotherapeutic process, separately or together, with the parents and patient. When pediatricians, nurse practitioners, or primary care physicians perform the initial evaluation, the informed consent process is more likely to be labeled as such in a briefer series of meetings.

In all settings, the informed consent discussions for gender-affirmative care should include three central ideas:

1. The decision to initiate gender transition may predispose the child to persist in their transgender identity long-term.
2. Many of the physical changes contemplated and undertaken are irreversible.
3. Careful long-term studies have not been done to verify that these interventions enable better physical and mental health or improved social functioning, or that they do not cause harm.

The informed consent process, culminating with a signed document, signifies that parents and patient have been educated about the short- and long-term risks, benefits and uncertainties associated with all relevant stages of the gender-affirmative interventions. The process must also inform the patients and families about the full range of alternative treatments, including the choice of not socially or medically treating the child's or adolescent's current state of gender/body incongruence.

Decisional capacity to consent needs to be assessed and family should be involved

Trans-identified youth typically present themselves as strongly desiring hormones and ultimately, surgery. It should not be assumed that their eagerness is matched with the capacity to carefully consider the consequences of their realized desires. Trans-identified youth younger than the age of consent should be part of the informed consent process, but they may not be mature enough to recognize or admit their concerns about the proposed intervention. For this reason, it is the parents who, after careful consideration, are responsible for signing an informed consent document.

The issue of the exact age at which adolescents are mature enough to consent to gender transition has proven contentious: courts have been asked to decide about competence to consent to gender-affirmative hormones for youth in the United Kingdom and Australia (Ouliaris, 2021). In the United States, the legal age for medical consent for gender-affirmative interventions varies by state.

When patients are age 18 and older, and in some jurisdictions as young as age 15 (Right to medical or dental treatment without parental consent, 2010), they do not legally require parental approval for medical procedures. But because an individual's change of gender has profound implications for parents, siblings, and other family members, it is usually prudent for clinicians to seek their input directly or indirectly during the informed consent process. This is done by requesting a meeting with the parents.

A recent study by a Dutch research team attempted to evaluate the decisional capacity of adolescents embarking on gender transition (Vrouenraets, de Vries, de Vries, van der Miesen, & Hein, 2021). The researchers administered the MacCAT-T tool, comprised of the *understanding*, *appreciating*, *reasoning*, and *expressing a choice* domains, to 74 adolescents who were 14.7 years old on average (with the minimum age of 10). They concluded that the adolescents were competent to consent for starting pubertal suppression, calling for similar research for the <12 group, particularly because "birth-assigned girls … may benefit from puberty suppression as early as 9 years of age" (Vrouenraets et al., 2021 p.7).

This study suffers from two significant limitations involving the MacCAT-T tool. It was never designed for children. Rather, it was designed to assess medical consent capacities of adults suffering from conditions such as dementia, schizophrenia, and other psychiatric disorders. There is a fundamental lack of equivalency between consenting to treatment by adults with cognitive impairments and obtaining consent from healthy children whose age-appropriate cognitive capacities are intact, but who lack the requisite life experiences to consent to profound life-changing medical interventions. We doubt, for example, whether even highly intelligent children who have not had sexual experiences can meaningfully comprehend the loss of future sexual function and reproductive abilities.

In addition, even for adults, the MacCAT-T tool has been criticized for its exclusive focus on cognitive aspects of capacity, failing to account for the non-cognitive aspects such as values, emotions and other biographic and context specific aspects inherent in the complexity of the decision process in real life (Breden & Vollmann, 2004). Children's values and emotions undergo tremendous change during the process of maturation.

The authors' conclusion about their young patients' competence to consent should be compared with what a panel of judges wrote in the challenge to the Tavistock treatment protocol (Bell v Tavistock, 2020):

> …the clinical intervention we are concerned with here is different in kind to other treatments or clinical interventions. In other cases, medical treatment is used to remedy, or alleviate the symptoms of, a diagnosed physical or mental condition, and the effects of that treatment are direct and usually apparent. The position in relation to puberty blockers would not seem to reflect that description. [para 135]

> …we consider the treatment in this case to be in entirely different territory from the type of medical treatment which is normally being considered. [para 140]

> … the combination here of lifelong and life changing treatment being given to children, with very limited knowledge of the degree to which it will or will not benefit them, is one that gives significant grounds for concern. [para 143]

It seems clear that perceptions of children as young as 10 years of age as medically competent vary by country, state, and the institution where the doctor works, and, by clinicians' beliefs about the long-term benefits of these interventions. We maintain that the claim that kids can consent to extreme life-altering interventions is a fundamentally a philosophical claim (Clark & Virani, 2021). Our view in this matter is that consent is primarily a parental function.

Informed consent should be viewed as a process rather than an event

Most institutions that care for transgender-identified individuals have devised obligatory consent forms that outline the risks and uncertainties of hormonal and surgical gender-affirmative interventions. However, the requisite signatures are frequently collected in a perfunctory manner (Schulz, 2018), akin to signatures collected ahead of a common surgical procedure. The purpose of such informed consent documents appears to be to protect practitioners from lawsuits, rather than attend to the primary ethical foundation of the process.

Although obtaining the signatures is important, the signed document should signify that the process of informed consent has been undertaken over an extended time period and is not simply quickly completed (Vrouenraets et al., 2021). We believe the latter approach poses an ethical concern (Levine, 2019).

The internal dynamics of the trans-identified young person and their families vary considerably. Parental capacities, their private marital and intrafamilial relationships, their cultural awareness, religious and political sensibilities all influence the amount of time necessary to undertake a thorough informed consent process. It is not prudent to suggest a specific duration for the process of informed consent, other than to emphasize that it requires a slow, patient, thoughtful question and answer period as the parents and patient contemplate the meaning of what is known and unknown and whether to embark on alternative approaches to the management of gender dysphoria before the age of full neurological maturity has been reached, mental health comorbidities have been addressed, and a true informed consent by the patient is more likely.

Final thoughts

Sixty years of experience providing medical and surgical assistance to transgender-identified persons have seen many changes in who is treated, when they are treated, and how they are treated. Today, the emphasis has shifted to the treatment of the unprecedented numbers of youth declaring a trans identity. As adolescents pursue social, medical, and surgical interventions, health care providers may experience unease about patients' cognitive and emotional capacities to make decisions with life-changing and enduring consequences. An unrushed informed consent process helps the provider, the parents, and the patient.

Three issues tend to obscure the salience of informed consent: conspicuous mental health problems, uncertainty about the minor's personal capacity to understand the irreversible nature of the interventions, and parental disagreement. Physical and psychiatric comorbidities can contribute to the formation of a new identity, develop as its consequence, or bear no connection to it. Assessing mental health and the minor's functionality is one of the reasons why rapid affirmative care may be dangerous for patients and their families. For example, when situations involve autism, learning disorders, sexual abuse, attachment problems, trauma, separation anxiety, previous depressed or anxious states, neglect, low IQ, past psychotic illness, eating disorders or parental mental illness, clinicians must choose between ignoring these potentially causative conditions and comorbidities and providing appropriate treatment before affirmative care (D'Angelo et al., 2020).

For youth less than the age of majority, informed consent via parents provides a legal route for treatment but it does not make the decisions to transition, provide hormones, or surgically remove breasts or testes less fraught with uncertainty. The best that health professionals can do is to ensure that the consent process informs the patient and parents of the current state of science, which is sorely lacking in quality research. It is the professionals' responsibility to ensure that the benefits patients and parents seek, and the risks they are assuming, are clearly appreciated as they prepare to make this often-excruciating decision.

Young people who have reached the age of majority, but who have not reached full maturation of the brain represent a unique challenge. It is well-recognized that brain remodeling proceeds through the third decade of life, with the prefrontal cortex responsible for executive function and impulse control the last to mature (Katz et al., 2016). The growing number of detransitioners who had been old enough to legally consent to transition, but who no longer felt they were transgender upon reaching their mid-20's, raises additional concerns about this vulnerable age group (Littman, 2021; Vandenbussche, 2021).

When the clinician is uncertain whether a young person is competent to comprehend the implications of the desired treatment—that is, when informed consent cannot inform the patient—the clinician may need more time with the patient. When parents or guardians do

not agree about whether to use puberty blockers or cross-sex hormones, clinicians are in an uneasy spot (Levine, 2021). This occurs in both intact and divorced families. Australia has given legal instructions to clinicians facing these uncertainties: the court is to be asked to decide (Ouliaris, 2021). The court system in the UK has been grappling with similar issues in recent years. While it is a rare case that ends up in a courtroom, clinicians devoted to a deliberate informed consent process are still likely to encounter ethical dilemmas that they cannot resolve.

Acknowledgments

The authors wish to thank SEGM staff for their grant and bibliographic support.

Funding

This work was supported by the Society for Evidence based Gender Medicine.

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Evidence review: Gonadotrophin releasing hormone analogues for children and adolescents with gender dysphoria

This document will help inform Dr Hilary Cass' independent review into gender identity services for children and young people. It was commissioned by NHS England and Improvement who commissioned the Cass review. It aims to assess the evidence for the clinical effectiveness, safety and cost-effectiveness of gonadotrophin releasing hormone (GnRH) analogues for children and adolescents aged 18 years or under with gender dysphoria.

The document was prepared by NICE in October 2020.

The content of this evidence review was up to date on 14 October 2020. See summaries of product characteristics (SPCs), British National Formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites for up-to-date information.

Contents

1. Introduction

This review aims to assess the evidence for the clinical effectiveness, safety and cost-effectiveness of gonadotrophin releasing hormone (GnRH) analogues for children and adolescents aged 18 years or under with gender dysphoria. The review follows the NHS England Specialised Commissioning process and template and is based on the criteria outlined in the PICO framework (see appendix A). This document will help inform Dr Hilary Cass' independent review into gender identity services for children and young people.

Gender dysphoria in children, also known as gender identity disorder or gender incongruence of childhood (World Health Organisation 2020), refers to discomfort or distress that is caused by a discrepancy between a person's gender identity (how they see themselves[1] regarding their gender) and that person's sex assigned at birth and the associated gender role, and/or primary and secondary sex characteristics (Diagnostic and Statistical Manual of Mental Disorders 2013).

GnRH analogues suppress puberty by delaying the development of secondary sexual characteristics. The intention is to alleviate the distress associated with the development of secondary sex characteristics, thereby providing a time for on-going discussion and exploration of gender identity before deciding whether to take less reversible steps. In England, the GnRH analogue triptorelin (a synthetic decapeptide analogue of natural GnRH, which has marketing authorisations for the treatment of prostate cancer, endometriosis and precocious puberty [onset before 8 years in girls and 10 years in boys]) is used for this purpose. The use of triptorelin for children and adolescents with gender dysphoria is off-label.

For children and adolescents with gender dysphoria it is recommended that management plans are tailored to the needs of the individual, and aim to ameliorate the potentially negative impact of gender dysphoria on general developmental processes, support young people and their families in managing the uncertainties inherent in gender identity development and provide on-going opportunities for exploration of gender identity. The plans may also include psychological support and exploration and, for some individuals, the use of GnRH analogues in adolescence to suppress puberty; this may be followed later with gender-affirming hormones of the desired sex (NHS England 2013).

2. Executive summary of the review

Nine observational studies were included in the evidence review. Five studies were retrospective observational studies (Brik et al. 2020, Joseph et al. 2019, Khatchadourian et al. 2014, Klink et al. 2015, Vlot et al. 2017), 3 studies were prospective longitudinal observational studies (Costa et al. 2015, de Vries et al. 2011, Schagen et al. 2016) and 1 study was a cross-sectional study (Staphorsius et al. 2015). Two studies (Costa et al. 2015

[1] Gender refers to the roles, behaviours, activities, attributes and opportunities that any society considers appropriate for girls and boys, and women and men (World Health Organisation, Health Topics: Gender).

and Staphorsius et al. 2015) provided comparative evidence and the remaining 7 studies used within-person, before and after comparisons.

The terminology used in this topic area is continually evolving and is different depending on stakeholder perspectives. In this evidence review we have used the phrase 'people's assigned sex at birth' rather than natal or biological sex, gonadotrophin releasing hormone (GnRH) analogues rather than 'puberty blockers' and gender-affirming hormones rather than 'cross sex hormones'. The research studies included in this evidence review may use historical terms which are no longer considered appropriate.

In children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Critical outcomes

The critical outcomes for decision making are the impact on gender dysphoria, mental health and quality of life. The quality of evidence for these outcomes was assessed as very low certainty using modified GRADE.

Impact on gender dysphoria
The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones does not affect gender dysphoria (measured using the Utrecht Gender Dysphoria Scale [UGDS]). The mean (±SD) gender dysphoria (UGDS) score was not statistically significantly different at baseline compared with follow-up (n=41, 53.20 [±7.91] versus 53.9 [±17.42], p=0.333).

Impact on mental health
The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones may reduce depression (measured using the Beck Depression Inventory-II [BDI-II]). The mean [±SD] BDI score was statistically significantly lower (improved) from baseline compared with follow-up (n=41, 8.31 [±7.12] versus 4.95 [±6.72], p=0.004).

The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones does not affect anger (measured using the Trait Anger Scale [TPI]). The mean [±SD] anger (TPI) score was not statistically significantly different at baseline compared with follow-up (n=41, 18.29 [±5.54] versus 17.88 [±5.24], p=0.503).

The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones does not affect anxiety (measured using the Trait Anxiety Scale [STAI]). The mean [±SD] anxiety (STAI) score was not statistically significantly different at baseline compared with follow-up (n=41, 39.43 [±10.07] versus 37.95 [±9.38], p=0.276).

Impact on quality of life
No evidence was identified.

Important outcomes

The important outcomes for decision making are impact on body image, psychosocial impact, engagement with health care services, impact on extent of and satisfaction with surgery and stopping treatment. The quality of evidence for all these outcomes was assessed as very low certainty using modified GRADE.

Impact on body image
The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones does not affect body image (measured using the Body Image Scale [BIS]). The mean [±SD] body image (BIS) scores were not statistically significantly different from baseline compared with follow-up for primary sexual characteristics (n=57, 4.10 [±0.56] versus 3.98 [±0.71], p=0.145), secondary sexual characteristics (n=57, 2.74 [±0.65] versus 2.82 [±0.68], p=0.569) or neutral body characteristics (n=57, 2.41 [±0.63] versus 2.47 [±0.56], p=0.620).

Psychosocial impact
The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones may improve psychosocial impact over time (measured using the Children's Global Assessment Scale [CGAS]). The mean [±SD] CGAS score was statistically significantly higher (improved) from baseline compared with follow-up (n=41, 70.24 [±10.12] versus 73.90 [±9.63], p=0.005).

This study also found that psychosocial functioning may improve over time (measured using the Child Behaviour Checklist [CBCL] and the self-administered Youth Self-Report [YSR]). The mean [±SD] CBCL scores were statistically significantly lower (improved) from baseline compared with follow-up for Total T score (n=54, 60.70 [±12.76] versus 54.46 [±11.23], p<0.001), internalising T score (n=54, 61.00 [±12.21] versus 52.17 [±9.81], p<0.001) and externalising T score (n=54, 58.04 [±12.99] versus 53.81 [±11.86], p=0.001). The mean [±SD] YSR scores were statistically significantly lower (improved) from baseline compared with follow-up for Total T score (n=54, 55.46 [±11.56] versus 50.00 [±10.56], p<0.001), internalising T score (n=54, 56.04 [±12.49] versus 49.78 [±11.63], p<0.001) and externalising T score (n=54, 53.30 [±11.87] versus 49.98 [±9.35], p=0.009). The proportion of adolescents scoring in the clinical range decreased from baseline to follow up on the CBCL total problem scale (44.4% versus 22.2%, p=0.001) and the internalising scale of the YSR (29.6% versus 11.1%, p=0.017).

The study by Costa et al. 2015 in 201 adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support or continued psychological support only, found that during treatment with GnRH analogues psychosocial impact in terms of global functioning may improve over time (measured using the CGAS). In the group receiving GnRH analogues, the mean [±SD] CGAS score was statistically significantly higher (improved) after 6 months (n=60, 64.70 [±13.34]) and 12 months (n=35, 67.40 [±13.39]) compared with baseline (n=101, 58.72 [±11.38], p=0.003 and p<0.001, respectively). However, there was no statistically significant difference in global functioning (CGAS scores) between the group receiving GnRH analogues plus psychological support and the group receiving psychological support only at any time point.

The study by Staphorsius et al. 2015 in 40 adolescents with gender dysphoria (20 of whom were receiving GnRH analogues) gave mean [±SD] CBCL scores for each group, but statistical analysis is unclear (transfemales receiving GnRH analogues 57.4 [±9.8], transfemales not receiving GnRH analogues 58.2 [±9.3], transmales receiving GnRH analogues 57.5 [±9.4], transmales not receiving GnRH analogues 63.9 [±10.5]).

Engagement with health care services
The study by Brik et al. 2018 in 143 children and adolescents with gender dysphoria receiving GnRH analogues found that 9 adolescents in the original sampling frame (9/214, 4.2%) were excluded from the study because they stopped attending appointments.

The study by Costa et al. 2015 in 201 adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support or continued psychological support only had a large loss to follow-up over time. The sample size at baseline and 6 months was 201, which dropped by 39.8% to 121 after 12 months and by 64.7% to 71 at 18 months follow-up. No explanation of the reasons for loss to follow-up are reported.

Impact on extent of and satisfaction with surgery
No evidence was identified.

Stopping treatment
The study by Brik et al. 2018 in 143 children and adolescents with gender dysphoria receiving GnRH analogues reported the reasons for stopping GnRH analogues. During the follow-up period 6.2% (9/143) of adolescents had stopped GnRH analogues after a median duration of 0.8 years (range 0.1 to 3.0). Five adolescents stopped treatment because they no longer wished to receive gender-affirming treatment for various reasons. In 4 adolescents (all transmales), GnRH analogues were stopped mainly because of adverse effects (such as mood and emotional lability), although they wanted to continue treatments for gender dysphoria.

The study by Khatchadourian et al. 2014 in 27 adolescents with gender dysphoria who started GnRH analogues reported the reasons for stopping them. Eleven out of 26 where data was available (42%) stopped GnRH analogues during follow up.

In children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Evidence was available for bone density, cognitive development or functioning, and other safety outcomes. The quality of evidence for all these outcomes was assessed as very low certainty using modified GRADE.

Bone density
The study by Joseph et al. 2019 in 70 adolescents with gender dysphoria found that GnRH analogues may reduce the expected increase in lumbar or femoral bone density (measured with the z-score). However, the z-scores were largely within 1 standard deviation of normal,

and actual lumbar or femoral bone density values were not statistically significantly different between baseline and follow-up:

- The mean z-score [±SD] for lumbar bone mineral apparent density (BMAD) was statistically significantly lower at 1 year compared with baseline in transfemales (baseline 0.859 [±0.154], 1 year −0.228 [±1.027], p=0.000) and transmales (baseline −0.186 [±1.230], 1 year −0.541 [±1.396], p=0.006).
- The mean z-score [±SD] for lumbar BMAD was statistically significantly lower after receiving GnRH analogues for 2 years compared with baseline in transfemales (baseline 0.486 [±0.809], 2 years −0.279 [±0.930], p=0.000) and transmales (baseline −0.361 [±1.439], 2 years −0.913 [±1.318], p=0.001).
- The mean z-score [±SD] for femoral neck bone mineral density (BMD) was statistically significantly lower after receiving GnRH analogues for 2 years compared with baseline in transfemales (baseline 0.0450 [±0.781], 2 years −0.600 [±1.059], p=0.002) and transmales (baseline −1.075 [±1.145], 2 years −1.779 [±0.816], p=0.001).

The study by Klink et al. 2015 in 34 adolescents with gender dysphoria found that GnRH analogues may reduce the expected increase in lumbar (transmales only), but not femoral bone density. However, the z-scores are largely within 1 standard deviation of normal. Actual lumbar or femoral bone density values were not statistically significantly different between baseline and follow-up (apart from BMD measurements in transmales):

- The mean z-score [±SD] for lumbar BMAD was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales, but was statistically significantly lower when starting gender-affirming hormones in transmales (GnRH analogues 0.28 [±0.90], gender-affirming hormones −0.50 [±0.81], p=0.004).

The study by Vlot et al. 2017 in 70 adolescents with gender dysphoria found that GnRH analogues may reduce the expected increase in lumbar or femoral bone density. However, the z-scores were largely within 1 standard deviation of normal. Actual lumbar or femoral bone density values were not statistically significantly different between baseline and follow-up (apart from in transmales with a bone age ≥14 years). This study reported change in bone density from starting GnRH analogues to starting gender-affirming hormones by bone age:

- The median z-score [range] for lumbar BMAD in transfemales with a bone age of <15 years was statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (GnRH analogues −0.20 [−1.82 to 1.18], gender-affirming hormones −1.52 [−2.36 to 0.42], p=0.001) but was not statistically significantly different in transfemales with a bone age ≥15 years.
- The median z-score [range] for lumbar BMAD in transmales with a bone age of <14 years was statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (GnRH analogues −0.05 [−0.78 to 2.94], gender-affirming hormones −0.84 [−2.20 to 0.87], p=0.003) and in transmales with a bone age ≥14 years (GnRH analogues 0.27 [−1.60 to 1.80], gender-affirming hormones −0.29 [−2.28 to 0.90], p≤0.0001).

- The median z-score [range] for femoral neck BMAD in transfemales with a bone age of <15 years was not statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (GnRH analogues −0.71 [−3.35 to 0.37], gender-affirming hormones −1.32 [−3.39 to 0.21], p≤0.1) or in transfemales with a bone age ≥15 years (GnRH analogues −0.44 [−1.37 to 0.93], gender-affirming hormones −0.36 [−1.50 to 0.46]).
- The z-score for femoral neck BMAD in transmales with a bone age of <14 years was not statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (GnRH analogues −0.01 [−1.30 to 0.91], gender-affirming hormone −0.37 [−2.28 to 0.47]) but was statistically significantly lower in transmales with a bone age ≥14 years (GnRH analogues 0.27 [−1.39 to 1.32], gender-affirming hormones −0.27 [−1.91 to 1.29], p=0.002).

Cognitive development or functioning

The study by Staphorsius et al. 2015 in 40 adolescents with gender dysphoria (20 of whom were receiving GnRH analogues) measured cognitive development or functioning (using an IQ test, and reaction time and accuracy measured using the Tower of London task):

- The mean (±SD) IQ in transfemales receiving GnRH analogues was 94.0 (±10.3) and 109.4 (±21.2) in the control group. In transmales receiving GnRH analogues the mean (±SD) IQ was 95.8 (±15.6) and 98.5 (±15.9) in the control group.
- The mean (±SD) reaction time in transfemales receiving GnRH analogues was 10.9 (±4.1) and 9.9 (±3.1) in the control group. In transmales receiving GnRH analogue it was 9.9 (±3.1) and 10.0 (±2.0) in the control group.
- The mean (±SD) accuracy score in transfemales receiving GnRH analogues was 73.9 (±9.1) and 83.4 (±9.5) in the control group. In transmales receiving GnRH analogues it was 85.7 (±10.5) and 88.8 (±9.7) in the control group.

No statistical analyses or interpretation of the results was reported.

Other safety outcomes

The study by Schagen et al. 2016 in 116 adolescents with gender dysphoria found that GnRH analogues do not affect renal or liver function:

- There was no statistically significant difference between baseline and 1 year results for serum creatinine in transfemales, but there was a statistically significant decrease between baseline and 1 year in transmales (p=0.01).
- Glutamyl transferase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels did not significantly change from baseline to 12 months of treatment.

The study by Khatchadourian et al. 2014 in 27 adolescents with gender dysphoria who started GnRH analogues narratively reported adverse effects from GnRH analogues in 26 adolescents:

- 1 transmale developed sterile abscesses; they were switched from leuprolide acetate to triptorelin, and this was well tolerated
- 1 transmale developed leg pains and headaches, which eventually resolved
- 1 participant gained 19 kg within 9 months of starting GnRH analogues.

In children and adolescents with gender dysphoria, what is the cost-effectiveness of GnRH analogues compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?

No cost-effectiveness evidence was found for GnRH analogues in children and adolescents with gender dysphoria.

From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may benefit from GnRH analogues more than the wider population of interest?

Some studies reported data separately for the following subgroups of children and adolescents with gender dysphoria: sex assigned at birth males (transfemales) and sex assigned at birth females (transmales). This included some direct comparisons of these subgroups, and differences were largely seen at baseline as well as follow up. No evidence was found for other specified subgroups.

Sex assigned at birth males (transfemales)
Impact on gender dysphoria
The study by Costa et al. 2015 in 201 adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support or continued psychological support only, found that gender dysphoria (measured using the UGDS) in sex assigned at birth males is lower than in sex assigned at birth females. Sex assigned at birth males had a statistically significantly lower (improved) mean [±SD] UGDS score of 51.6 [±9.7] compared with sex assigned at birth females (56.1 [±4.3], p<0.001), but it was not reported if this was at baseline or follow-up.

The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that gender dysphoria (measured using the UGDS) in sex assigned at birth males is lower than in sex assigned at birth females at baseline and follow up. The mean [±SD] UGDS score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean UGDS score: 47.95 [±9.70] versus 56.57 [±3.89]) and follow up (n=not reported, 49.67 [±9.47] versus 56.62 [±4.00]); between sex difference p<0.001).

Impact on mental health
The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that the impact on mental health (depression, anger and anxiety) may be different in sex assigned at birth males compared with sex assigned at birth females. Over time there was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for depression, but sex assigned at birth males had statistically significantly lower levels of anger and anxiety than sex assigned at birth females at baseline and follow up.

- The mean [±SD] depression (BDI-II) score was not statistically significantly different in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean BDI score [±SD]: 5.71 [±4.31] versus 10.34 [±8.24]) and follow-up (n=not reported, 3.50 [±4.58] versus 6.09 [±7.93]), between sex difference p=0.057

- The mean [±SD] anger (TPI) score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean TPI score [±SD]: 5.22 [±2.76] versus 6.43 [±2.78]) and follow-up (n=not reported, 5.00 [±3.07] versus 6.39 [±2.59]), between sex difference p=0.022
- The mean [±SD] anxiety (STAI) score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean STAI score [±SD]: 4.33 [±2.68] versus 7.00 [±2.36]) and follow-up (n=not reported, 4.39 [±2.64] versus 6.17 [±2.69]), between sex difference p<0.001.

Impact on body image

The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that the impact on body image may be different in sex assigned at birth males compared with sex assigned at birth females. Sex assigned at birth males are less dissatisfied with their primary and secondary sex characteristics than sex assigned at birth females at both baseline and follow up, but the satisfaction with neutral body characteristics is not different.

- The mean [±SD] BIS score for primary sex characteristics was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean BIS score [±SD]: 4.02 [±0.61] versus 4.16 [±0.52]) and follow up (n=not reported, 3.74 [±0.78] versus 4.17 [±0.58]) between sex difference p=0.047.
- The mean [±SD] BIS score for secondary sex was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean BIS score [±SD]: 2.66 [±0.50] versus 2.81 [±0.76]) and follow up (n=not reported, 2.39 [±0.69] versus 3.18 [±0.42]), between sex difference p=0.001.
- The mean [±SD] BIS score for neutral body characteristics was not statistically significantly different in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, 2.60 [±0.58] versus 2.24 [±0.62], between sex difference p=0.777).

Psychosocial impact

The study by Costa et al. 2015 in 201 adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support or continued psychological support only, found that sex assigned at birth males had statistically significant lower mean [±SD] CGAS scores at baseline compared with sex assigned at birth females (n=201, 55.4 [±12.7] versus 59.2 [±11.8], p=0.03), but no conclusions could be drawn.

The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that psychosocial impact in terms of global functioning (CGAS) and psychosocial functioning (CBCL and YSR) may be different in sex assigned at birth males compared with sex assigned at birth females, but no conclusions could be drawn.

- There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females (at baseline or follow up) for the CBCL Total T

score, the CBCL internalising T score, the YSR Total T score or the YSR internalising T score.

- Sex assigned at birth males had statistically higher mean [±SD] CGAS scores compared with sex assigned at birth females at baseline (n=54, 73.10 [±8.44] versus 67.25 [±11.06]) and follow up (n=54, 77.33 [±8.69] versus 70.30 [±9.44]), between sex difference p=0.021.
- Sex assigned at birth males had statistically lower mean [±SD] CBCL externalising T scores compared with sex assigned at birth females at baseline (n=54, 54.71 [±12.91] versus 60.70 [±12.64]) and follow up (n=54, 48.75 [±10.22] versus 57.87 [±11.66]), between sex difference p=0.015.
- Sex assigned at birth males had statistically lower mean [±SD] YSR externalising T scores compared with sex assigned at birth females at both baseline (n=54, 48.72 [±11.38] versus 57.24 [±10.59]) and follow up (n=54, 46.52 [±9.23] versus 52.97 [±8.51]), between sex difference p=0.004.

Bone density

The studies by Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017 provided evidence on bone density in sex assigned at birth males (see above for details).

Cognitive development or functioning

The study by Staphorsius et al. 2015 provided evidence on cognitive development or functioning in sex assigned at birth males (see above for details).

Other safety outcomes

The study by Schagen et al. 2016 provided evidence on renal function in sex assigned at birth males (see above).

Sex assigned at birth females (transmales)

Impact on gender dysphoria

The studies by de Vries et al. 2011 and Costa et al. 2015 found that gender dysphoria (measured using the UGDS) in sex assigned at birth females is higher than in sex assigned at birth males at baseline and follow up (see above for details).

Impact on mental health

The study by de Vries et al. 2011 found that the impact on mental health (depression, anger and anxiety) may be different in sex assigned at birth females compared with sex assigned at birth males. Over time there was no statistically significant difference between sex assigned at birth females and sex assigned at birth males for depression, but sex assigned at birth females had statistically significantly greater levels of anger and anxiety than sex assigned at birth males at both baseline and follow up (see above for details).

Impact on body image

The study by de Vries et al. 2011 found that the impact on body image may be different in sex assigned at birth females compared with sex assigned at birth males. Sex assigned at birth females are more dissatisfied with their primary and secondary sex characteristics than sex assigned at birth males at both baseline and follow up, but the satisfaction with neutral body characteristics is not different (see above for details).

Psychosocial impact
The studies by de Vries et al. 2011 and Costa et al. 2015 found that psychosocial impact in terms of global functioning (CGAS) and psychosocial functioning (CBCL and YSR) may be different in sex assigned at birth females compared with sex assigned at birth males, but no conclusions could be drawn (see above for details).

Bone density
The studies by Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017 provided evidence on bone density in sex assigned at birth females (see above for details).

Cognitive development or functioning
The study by Staphorsius et al. 2015 provided evidence on cognitive development or functioning in sex assigned at birth females (see above for details).

Other safety outcomes
The study by Schagen et al. 2016 provided evidence on renal function in sex assigned at birth females (see above for details).

From the evidence selected:

(a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?

(b) what were the ages at which participants commenced treatment with GnRH analogues?

(c) what was the duration of treatment with GnRH analogues?

All studies that reported diagnostic criteria for gender dysphoria (6/9 studies) used the version of the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria that was in use at the time. In 5 studies (Costa et al. 2015, Klink et al. 2015, Schagen et al. 2016, Staphorsius et al. 2015 and Vlot et al. 2017) the DSM-fourth edition, text revision (IV-TR) criteria were used. The study by Brik et al. 2020 used DSM-V criteria. It was not reported how gender dysphoria was defined in the remaining 3 studies.

The studies show variation in the age (11 to 18 years old) at which children and adolescents with gender dysphoria started GnRH analogues.

Most studies did not report the duration of treatment with GnRH analogues (Joseph et al. 2019, Khatchadourian et al. 2014, Vlot et al. 2017, Costa et al. 2015, de Vries et al. 2011, Schagen et al. 2016), but where this was reported (Brik et al. 2020, Klink et al. 2015, Staphorsius et al. 2015) there was a wide variation ranging from a few months to about 5 years.

Discussion

A key limitation to identifying the effectiveness and safety of GnRH analogues for children and adolescents with gender dysphoria is the lack of reliable comparative studies. The lack of clear, expected outcomes from treatment with a GnRH analogue (the purpose of which is to suppress secondary sexual characteristics which may cause distress from unwanted pubertal changes) also makes interpreting the evidence difficult.

The studies included in this evidence review are all small, uncontrolled observational studies, which are subject to bias and confounding, and all the results are of very low certainty using modified GRADE. They all reported physical and mental health comorbidities and concomitant treatments very poorly. All the studies are from a limited number of, mainly European, care facilities. They are described as either tertiary referral or expert services but the low number of services providing such care and publishing evidence may bias the results towards the outcomes in these services only and limit extrapolation.

Many of the studies did not report statistical significance or confidence intervals. Changes in outcome scores for clinical effectiveness and bone density were assessed with regards to statistical significance. However, there is relatively little interpretation of whether the changes in outcomes are clinically meaningful.

In the observational, retrospective studies providing evidence on bone density, participants acted as their own controls and change in bone density was determined between starting GnRH analogues and follow up. Observational studies such as these can only show an association with GnRH analogues and bone density; they cannot show that GnRH analogues caused any differences in bone density seen. Because there was no comparator group and participants acted as their own controls, it is not known whether the findings are associated with GnRH analogues or due to changes over time.

Conclusion

The results of the studies that reported impact on the critical outcomes of gender dysphoria and mental health (depression, anger and anxiety), and the important outcomes of body image and psychosocial impact (global and psychosocial functioning), in children and adolescents with gender dysphoria are of very low certainty using modified GRADE. They suggest little change with GnRH analogues from baseline to follow-up.

Studies that found differences in outcomes could represent changes that are either of questionable clinical value, or the studies themselves are not reliable and changes could be due to confounding, bias or chance. It is plausible, however, that a lack of difference in scores from baseline to follow-up is the effect of GnRH analogues in children and adolescents with gender dysphoria, in whom the development of secondary sexual characteristics might be expected to be associated with an increased impact on gender dysphoria, depression, anxiety, anger and distress over time without treatment. The study by de Vries et al. 2011 reported statistically significant reductions in the Child Behaviour Checklist (CBCL) and Youth Self-Report (YSR) scores from baseline to follow up, which include measures of distress. As the aim of GnRH analogues is to reduce distress caused by the development of secondary sexual characteristics, this may be an important finding. However, as the studies all lack appropriate controls who were not receiving GnRH analogues, any positive changes could be a regression to mean.

The results of the studies that reported bone density outcomes suggest that GnRH analogues may reduce the expected increase in bone density (which is expected during puberty). However, as the studies themselves are not reliable, the results could be due to confounding, bias or chance. While controlled trials may not be possible, comparative studies are needed to understand this association and whether the effects of GnRH analogues on bone density are seen after they are stopped. All the studies that reported safety outcomes provided very low certainty evidence.

No cost-effectiveness evidence was found to determine whether or not GnRH analogues are cost-effective for children and adolescents with gender dysphoria.

The results of the studies that reported outcomes for subgroups of children and adolescents with gender dysphoria, suggest there may be differences between sex assigned at birth males (transfemales) and sex assigned at birth females (transmales).

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
2. For children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
3. For children and adolescents with gender dysphoria, what is the cost-effectiveness of GnRH analogues compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?
4. From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may derive more (or less) advantage from treatment with GnRH analogues than the wider population of children and adolescents with gender dysphoria?
5. From the evidence selected,
    a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?
    b) what were the ages at which participants commenced treatment with GnRH analogues?
    c) what was the duration of treatment with GnRH analogues?

See appendix A for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 23 July 2020.

See appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO framework. Full text references of potentially

relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See appendix C for evidence selection details and appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See appendix G for GRADE Profiles.

4. Summary of included studies

Nine observational studies were identified for inclusion. Five studies were retrospective observational studies (Brik et al. 2020, Joseph et al. 2019, Khatchadourian et al. 2014, Klink et al. 2015, Vlot et al. 2017), 3 studies were prospective longitudinal observational studies (Costa et al. 2015, de Vries et al. 2011, Schagen et al. 2016) and 1 study was a cross-sectional study (Staphorsius et al. 2015).

The terminology used in this topic area is continually evolving and is different depending on stakeholder perspectives. In this evidence review we have used the phrase 'people's assigned sex at birth' rather than natal or biological sex, gonadotrophin releasing hormone (GnRH) analogues rather than 'puberty blockers' and gender-affirming hormones rather than 'cross sex hormones'. The research studies included in this evidence review may use historical terms which are no longer considered appropriate.

Table 1 provides a summary of these included studies and full details are given in appendix E.

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Brik et al. 2020 Retrospective observational single-centre study Netherlands	The study was conducted at the Curium-Leiden University Medical Centre gender clinic in Leiden, the Netherlands and involved adolescents with gender dysphoria. The sample size was 143 adolescents (median age at start of treatment was 15.0 years, range 11.1 to 18.6 years in transfemales; 16.1 years, range 10.1 to 17.9 years in transmales) from a sampling frame of 269 children and adolescents registered at the clinic between November 2010 and January 2018.	**Intervention** 143 children and adolescents receiving GnRH analogues (no specific treatment, dose, route or frequency of administration reported). The median duration was 2.1 years (range 1.6–2.8 years). **Comparison** No comparator.	**Critical Outcomes** • No critical outcomes reported **Important outcomes** • Stopping treatment

Study	Population	Intervention and comparison	Outcomes reported
	Participants were included in the study if they were diagnosed with gender dysphoria according to the DSM-5 criteria, registered at the clinic, were prepubertal and within the appropriate age range, and had started GnRH analogues. No concomitant treatments were reported.		
Costa et al. 2015 Prospective longitudinal observational single centre cohort study United Kingdom	The study was conducted at the Gender Identity Development Service in London and involved adolescents with gender dysphoria. The sample size was 201 adolescents (mean [±SD] age 15.52±1.41 years, range 12 to 17 years) from a sampling frame of 436 consecutive adolescents referred to the service between 2010 and 2014. The mean [±SD] age at the start of GnRH analogues was 16.48 [±1.26] years, range 13 to 17 years. Participants were invited to participate following a 6-month diagnostic process using DSM-IV-TR criteria. No concomitant treatments were reported.	**Intervention** 101 adolescents assessed as being immediately eligible for GnRH analogues (no specific treatment, dose or route of administration reported) plus psychological support. The average duration of treatment was approximately 12 months (no exact figure given). **Comparison** 100 adolescents assessed as not immediately eligible for GnRH analogues (more time needed to make the decision to start GnRH analogues) who had psychological support only. None received GnRH analogues throughout the study.	**Critical Outcomes** • No critical outcomes reported **Important outcomes** • Psychosocial impact
de Vries et al. 2011 Prospective longitudinal observational single centre before and after study Netherlands	The study was conducted at the Amsterdam gender identity clinic of the VU University Medical Centre and involved adolescents who were defined as “transsexual”. The sample size was 70 adolescents receiving GnRH analogues (mean age [±SD] at assessment 13.6±1.8 years) from a sampling frame of 196 consecutive adolescents referred to the service between 2000 and 2008. Participants were invited to participate if they subsequently started gender-affirming hormones between 2003 and 2009. No diagnostic criteria or concomitant treatments were reported.	**Intervention** 70 individuals assessed at baseline (T0) before the start of GnRH analogues (no specific treatment, dose or route of administration reported). **Comparison** No comparator.	**Critical Outcomes** • Gender dysphoria • Mental health (depression, anger and anxiety) **Important outcomes** • Body image • Psychosocial impact

Study	Population	Intervention and comparison	Outcomes reported
Joseph et al. 2019 Retrospective longitudinal observational single centre study United Kingdom	This study was conducted at the Early intervention clinic at University College London Hospital (all participants had been seen at the Gender Identity Development Service in London) and involved adolescents with gender dysphoria. The sample size was 70 adolescents with gender dysphoria (no diagnostic criteria described) all offered GnRH analogues. The mean age at the start of treatment was 13.2 years (SD ±1.4) for transfemales and 12.6 years (SD ±1.0) for transmales. Details of the sampling frame were not reported. Further details of how the sample was drawn are not reported. No concomitant treatments were reported.	**Intervention** GnRH analogues. No specific treatment, duration, dose or route of administration reported. **Comparison** No comparator.	**Critical Outcomes** • No critical outcomes reported **Important outcomes** • Safety: bone density
Khatchadourian et al. 2014 Retrospective observational chart review single centre study Canada	This study was conducted at the Endocrinology and Diabetes Unit at British Columbia Children's Hospital, Canada and involved youths with gender dysphoria. The sample size was 27 young people with gender dysphoria who started GnRH analogues (at mean age 14.7 [SD ±1.9] years) out of 84 young people seen at the unit between 1998 and 2011. Diagnostic criteria and concomitant treatments were not reported.	**Intervention** 84 young people with gender dysphoria. For GnRH analogues no specific treatment, duration, dose or route of administration reported. **Comparison** No comparator.	**Critical Outcomes** • No critical outcomes reported **Important outcomes** • Stopping treatment • Safety: adverse effects
Klink et al. 2015 Retrospective longitudinal observational single centre study Netherlands	This study was conducted in the Netherlands at a tertiary referral centre. It is unclear which centre this was. The sample size was 34 adolescents (mean age 14.9 [SD ±1.9] years for transfemales and 15.0 [SD ±2.0] years for transmales at start of GnRH analogues). Details of the sampling frame are not reported. Participants were included if they met DSM-IV-TR criteria for gender identity disorder of adolescence and had been treated with GnRH analogues and gender-affirming hormones during their pubertal years. No concomitant treatments were reported.	**Intervention** The intervention was GnRH analogue monotherapy (triptorelin 3.75 mg subcutaneously every 4 weeks) followed by gender-affirming hormones with discontinuation of GnRH analogues after gonadectomy. Duration of GnRH analogues was 1.3 years (range 0.5 to 3.8 years) in transfemales and 1.5 years (0.25 to 5.2 years in transmales. **Comparison** No comparator.	**Critical Outcomes** • No critical outcomes reported **Important outcomes** • Safety: bone density

Study	Population	Intervention and comparison	Outcomes reported
Schagen et al. 2016 Prospective longitudinal study Netherlands	This study was conducted at the Centre of Expertise on Gender Dysphoria at the VU University Medical Centre (Amsterdam, Netherlands) and involved adolescents with gender dysphoria. The sample size was 116 adolescents (median age [range] 13.6 years [11.6 to 17.9] in transfemales and 14.2 years [11.1 to 18.6] in transmales during first year of GnRH analogues) out of 128 adolescents who started GnRH analogues. Participants were included if they met DSM-IV-TR criteria for gender dysphoria, had lifelong extreme gender dysphoria, were psychologically stable and were living in a supportive environment. No concomitant treatments were reported.	**Intervention** The intervention was GnRH analogue monotherapy (triptorelin 3.75 mg at 0, 2 and 4 weeks followed by intramuscular injections every 4 weeks, for at least 3 months). **Comparison** No comparator.	**Critical Outcomes** • No critical outcomes reported **Important outcomes** • Safety: liver and renal function.
Staphorsius et al. 2015 Cross-sectional (single time point) assessment single centre study Netherlands	This study was conducted at the VU University Medical Centre (Amsterdam, Netherlands) and involved adolescents with gender dysphoria. The sample size was 85, of whom 40 were adolescents with gender dysphoria (20 of whom were being treated with GnRH analogues) and 45 were controls without gender dysphoria (not further reported here). Mean (±SD) age 15.1 (±2.4) years in transfemales and 15.8 (±1.9) years in transmales. Details of the sampling frame are not reported. Participants were included if they were diagnosed with Gender Identity Disorder according to the DSM-IV-TR and at least 12 years old and Tanner stage of at least B2 or G2 to G3 with measurable oestradiol and testosterone levels in girls and boys, respectively. No concomitant treatments were reported.	**Intervention** The intervention was a GnRH analogue (triptorelin 3.75 mg every 4 weeks subcutaneously or intramuscularly). The mean duration of treatment was 1.6 years (SD ±1.0). **Comparison** Adolescents with gender dysphoria not treated with GnRH analogues.	**Critical Outcomes** • No critical outcomes reported **Important outcomes** • Psychosocial impact • Safety: cognitive functioning
Vlot et al. 2017 Retrospective observational data analysis study	This study was conducted at the VU University Medical Centre (Amsterdam, Netherlands) and involved adolescents with gender dysphoria. The sample size was 70 adolescents (median age [range] 15.1 years [11.7 to 18.6] for	**Intervention** The intervention was a GnRH analogue (triptorelin 3.75 mg every 4 weeks subcutaneously). **Comparison** No comparator.	**Critical Outcomes** • No critical outcomes reported **Important outcomes**

Study	Population	Intervention and comparison	Outcomes reported
Netherlands	transmales and 13.5 years [11.5 to 18.3] for transfemales at start of GnRH analogues). Details of the sampling frame are not reported. Participants were included if they had a diagnosis of gender dysphoria according to DSM-IV-TR criteria who were receiving GnRH analogues and then gender-affirming hormones. No concomitant treatments were reported.		• Safety: bone density
Abbreviations: DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision; GnRH, Gonadotrophin releasing hormone; SD, Standard deviation.			

5. Results

In children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Impact on gender dysphoria **Certainty of evidence: very low**	This is a critical outcome because gender dysphoria in children and adolescents is associated with significant distress and problems with functioning. One uncontrolled, prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on gender dysphoria in adolescents, measured using the Utrecht Gender Dysphoria Scale (UGDS). The UGDS is a validated screening tool for both adolescents and adults to assess gender dysphoria. It consists of 12 items, to be answered on a 1- to 5-point scale, resulting in a sum score between 12 and 60. The higher the UGDS score the greater the gender dysphoria. The study measured the impact on gender dysphoria at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). The mean (±SD) UGDS score was not statistically significantly different at baseline compared with follow-up (n=41, 53.20 [±7.91] versus 53.9 [±17.42], p=0.333) **(VERY LOW)**.

	This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, does not affect gender dysphoria.
Impact on mental health: depression **Certainty of evidence: very low**	This is a critical outcome because self-harm and thoughts of suicide have the potential to result in significant physical harm and, for completed suicides, the death of the young person. One uncontrolled, prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on depression in children and adolescents with gender dysphoria. Depression was measured using the Beck Depression Inventory-II (BDI-II). The BDI-II is a valid, reliable, and widely used tool for assessing depressive symptoms. There are no specific scores to categorise depression severity, but it is suggested that 0 to 13 is minimal symptoms, 14 to 19 is mild depression, 20 to 28 is moderate depression, and severe depression is 29 to 63. The study provided evidence for depression measured at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). The mean (±SD) depression (BDI) score was statistically significantly lower (improved) from baseline compared with follow-up (n=41, 8.31 [±7.12] versus 4.95 [±6.72], p=0.004) **(VERY LOW)**. **This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, may reduce depression.**
Impact on mental health: anger **Certainty of evidence: very low**	This is a critical outcome because self-harm and thoughts of suicide have the potential to result in significant physical harm and, for completed suicides, the death of the young person. One uncontrolled, prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on anger in children and adolescents with gender dysphoria. Anger was measured using the Trait Anger Scale of the State-Trait Personality Inventory (TPI). This is a validated 20-item inventory tool which measures the intensity of anger as the disposition to experience angry feelings as a personality trait. Higher scores indicate greater anger. The study provided evidence for anger measured at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). The mean (±SD) anger (TPI) score was not statistically significantly different at baseline compared with follow-up (n=41, 18.29 [±5.54] versus 17.88 [±5.24], p=0.503) **(VERY LOW)**. **This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, does not affect anger.**

Impact on mental health: anxiety **Certainty of evidence: very low**	This is a critical outcome because self-harm and thoughts of suicide have the potential to result in significant physical harm and, for completed suicides, the death of the young person. One uncontrolled, prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on anxiety in children and adolescents with gender dysphoria. Anxiety was measured using the Trait Anxiety Scale of the State-Trait Personality Inventory (STAI). This is a validated and commonly used measure of trait and state anxiety. It has 20 items and can be used in clinical settings to diagnose anxiety and to distinguish it from depressive illness. Higher scores indicate greater anxiety. The study provided evidence for anxiety at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). The mean (±SD) anxiety (STAI) score was not statistically significantly different at baseline compared with follow-up (n=41, 39.43 [±10.07] versus 37.95 [±9.38], p=0.276) (**VERY LOW)**. **This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, does not affect levels of anxiety.**
Quality of life	This is a critical outcome because gender dysphoria in children and adolescents may be associated with a significant reduction in health-related quality of life. No evidence was identified.
Important outcomes	
Impact on body image **Certainty of evidence: very low**	This is an important outcome because some children and adolescents with gender dysphoria may want to take steps to suppress features of their physical appearance associated with their sex assigned at birth or accentuate physical features of their desired gender. One uncontrolled, prospective observational longitudinal study provided evidence relating to the impact on body image (de Vries et al. 2011). Body image was measured using the Body Image Scale (BIS) which is a validated 30-item scale covering 3 aspects: primary, secondary and neutral body characteristics. Higher scores represent a higher degree of body dissatisfaction. The study (de Vries et al. 2011) provided evidence for body image measured at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). The mean (±SD) body image (BIS) scores for were not statistically significantly different from baseline compared with follow-up for:

	• primary sexual characteristics (n=57, 4.10 [±0.56] versus 3.98 [±0.71], p=0.145) • secondary sexual characteristics (n=57, 2.74 [±0.65] versus 2.82 [±0.68], p=0.569) • neutral body characteristics (n=57, 2.41 [±0.63] versus 2.47 [±0.56], p=0.620) **(VERY LOW)**. **This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender affirming hormones, does not affect body image.**
Psychosocial impact: global functioning **Certainty of evidence: very low**	This is an important outcome because gender dysphoria in children and adolescents is associated with internalising and externalising behaviours, and emotional and behavioural problems which may impact on social and occupational functioning. One uncontrolled, observational, prospective cohort study (de Vries et al 2011) and one prospective cross-sectional cohort study (Costa et al. 2015) provided evidence relating to psychosocial impact in terms of global functioning. Global functioning was measured using the Children's Global Assessment Scale (CGAS). The CGAS tool is a validated measure of global functioning on a single rating scale from 1 to 100. Lower scores indicate poorer functioning. One study (de Vries et al. 2011) provided evidence for global functioning (CGAS) at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). The mean (±SD) CGAS score was statistically significantly higher (improved) from baseline compared with follow-up (n=41, 70.24 [±10.12] versus 73.90 [±9.63], p=0.005) **(VERY LOW)**. One study (Costa et al. 2015) in adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support (the immediately eligible group) or continued psychological support only (the delayed eligible group who did not receive GnRH analogues) provided evidence for global functioning (CGAS) measured at 4 time points: • at baseline (T0) in both groups, • after 6 months of psychological support in both groups (T1), • after 6 months of GnRH analogues and 12 months of psychological support in the immediately eligible group and 12 months of psychological support only in the delayed eligible group (T2), and • after 18 months of psychological support and 12 months of GnRH analogues in the immediately eligible group and after 18 months of psychological support only in the delayed eligible group (T3). The mean [±SD] CGAS score was statistically significantly higher (improved) for all adolescents (including those not receiving GnRH analogues) at T1, T2 or T3 compared with baseline (T0).

	For the immediately eligible group (who received GnRH analogues) versus the delayed eligible group (who did not receive GnRH analogues) there were no statistically significant differences in CGAS scores between the 2 groups at baseline T0 (n=201, p=0.23), T1 (n=201, p=0.73), T2 (n=121, p=0.49) or T3 (n=71, p=0.14) time points. For the immediately eligible group (who received GnRH analogues), the mean (±SD) CGAS score was not statistically significantly different at: • T1 compared with T0 • T2 compared with T1 • T3 compared with T2. The mean (±SD) CGAS score was statistically significantly higher (improved) at: • T2 compared with T0 (n=60, 64.70 [±13.34] versus n=101, 58.72 [±11.38], p=0.003) • T3 compared with T0 (n=35, 67.40 [±13.39] versus n=101, 58.72 [±11.38], p<0.001) • T3 compared with T1 (n=35, 67.40 [±13.93] versus n=101, 60.89 [±12.17], p<0.001) **(VERY LOW)**. **These studies provide very low certainty evidence that during treatment with GnRH analogues, global functioning may improve over time. However, there was no statistically significant difference in global functioning between GnRH analogues plus psychological support compared with psychological support only at any time point.**
Psychosocial impact: psychosocial functioning **Certainty of evidence: very low**	This is an important outcome because gender dysphoria in children and adolescents is associated with internalising and externalising behaviours, and emotional and behavioural problems which may impact on social and occupational functioning. Two studies provided evidence for this outcome. One uncontrolled, observational, prospective cohort study (de Vries et al, 2011) and 1 cross-sectional observational study (Staphorsius et al. 2015) assessed psychosocial functioning using the Child Behaviour Checklist (CBCL) and the self-administered Youth Self-Report (YSR). The CBCL is a checklist parents complete to detect emotional and behavioural problems in children and adolescents. YSR is similar but is self-completed by the child or adolescent. The scales consist of a Total problems score, which is the sum of the scores of all the problem items. An internalising problem scale sums the anxious/depressed, withdrawn-depressed, and somatic complaints scores while the externalising problem scale combines rule-breaking and aggressive behaviour. The standard scores are scaled so that 50 is average for the child or adolescent's age and gender, with a SD of 10 points. Higher scores indicate greater problems, with a T-score above 63 considered to be in the clinical range. One study (de Vries et al. 2011) provided evidence for psychosocial functioning (CBCL and YSR scores) at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and

	• shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). At follow up, the mean (±SD) CBCL scores were statistically significantly lower (improved) compared with baseline for: • Total T score (n=54, 60.70 [±12.76] versus 54.46 [±11.23], p<0.001 • Internalising T score (n=54, 61.00 [±12.21] versus 52.17 [±9.81], p<0.001) • Externalising T score (n=54, 58.04 [±12.99] versus 53.81 [±11.86], p=0.001). At follow up, the mean (±SD) YSR scores were statistically significantly lower (improved) compared with baseline for: • Total T score (n=54, 55.46 [±11.56] versus 50.00 [±10.56], p<0.001) • Internalising T score (n=54, 56.04 [±12.49] versus 49.78 [±11.63], p<0.001) • Externalising T score (n=54, 53.30 [±11.87] versus 49.98 [±9.35], p=0.009). The proportion of adolescents scoring in the clinical range decreased from baseline to follow up on the CBCL total problem scale (44.4% versus 22.2%, p=0.001) and the internalising scale of the YSR (29.6% versus 11.1%, p=0.017) **(VERY LOW)**. One study (Staphorsius et al. 2015) assessed CBCL in a cohort of adolescents with gender dysphoria (transfemale: n=18, mean [±SD] age 15.1 [±2.4] years and transmale: n=22, mean [±SD] age 15.8 [±1.9] years) either receiving GnRH analogues (transfemale, n=8 and transmale, n=12), or not receiving GnRH analogues (transfemale, n=10 and transmale, n=10). The mean (±SD) CBCL scores for each group were (statistical analysis unclear): • transfemales (total) 57.8 [±9.2] • transfemales receiving GnRH analogues 57.4 [±9.8] • transfemales not receiving GnRH analogues 58.2 [±9.3] • transmales (total) 60.4 [±10.2] • transmales receiving GnRH analogues 57.5 [±9.4] • transmales not receiving GnRH analogues 63.9 [±10.5] **(VERY LOW)**. **These studies provide very low certainty evidence that during treatment with GnRH analogues psychosocial functioning may improve, with the proportion of adolescents in the clinical range for some CBCL and YSR scores decreasing over time.**
Engagement with health care services **Certainty of evidence: very low**	This is an important outcome because patient engagement with health care services will impact on their clinical outcomes. Two uncontrolled observational cohort studies provided evidence relating to loss to follow up, which could be a marker of engagement with health care services (Brik et al. 2018 and Costa et al. 2015).

	In one retrospective study (Brik et al. 2018), 9 adolescents (9/214, 4.2%) who had stopped attending appointments were excluded from the study between November 2010 and July 2019 **(VERY LOW)**. One prospective study (Costa et al. 2015) had evidence for a large loss to follow-up over time. The sample size at baseline (T0) and 6 months (T1) was 201, which dropped by 39.8% to 121 after 12 months (T2) and by 64.7% to 71 at 18 months follow-up (T3). No explanation of the reasons for loss to follow-up are reported **(VERY LOW)**. Due to their design there was no reported loss to follow-up in the other 3 effectiveness studies (de Vries et al 2011; Khatchadourian et al. 2014; Staphorsius et al. 2015). **These studies provide very low certainty evidence about loss to follow up, which could be a marker of engagement with health care services, during treatment with GnRH analogues. Due to the large variation in rates between studies no conclusions could be drawn.**
Impact on extent of and satisfaction with surgery	This is an important outcome because some children and adolescents with gender dysphoria may proceed to transitioning surgery. No evidence was identified.

Stopping treatment
 	
Certainty of evidence: very low
	This is an important outcome because there is uncertainty about the short- and long-term safety and adverse effects of GnRH analogues in children and adolescents with gender dysphoria.
	
	Two uncontrolled, retrospective, observational cohort studies provided evidence relating to stopping GnRH analogues. One study had complete reporting of the cohort (Brik et al. 2018), the other (Khatchadourian et al. 2014) had incomplete reporting of its cohort, particularly for transfemales where outcomes for only 4/11 were reported.
	
	Brik et al. 2018 narratively reported the reasons for stopping GnRH analogues in a cohort of 143 adolescents (38 transfemales and 105 transmales). Median age at the start of GnRH analogues was 15.0 years (range, 11.1–18.6 years) in transfemales and 16.1 years (range, 10.1–17.9 years) in transmales. Of these adolescents, 125 (87%, 36 transfemales, 89 transmales) subsequently started gender-affirming hormones after 1.0 (0.5–3.8) and 0.8 (0.3–3.7) years of GnRH analogues. At the time of data collection, the median duration of GnRH analogue use was 2.1 years (1.6–2.8).
	
	During the follow-up period 6.3% (9/143) of adolescents had discontinued GnRH analogues after a median duration of 0.8 years (range 0.1 to 3.0). The percentages and reasons for stopping were:
	• 2.8% (4/143) stopped GnRH analogues although they wanted to continue endocrine treatments for gender dysphoria:
	  ○ 1 transmale stopped due to increase in mood problems, suicidal thoughts and confusion attributed to GnRH analogues
	  ○ 1 transmale had hot flushes, increased migraines, fear of injections, stress at school and unrelated medical issues, and temporarily stopped treatment (after 4 months) and restarted 5 months later.

	○ 1 transmale had mood swings 4 months after starting GnRH analogues. After 2.2 years had unexplained severe nausea and rapid weight loss and discontinued GnRH analogues after 2.4 years ○ 1 transmale stopped GnRH analogues because of inability to regularly collect medication and attend appointments for injections. • 3.5% (5/143) stopped treatment because they no longer wished to receive gender-affirming treatment for various reasons **(VERY LOW)**. Khatchadourian et al. 2014 narratively reported the reasons for stopping GnRH analogues in a cohort of 26 adolescents (15 transmales and 11 transfemales), 42% (11/26) discontinued GnRH analogues during follow-up between 1998 and 2011. Of 15 transmales receiving GnRH analogues, 14 received testosterone during the observation period, of which: • 7 continued GnRH analogues after starting testosterone • 7 stopped GnRH analogues after a median of 3.0 years (range 0.2 to 9.2 years), of which: ○ 5 stopped after hysterectomy and salpingo-oophorectomy ○ 1 stopped after 2.2 years (transitioned to gender-affirming hormones) ○ 1 stopped after <2 months due to mood and emotional lability **(VERY LOW)**. Of 11 transfemales receiving GnRH analogues, 5 received oestrogen during the observation period, of which: • 4 continued GnRH analogues after starting oestrogen • 1 stopped GnRH analogues when taking oestrogen (no reason reported) **(VERY LOW)**. Of the remaining 6 transfemales taking GnRH analogues: • 1 stopped GnRH analogues after a few months due to emotional lability • 1 stopped GnRH analogues before taking oestrogen (the following year delayed due to heavy smoking) • 1 stopped GnRH analogues after 13 months due not to pursuing transition **(VERY LOW)**. **These studies provide very low certainty evidence for the number of adolescents who stop GnRH analogues and the reasons for this.**

Abbreviations: GnRH, gonadotrophin releasing hormone; SD, standard deviation.

In children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Outcome	Evidence statement

Safety	
Change in bone density: lumbar **Certainty of evidence: very low**	This is an important outcome because puberty is an important time for bone development and puberty suppression may affect bone development, as shown by changes in lumbar bone density. Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on bone density (based on lumbar BMAD) between starting with a GnRH analogue and at 1 and 2 year intervals (Joseph et al. 2019), and between starting GnRH analogues and starting gender-affirming hormones (Klink et al. 2015 and Vlot et al. 2017). All outcomes were reported separately for transfemales and transmales; also see subgroups table below. BMAD is a size adjusted value of BMD incorporating body size measurements using UK norms in growing adolescents. It was reported as g/cm^3 and as z-scores. Z-scores report how many standard deviations from the mean a measurement sits. A z-score of 0 is equal to the mean, a z-score of −1 is equal to 1 standard deviation below the mean, and a z-score of +1 is equal to 1 standard deviation above the mean. One retrospective observational study (Joseph et al. 2019, n=70) provided non-comparative evidence on change in lumbar BMAD increase using z-scores. • The z-score for lumbar BMAD was statistically significantly lower at 2 years compared with baseline in transfemales (z-score [±SD]: baseline 0.486 [0.809], 2 years −0.279 [0.930], p=0.000) and transmales (baseline −0.361 [1.439], 2 years −0.913 [1.318], p=0.001) **(VERY LOW)**. • The z-score for lumbar BMAD was statistically significantly lower at 1 year compared with baseline in transfemales (baseline 0.859 [0.154], 1 year −0.228 [1.027], p=0.000) and transmales (baseline −0.186 [1.230], 1 year −0.541 [1.396], p=0.006) **(VERY LOW)**. • Actual lumbar BMAD values in g/cm^3 were not statistically significantly different between baseline and 1 or 2 years in transfemales or transmales **(VERY LOW)**. Two retrospective observational studies (Klink et al. 2015 and Vlot et al. 2017, n=104 in total) provided non-comparative evidence on change in lumbar BMAD between starting GnRH analogues and starting gender-affirming hormones. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. In Klink et al. 2015 the z-score for lumbar BMAD was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales but was statistically significantly lower when starting gender-affirming hormones in transmales (z-score mean [±SD]: GnRH analogue 0.28 [±0.90], gender-affirming hormone −0.50 [±0.81], p=0.004). Actual lumbar BMAD values in g/cm^3 were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales or transmales **(VERY LOW)**.

	Vlot et al. 2017 reported change from starting GnRH analogues to starting gender-affirming hormones in lumbar BMAD by bone age. • The z-score for lumbar BMAD in transfemales with a bone age of <15 years was statistically significantly lower at starting gender-affirming hormone treatment than at starting GnRH analogues (z-score median [range]: GnRH analogue −0.20 [−1.82 to 1.18], gender-affirming hormone −1.52 [−2.36 to 0.42], p=0.001) but was not statistically significantly different in transfemales with a bone age ≥15 years **(VERY LOW)**. • The z-score for lumbar BMAD in transmales with a bone age of <14 years was statistically significantly lower at starting gender-affirming hormone treatment than at starting GnRH analogues (z-score median [range]: GnRH analogue −0.05 [−0.78 to 2.94], gender-affirming hormone −0.84 [−2.20 to 0.87], p=0.003) and in transmales with a bone age ≥14 years (GnRH analogue 0.27 [−1.60 to 1.80], gender-affirming hormone −0.29 [−2.28 to 0.90], p≤0.0001) **(VERY LOW)**. • Actual lumbar BMAD values in g/cm^3 were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales or transmales with young or old bone age **(VERY LOW)**. Two uncontrolled, observational, retrospective studies provided evidence for the effect of GnRH analogues on bone density (based on lumbar BMD) between starting GnRH analogues and either at 1 or 2 year intervals (Joseph et al. 2019), or starting gender-affirming hormones (Klink et al. 2015). All outcomes were reported separately for transfemales and transmales; also see subgroups table below. One retrospective observational study (Joseph et al. 2019, n=70) provided non-comparative evidence on change in lumbar BMD increase using z-scores. • The z-score for lumbar BMD was statistically significantly lower at 2 years compared with baseline in transfemales (z-score mean [±SD]: baseline 0.130 [0.972], 2 years −0.890 [±1.075], p=0.000) and transmales (baseline −0.715 [±1.406], 2 years −2.000 [1.384], p=0.000) **(VERY LOW)**. • The z-score for lumbar BMD was statistically significantly lower at 1 year compared with baseline in transfemales (z-score mean [±SD]: baseline −0.016 [±1.106], 1 year −0.461 [±1.121], p=0.003) and transmales (baseline −0.395 [±1.428], 1 year −1.276 [±1.410], p=0.000) **(VERY LOW)**. • With the exception of transmales, where lumbar BMD in kg/m^2 increased between baseline and 1 year (mean [±SD]: baseline 0.694 [±0.149], 1 year 0.718 [±0.124], p=0.006), actual lumbar BMD values were not statistically significantly different between baseline and 1 or 2 years in transfemales or between 0 and 2 years in transmales **(VERY LOW)**. One retrospective observational study (Klink et al. 2015, n=34) provided non-comparative evidence on change in lumbar BMD between starting GnRH analogues and starting gender-affirming hormones. • The z-score for lumbar BMD was not statistically significantly different between starting GnRH analogue and starting gender-affirming hormone treatment in transfemales, but was

	statistically significantly lower when starting gender-affirming hormones in transmales (z-score mean [±SD]: GnRH analogue 0.17 [±1.18], gender-affirming hormone −0.72 [±0.99], p<0.001) **(VERY LOW)**. • Actual lumbar BMD in g/cm^2 was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales but was statistically significantly lower when starting gender-affirming hormones in transmales (mean [±SD]: GnRH analogues 0.95 [±0.12], gender-affirming hormones 0.91 [±0.10], p=0.006) **(VERY LOW)**. **These studies provide very low certainty evidence that GnRH analogues reduce the expected increase in lumbar bone density (BMAD or BMD) compared with baseline (although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual lumbar bone density (BMAD or BMD).**
Change in bone density: femoral **Certainty of evidence: very low**	This is an important outcome because puberty is an important time for bone development and puberty suppression may affect bone development, as shown by changes in femoral bone density. Two uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on bone density (based on femoral BMAD) between starting treatment with a GnRH analogue and starting gender-affirming hormones (Klink et al. 2015 and Vlot et al. 2017). All outcomes were reported separately for transfemales and transmales; also see subgroups table below. One retrospective observational study (Klink et al. 2015, n=34) provided non-comparative evidence on change in femoral area BMAD between starting GnRH analogues and starting gender-affirming hormones. All outcomes were reported separately for transfemales and transmales. • The z-score for femoral area BMAD was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales or transmales **(VERY LOW)**. • Actual femoral area BMAD values were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transmales or transfemales **(VERY LOW)**. One retrospective observational study (Vlot et al. 2017, n=70) provided non-comparative evidence on change in femoral neck (hip) BMAD between starting GnRH analogues and starting gender-affirming hormones. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. • The z-score for femoral neck BMAD in transfemales with a bone age of <15 years was not statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (z-score median [range]: GnRH analogue −0.71 [−3.35 to 0.37], gender-affirming hormone −1.32 [−3.39 to 0.21], p≤0.1) or in transfemales with a bone age ≥15 years (GnRH analogue −0.44 [−1.37 to 0.93], gender-affirming hormone −0.36 [−1.50 to 0.46]) **(VERY LOW)**.

	• The z-score for femoral neck BMAD in transmales with a bone age of <14 years was not statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (z-score median [range]: GnRH analogue −0.01 [−1.30 to 0.91], gender-affirming hormone −0.37 [−2.28 to 0.47]) but was statistically significantly lower in transmales with a bone age ≥14 years (GnRH analogue 0.27 [−1.39 to 1.32], gender-affirming hormone −0.27 [−1.91 to 1.29], p=0.002) **(VERY LOW)**. • Actual femoral neck BMAD values were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales or in transmales with a young bone age, but were statistically significantly lower in transmales with a bone age ≥14 years (GnRH analogue 0.33 [0.25 to 0.39), gender-affirming hormone 0.30 [0.23 to 0.41], p≤0.01) **(VERY LOW)**. Two uncontrolled, observational, retrospective studies provided evidence for the effect of GnRH analogues on bone density (based on femoral BMD) between starting GnRH analogues and either at 1 or 2 year intervals (Joseph et al. 2019), or starting gender-affirming hormones (Klink et al. 2015). All outcomes were reported separately for transfemales and transmales; also see subgroups table below. One retrospective observational study (Joseph et al. 2019, n=70) provided non-comparative evidence on change in femoral neck BMD increase using z-scores. All outcomes were reported separately for transfemales and transmales. • The z-score for femoral neck BMD was statistically significantly lower at 2 years compared with baseline in transfemales (z-score mean [±SD]: baseline 0.0450 [±0.781], 2 years −0.600 [±1.059], p=0.002) and transmales (baseline −1.075 [±1.145], 2 years −1.779 [±0.816], p=0.001) **(VERY LOW)**. • The z-score for femoral neck BMD was statistically significantly lower at 1 year compared with baseline in transfemales (z-score mean [±SD]: baseline 0.157 [±0.905], 1 year −0.340 [±0.816], p=0.002) and transmales (baseline −0.863 [±1.215], 1 year −1.440 [±1.075], p=0.000) **(VERY LOW)**. • Actual femoral neck BMD values in kg/m^2 were not statistically significantly different between baseline and 1 or 2 years in transmales or transfemales **(VERY LOW)**. One retrospective observational study (Klink et al. 2015, n=34) provided non-comparative evidence on change in femoral area BMD between starting GnRH analogues and starting gender-affirming hormones. All outcomes were reported separately for transfemales and transmales. • The z-score for femoral area BMD was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales, but was statistically significantly lower in transmales (z-score mean [±SD]: GnRH analogue 0.36 [±0.88], gender-affirming hormone −0.35 [±0.79], p=0.001) **(VERY LOW)**. • Actual femoral area BMD values were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales, but were

	statistically significantly lower in transmales (mean [±SD] GnRH analogue 0.92 [±0.10], gender-affirming hormone 0.88 [±0.09], p=0.005) **(VERY LOW)**. **These studies provide very low certainty evidence that GnRH analogues may reduce the expected increase in femoral bone density (femoral neck or area BMAD or BMD) compared with baseline (although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual femoral bone density (femoral area BMAD or femoral neck BMD), apart from actual femoral area BMD in transmales.**
Cognitive development or functioning **Certainty of evidence: very low**	This is an important outcome because puberty is an important time for cognitive development and puberty suppression may affect cognitive development or functioning. One cross-sectional observational study (Staphorsius et al. 2015, n=70) provided comparative evidence on cognitive development or functioning in adolescents with gender dysphoria on GnRH analogues compared with adolescents with gender dysphoria not on GnRH analogues. Cognitive functioning was measured using an IQ test. Reaction time (in seconds) and accuracy (percentage of correct trials) were measured using the Tower of London (ToL) task. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. No statistical analyses or interpretation of the results in these groups were reported: • IQ in transfemales (mean [±SD] GnRH analogue 94.0 [±10.3], control 109.4 [±21.2]). IQ transmales (GnRH analogue 95.8 [±15.6], control 98.5 [±15.9]. • Reaction time in transfemales (mean [±SD] GnRH analogue 10.9 [±4.1], control: 9.9 [±3.1]). Reaction time transmales (GnRH analogue 9.9 [±3.1], control 10.0 [±2.0]). • Accuracy score in transfemales (GnRH analogue 73.9 [±9.1], control 83.4 [±9.5]. Accuracy score in transmales (GnRH analogue 85.7 [±10.5], control 88.8 [±9.7]. **This study provides very low certainty evidence (with no statistical analysis) on the effects of GnRH analogues on cognitive development or functioning. No conclusions could be drawn.**
Other safety outcomes: kidney function **Certainty of evidence: very low**	This is an important outcome because if renal damage (raised serum creatinine is a marker of this) is suspected, GnRH analogues may need to be stopped. One prospective observational study (Schagen et al. 2016, n=116) provided non-comparative evidence on change in serum creatinine between starting GnRH analogues and at 1 year. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. • There was no statistically significant difference between baseline and 1 year for serum creatinine in transfemales (mean [±SD] baseline 70 [±12], 1 year 66 [±13], p=0.20). • There was a statistically significant decrease between baseline and 1 year for serum creatinine in transmales (baseline 73 [±8], 1 year 68 [±13], p=0.01).

	This study provides very low certainty evidence that GnRH analogues do not affect renal function.
Other safety outcomes: liver function **Certainty of evidence: very low**	This is an important outcome because if treatment-induced liver injury (raised liver enzymes are a marker of this) is suspected, GnRH analogues may need to be stopped. One prospective observational study (Schagen et al. 2016, n=116) provided non-comparative evidence on elevated liver enzymes between starting GnRH analogues and during use. No comparative values or statistical analyses were reported. • Glutamyl transferase was not elevated at baseline or during use in any person. • Mild elevations of AST and ALT above the reference range were present at baseline but were not more prevalent during use than at baseline. • Glutamyl transferase, AST, and ALT levels did not significantly change from baseline to 12 months of use. **This study provides very low certainty evidence (with no statistical analysis) that GnRH analogues do not affect liver function.**
Other safety outcomes: adverse effects **Certainty of evidence: very low**	This is an important outcome because if there are adverse effects, GnRH analogues may need to be stopped. One uncontrolled, retrospective, observational cohort study (Khatchadourian et al. 2014) provided evidence relating to adverse effects from GnRH analogues. It had incomplete reporting of its cohort, particularly for transfemales where outcomes for only 4/11 were reported. Khatchadourian et al. 2014 reported adverse effects in a cohort of 26 adolescents (15 transmales and 11 transfemales) receiving GnRH analogues. Of these: • 1 transmale developed sterile abscesses; they were switched from leuprolide acetate to triptorelin, and this was well tolerated. • 1 transmale developed leg pains and headaches, which eventually resolved • 1 participant gained 19 kg within 9 months of starting GnRH analogues. **This study provides very low certainty evidence about potential adverse effects of GnRH analogues. No conclusions could be drawn.**

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMAD, bone mineral apparent density; BMD, bone mineral density; GnRH, gonadotrophin releasing hormone; IQ, intelligence quotient; NS, not significant; SD, standard deviation.

In children and adolescents with gender dysphoria, what is the cost-effectiveness of GnRH analogues compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Outcome	Evidence statement

Cost-effectiveness	No studies were identified to assess the cost-effectiveness of GnRH analogues for children and adolescents with gender dysphoria.

From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may benefit from GnRH analogues more than the wider population of interest?

Subgroup	Evidence statement
Sex assigned at birth males (transfemales) **Certainty of evidence: Very low**	Some studies reported data separately for sex assigned at birth males (transfemales). This included some direct comparisons with sex assigned at birth females (transmales). **Impact on gender dysphoria** One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence for gender dysphoria in sex assigned at birth males. See the clinical effectiveness results table above for a full description of the study. The mean (±SD) UGDS score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean UGDS score [±SD]: 47.95 [±9.70] versus 56.57 [±3.89]) and T1 (n=not reported, 49.67 [±9.47] versus 56.62 [±4.00]); between sex difference p<0.001 **(VERY LOW)**. One further prospective observational longitudinal study (Costa et al. 2015) provided evidence for the impact on gender dysphoria in sex assigned at birth males. See the clinical effectiveness results table above for a full description of the study. Sex assigned at birth males had a statistically significantly lower (improved) mean (±SD) UGDS score of 51.6 [±9.7] compared with sex assigned at birth females (56.1 [±4.3], p<0.001). However, it was not reported if this was baseline or follow-up **(VERY LOW)**. **These studies provide very low certainty evidence that in sex assigned at birth males (transfemales), gender dysphoria is lower than in sex assigned at birth females (transmales).** **Impact on mental health** One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence for the impact on mental health (depression, anger and anxiety) in sex assigned at birth males. See the clinical effectiveness results table above for a full description of the study. • The mean (±SD) depression (BDI-II) score was not statistically significantly different in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean BDI score [±SD]: 5.71 [±4.31] versus 10.34 [±8.24]) and T1 (n=not reported, 3.50 [±4.58] versus 6.09 [±7.93]), between sex difference p=0.057 • The mean (±SD) anger (TPI) score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean TPI score [±SD]: 5.22 [±2.76]

versus 6.43 [±2.78]) and T1 (n=not reported, 5.00 [±3.07] versus 6.39 [±2.59]), between sex difference p=0.022
- The mean (±SD) anxiety (STAI) score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean STAI score [±SD]: 4.33 [±2.68] versus 7.00 [±2.36]) and T1 (n=not reported, 4.39 [±2.64] versus 6.17 [±2.69]), between sex difference p<0.001 **(VERY LOW)**.

This study provides very low certainty evidence that the impact on mental health (depression, anger and anxiety) may be different in sex assigned at birth males (transfemales) compared with sex assigned at birth females (transmales). Over time there was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for depression. However, sex assigned at birth males had statistically significantly lower levels of anger and anxiety than sex assigned at birth females at both baseline and follow up.

Impact on body image
One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on body image in sex assigned at birth males.
- The mean (±SD) BIS score for primary sex characteristics was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean BIS score [±SD]: 4.02 [±0.61] versus 4.16 [±0.52]) and T1 (n=not reported, 3.74 [±0.78] versus 4.17 [±0.58]), between sex difference p=0.047
- The mean (±SD) BIS score for secondary sex was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean BIS score [±SD]: 2.66 [±0.50] versus 2.81 [±0.76]) and T1 (n=not reported, 2.39 [±0.69] versus 3.18 [±0.42]), between sex difference p=0.001
- The mean (±SD) BIS score for neutral body characteristics was not statistically significantly different in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean BIS score [±SD]: 2.60 [±0.58] versus 2.24 [±0.62]) and T1 (n=not reported, 2.32 [±0.59] versus 2.61 [±0.50]), between sex difference p=0.777 **(VERY LOW)**.

This study provides very low certainty evidence that the impact on body image may be different in sex assigned at birth males (transfemales) compared with sex assigned at birth females (transmales). Sex assigned at birth males are less dissatisfied with their primary and secondary sex characteristics than sex assigned at birth females at both baseline and follow up, but the satisfaction with neutral body characteristics is not different.

Psychosocial impact
One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence for psychosocial impact in terms

	of global functioning (CGAS) and psychosocial functioning (CBCL and YSR) in sex assigned at birth males. • Sex assigned at birth males had statistically higher mean (±SD) CGAS scores compared with sex assigned at birth females at both baseline (T0) (n=54, 73.10 [±8.44] versus 67.25 [±11.06]) and T1 (n=54, 77.33 [±8.69] versus 70.30 [±9.44]), between sex difference p=0.021 • There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for the CBCL Total T score at T0 or T1 (n=54, p=0.110) • There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for the CBCL internalising T score at T0 or T1 (n=54, p=0.286) • Sex assigned at birth males had statistically lower mean (±SD) CBCL externalising T scores compared with sex assigned at birth females at both T0 (n=54, 54.71 [±12.91] versus 60.70 [±12.64]) and T1 (n=54, 48.75 [±10.22] versus 57.87 [±11.66]), between sex difference p=0.015 • There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for the YSR Total T score at T0 or T1 (n=54, p=0.164) • There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for the YSR internalising T score at T0 or T1 (n=54, p=0.825) • Sex assigned at birth males had statistically lower mean (±SD) YSR externalising T scores compared with sex assigned at birth females at both T0 (n=54, 48.72 [±11.38] versus 57.24 [±10.59]) and T1 (n=54, 46.52 [±9.23] versus 52.97 [±8.51]), between sex difference p=0.004 **(VERY LOW)**. One uncontrolled, observational, prospective cohort study (Costa et al. 2015) provided evidence for psychosocial impact in terms of global functioning (CGAS) in sex assigned at birth males. • Sex assigned at birth males had statistically significant lower mean (±SD CGAS scores at baseline) compared with sex assigned at birth females (n=201, 55.4 [±12.7] versus 59.2 [±11.8], p=0.03) **(VERY LOW)**. **These studies provide very low certainty evidence that psychosocial impact may be different in sex assigned at birth males (transfemales) compared with sex assigned at birth females (transmales). However, no conclusions could be drawn.** **Change in bone density: lumbar** Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on lumbar bone density in sex assigned at birth males (Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017). See the safety results table above for a full description of the results. **These studies provide very low certainty evidence that GnRH analogues reduce the expected increase in lumbar bone density (BMAD or BMD) in sex assigned at birth males (transfemales; although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically**

	significantly decrease actual lumbar bone density (BMAD or BMD) in sex assigned at birth males (transfemales). **Change in bone density: femoral** Three uncontrolled, observational, retrospective studies provided evidence for the effect of GnRH analogues on femoral bone density in sex assigned at birth males (Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017). See the safety results table above for a full description of the results. **These studies provide very low certainty evidence that GnRH analogues may reduce the expected increase in femoral bone density (femoral neck or area BMAD or BMD) in sex assigned at birth males (transfemales; although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual femoral bone density (femoral area BMAD or femoral neck BMD) in sex assigned at birth males (transfemales).** **Cognitive development or functioning** One cross-sectional observational study (Staphorsius et al. 2015) provided comparative evidence on cognitive development or functioning in sex assigned at birth males. See the safety results table above for a full description of the results. **This study provides very low certainty evidence (with no statistical analysis) on the effects of GnRH analogues on cognitive development or functioning in sex assigned at birth males (transfemales). No conclusions could be drawn.** **Other safety outcomes: kidney function** One prospective observational study (Schagen et al. 2016) provided non-comparative evidence on change in serum creatinine in sex assigned at birth males. See the safety results table above for a full description of the results. **This study provides very low certainty evidence that GnRH analogues do not affect renal function in sex assigned at birth males (transfemales).**
Sex assigned at birth females (transmales) **Certainty of evidence: Very low**	Some studies reported data separately for sex assigned at birth females (transmales). This included some direct comparisons with sex assigned at birth males (transfemales). **Impact on gender dysphoria** One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) and one prospective observational longitudinal study (Costa et al. 2015) provided evidence for gender dysphoria in sex assigned at birth females. See the sex assigned at birth males (transfemales) row above for a full description of the results. **These studies provide very low certainty evidence that in sex assigned at birth females (transmales), gender dysphoria is higher than in sex assigned at birth males (transfemales) at both baseline and follow up.**

	Impact on mental health One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on mental health (depression, anger and anxiety) in sex assigned at birth females. See the sex assigned at birth males (transfemales) row above for a full description of the results. **This study provides very low certainty evidence that the impact on mental health (depression, anger and anxiety) may be different in sex assigned at birth females (transmales) compared with sex assigned at birth males (transfemales). Over time there was no statistically significant difference between sex assigned at birth females and sex assigned at birth males for depression. However, sex assigned at birth females had statistically significantly greater levels of anger and anxiety than sex assigned at birth males at baseline and follow up.** **Impact on body image** One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on body image in sex assigned at birth females. See the sex assigned at birth males (transfemales) row above for a full description of the results. **This study provides very low certainty evidence that the impact on body image may be different in sex assigned at birth females (transmales) compared with sex assigned at birth males (transfemales). Sex assigned at birth females are more dissatisfied with their primary and secondary sex characteristics than sex assigned at birth males at both baseline and follow up, but the satisfaction with neutral body characteristics is not different.** **Psychosocial impact** One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence for psychosocial impact in terms of global functioning (CGAS) and psychosocial functioning (CBCL and YSR) in sex assigned at birth females. One uncontrolled, observational, prospective cohort study (Costa et al. 2015) provided evidence for psychosocial impact in terms of global functioning (CGAS) in sex assigned at birth females. See the sex assigned at birth males (transfemales) row above for a full description of the results. **These studies provide very low certainty evidence that psychosocial impact may be different in sex assigned at birth females (transmales) compared with sex assigned at birth males (transfemales). However, no conclusions could be drawn.** **Change in bone density: lumbar** Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on lumbar bone density in sex assigned at birth females (Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017). See the safety results table above for a full description of the results.

	These studies provide very low certainty evidence that GnRH analogues reduce the expected increase in lumbar bone density (BMAD or BMD) in sex assigned at birth females (transmales; although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual lumbar bone density (BMAD or BMD) in sex assigned at birth females (transmales). **Change in bone density: femoral** Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on femoral bone density in sex assigned at birth females (Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017). See the safety results table above for a full description of the results. **These studies provide very low certainty evidence that GnRH analogues may reduce the expected increase in femoral bone density (femoral neck or area BMAD or BMD) in sex assigned at birth females (transmales; although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual femoral bone density (femoral area BMAD or femoral neck BMD) in sex assigned at birth females (transmales), apart from actual femoral area.** **Cognitive development or functioning** One cross-sectional observational study (Staphorsius et al. 2015) provided comparative evidence on cognitive development or functioning in sex assigned at birth females. See the safety results table above for a full description of the results. **This study provides very low certainty evidence (with no statistical analysis) on the effects of GnRH analogues on cognitive development or functioning in sex assigned at birth females (transmales). No conclusions could be drawn.** **Other safety outcomes: kidney function** One prospective observational study (Schagen et al. 2016) provided non-comparative evidence on change in serum creatinine in sex assigned at birth females (transmales). See the safety results table above for a full description of the results. **This study provides very low certainty evidence that GnRH analogues do not affect renal function in sex assigned at birth females (transmales).**
Duration of gender dysphoria	No evidence was identified.
Age at onset of gender dysphoria	No evidence was identified.
Age at which GnRH analogue started	No evidence was identified.
Age at onset of puberty	No evidence was identified.

Tanner stage at which GnRH analogue started	No evidence was identified.
Diagnosis of autistic spectrum disorder	No evidence was identified.
Diagnosis of mental health condition	No evidence was identified.

Abbreviations: BDI-II, Beck Depression Inventory-II; BIS, Body Image Scale; CBCL, Child Behaviour Checklist; CGAS, Children's Global Assessment Scale; SD, standard deviation; STAI, Trait Anxiety Scale of the State-Trait Personality Inventory; TPI, Trait Anger Scale of the State-Trait Personality Inventory; UGDS, Utrecht Gender Dysphoria Scale; YSR, Youth Self-Report

From the evidence selected,

(a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?

(b) what were the ages at which participants commenced treatment with GnRH analogues?

(c) what was the duration of treatment with GnRH analogues?

<table>
<tr><th>Outcome</th><th>Evidence statement</th></tr>
<tr><td>Diagnostic criteria</td><td>In 5 studies (Costa et al. 2015, Klink et al. 2015, Schagen et al. 2016, Staphorsius et al. 2015 and Vlot et al. 2017) the DSM-IV-TR criteria of gender identity disorder was used.

The study by Brik et al. 2020 used DSM-V criteria. The DSM-V has one overarching definition of gender dysphoria with separate specific criteria for children and for adolescents and adults. The general definition describes a conflict associated with significant distress and/or problems functioning associated with this conflict between the way they feel and the way they think of themselves which must have lasted at least 6 months.

It was not reported how gender dysphoria was defined in the remaining 3 studies (VERY LOW).

From the evidence selected, all studies that reported diagnostic criteria for gender dysphoria (6/9 studies) used the DSM criteria in use at the time the study was conducted.</td></tr>
<tr><td>Age when GnRH analogues started</td><td>8/9 studies reported the age at which participants started GnRH analogues, either as the mean age (with SD) or median age (with the range):

<table>
<tr><th>Study</th><th>Mean age (±SD)</th></tr>
<tr><td>Costa et al. 2015</td><td>16.5 years (±1.3)</td></tr>
<tr><td>de Vries et al. 2011</td><td>13.6 years (±1.8)</td></tr>
<tr><td>Joseph et al. 2019</td><td>13.2 years (±1.4) in transfemales
12.6 years (±1.0) in transmales</td></tr>
<tr><td>Khatchadourian et al. 2014</td><td>14.7 years (±1.9)</td></tr>
</table>
</td></tr>
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<table>
<tr><td></td><td>
<table>
<tr><td>Klink et al. 2015</td><td>14.9 years (±1.9) in transfemales
15.0 years (±2.0) in transmales</td></tr>
</table>
<table>
<tr><th>Study</th><th>Median age (range)</th></tr>
<tr><td>Brik et al. 2020</td><td>15.5 years (11.1–18.6) in transfemales
16.1 years (10.1–17.9) in transmales</td></tr>
<tr><td>Schagen et al. 2016</td><td>13.6 years (11.6–17.9) in transfemales
14.2 years (11.1–18.6) in transmales</td></tr>
<tr><td>Vlot et al. 2017</td><td>13.5 years (11.5–18.3) in transfemales
15.1 years (11.7–18.6) in transmales</td></tr>
</table>
Age at the start of GnRH analogues was not reported in Staphorsius et al. 2015, but participants were required to be at least 12 years (VERY LOW).

The evidence included showed wide variation in the age (11 to 18 years old) at which children and adolescents with gender dysphoria started GnRH analogues.
</td></tr>
<tr><td>Duration of treatment</td><td>The duration of treatment with GnRH analogues was reported in 3/9 studies. The median duration was:
• 2.1 years (range 1.6–2.8) in Brik et al. 2020.
• 1.3 years (range 0.5–3.8) in transfemales and 1.5 years (range 0.25–5.2) in transmales in Klink et al. 2015.

In Staphorsius et al. 2015, the mean duration was 1.6 years (SD ±1.0).

In de Vries et al. 2011, the mean duration of time between starting GnRH analogues and gender-affirming hormones was 1.88 years (SD ±1.05).

The evidence included showed wide variation in the duration of treatment with GnRH analogues, but most studies did not report this information. Treatment duration ranged from a few months up to about 5 years.</td></tr>
</table>

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders criteria; SD, standard deviation.

6. Discussion

A key limitation to identifying the effectiveness and safety of GnRH analogues for children and adolescents with gender dysphoria is the lack of reliable comparative studies. The lack of clear, expected outcomes from treatment with a GnRH analogue (the purpose of which is to suppress secondary sexual characteristics which may cause distress from unwanted pubertal changes) also makes interpreting the evidence difficult. The size of the population with gender dysphoria means conducting a prospective trial may be unrealistic, at least on a single centre basis. There may also be ethical issues with a 'no treatment arm' in comparative trials of GnRH analogues, where there may be poor mental health outcomes if treatment is withheld. However, the use of an active comparator such as close psychological support may reduce ethical concerns in future trials.

The studies included in this evidence review are all small, uncontrolled observational studies, which are subject to bias and confounding, and are of very low certainty as

assessed using modified GRADE. All the included studies reported physical and mental health comorbidities and concomitant treatments very poorly. For example, very little data are reported on how many children and adolescents needed additional mental health support, and for what reasons, or whether additional interventions, and what form and duration (for example drug treatment or counselling) that took. This is a possible confounder for the treatment outcomes in the studies because changes in critical and important outcomes may be attributable to external care rather than the psychological support or GnRH analogues used in the studies.

The studies that reported diagnostic criteria for gender dysphoria (6/9 studies) used the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria in use at the time the study was conducted (either DSM-IV-TR or DSM-V). The definition was unclear in the remaining studies. There was wide variation in the ages at which participants started a GnRH analogue, typically ranging from about 11 to 18 years. Similarly, there was a wide variation in the duration of use, but few studies reported this.

Changes in outcome scores for clinical effectiveness were assessed for statistical significance in the 3 studies reporting these outcomes (Costa et al. 2015; de Vries et al. 2011; Staphorsius et al. 2015). However, there is relatively little interpretation of whether the changes in outcome scores seen in these studies are clinically meaningful.

For some outcomes there was no statistically significant difference from before starting GnRH analogues until just before starting gender-affirming hormones. These were the Utrecht Gender Dysphoria Scale (UGDS) (which was assessed in 1 study de Vries et al. 2011), the Trait Anger (TPI) and Trait Anxiety (STAI) Scales (which were assessed in 1 study de Vries et al. 2011), and Body Image Scale (BIS) which was assessed in 1 study (de Vries et al. 2011).

The Beck Depression Inventory (BDI-II) was used in 1 study (de Vries et al. 2011) to assess change in depression from before starting GnRH analogues to just before starting gender-affirming hormones. The result is statistically significant, with the mean (±SD) BDI-II score decreasing from 8.31 (±7.12) at baseline to 4.95 (±6.27) at follow up (p=0.004). However, both scores fall into the minimal range using the general guidelines for interpretation of BDI-II (0 to 13 minimal, 14 to 19 mild depression, 20 to 28 moderate depression and 29 to 63 severe depression), suggesting that while statistically significant, it is unclear if this is a clinically meaningful change.

Psychosocial outcomes were assessed in 3 studies (Costa et al. 2015; de Vries et al. 2011; Staphorsius et al. 2015) using the Children's Global Assessment Scale (CGAS) and Child Behavior Checklist/Youth Self-Report (CBCL/YSR). The CGAS score was assessed in 2 studies (Costa et al. 2015; de Vries et al. 2011). In de Vries et al. 2011 the mean (±SD) CGAS score statistically significantly increased over time from 70.24 [±10.12] at baseline to 73.90 [±9.63] at follow up. CGAS scores are clinically categorised into 10 categories (10 to 1, 20 to 11 and so on until 100 to 91) and both scores reported were in a single category (71 to 80, no more than slight impairment) suggesting that while statistically significant, it is unclear if this is a clinically meaningful change. The Costa et al. 2015 study does highlight a larger change in CGAS scores from baseline to follow-up (mean [±SD] 58.72 [±11.38] compared with 67.40 [±13.39]), but whether this is clinically meaningful is unclear. The average score moved from the clinical category of 60 to 51 (variable functioning with sporadic difficulties) at baseline to 70 to 61 (some difficulty in a single area, but generally

functioning pretty well) at follow up, but the large standard deviations suggest clinically significant overlaps between the scores from baseline to follow-up.

Psychosocial functioning using the CBCL/YSR was assessed in 2 studies (de Vries et al. 2011; Staphorsius et al. 2015). In de Vries et al. 2011 there was a statistically significant reduction in both CBCL and YSR scores from before starting GnRH analogues to just before starting gender-affirming hormones. The study interpreted the CBCL/YSR with a proportion of adolescents who scored in the clinical range (a T-score above 63), which allows changes in clinically meaningful scores to be assessed, and proportions of adolescents in the clinical range for some CBCL and YSR scores decreased over time. One cross-sectional study (Staphorsius et al. 2015) assessed CBCL scores only, but it was unclear if this was the Total T score, or whether subscales of internalising or externalising scores were also assessed, and whether the results were statistically significant.

The 2 prospective observational studies (Costa et al. 2015; de Vries et al. 2011) are confounded by a number of common factors. Firstly, the single assessment of scores at baseline means it is unclear if scores were stable, already improving or declining before starting treatment. Secondly, in an uncontrolled study any changes in scores from baseline to follow-up could be attributed to a regression-to-mean, for example getting older has been positively associated with maturity and wellbeing. The studies use mean and standard deviations in the descriptive statistics and analyses; however, they do not report testing the normality of data which would support the use of parametric measures. The study by de Vries et al. 2011 used general linear models (regression) to examine between and within group variances (changes in outcomes). In using such models, the data is assumed to be balanced (measured at regular intervals and without missing data), but the large ranges in ages at which participants were assessed and started on various interventions suggests that ascertainment of outcome was unlikely to be regular and missing data was likely. Missing data was handled through listwise deletion (omits those cases with the missing data and analyses the remaining data) which is acceptable if data loss is completely random but for some outcomes where there was incomplete data for individual items this was not random (items were introduced by the authors after the first eligible adolescents had started GnRH analogues). The study provided no detail on whether these assumptions for the modeling were met, they also provided no adequate assessment of whether any regression diagnostics (analysis that seek to assess the validity of a model) or model fit (how much of the variance in outcome is explained by the between and within group variance) were undertaken.

The 2 retrospective observational studies (Brik et al. 2020; Khatchadourian et al. 2014) both only report absolute numbers for each trajectory along with reasons for stopping GnRH analogues. It is difficult to assess outcomes from such single centre studies because there is little comparative data for outcomes from other such services. A lack of any critical or other important outcomes also means the success of the treatment across all the participants is difficult to judge.

Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on bone density (Joseph et al. 2019; Klink et al. 2015; Vlot et al. 2017). In all 3 studies, the participants acted as their own controls and change in bone density was determined between starting GnRH analogues and either after 1 and 2 year follow-up timepoints (Joseph et al. 2019) or when gender-affirming hormones were started

(Klink et al. 2015 and Vlot et al. 2017). Observational studies such as these can only show an association with GnRH analogues and bone density; they cannot show that GnRH analogues caused any differences in bone density seen. Because there was no comparator group and participants acted as their own controls, it is unclear whether the findings are associated with GnRH analogues or due to changes over time. The authors reported z-scores which allows for comparison with the expected increase in bone density in the general population. However, because no concomitant treatments or comorbidities were reported it is possible that the findings may not be because of GnRH analogues and there is another way in which the study population differs from the general population.

All the studies are from a limited number of, mainly European, care facilities. They are described as either tertiary referral or expert services but the low number of services providing such care and publishing evidence may bias the results towards the outcomes in these services only and limit extrapolation.

The first study (Brik et al. 2020) was an uncontrolled, retrospective, observational study that assessed the outcome trajectories of adolescents receiving GnRH analogues for gender dysphoria. This study followed-up 143 individuals who had received GnRH analogues (38 transfemales and 105 transmales) using clinical records to show outcomes for up to 9 years (continuing use of GnRH analogues, reasons for stopping GnRH analogues and onward care such as gender-affirming hormone use). The methods and results are well reported, but no analysis of data was undertaken. The views of adolescents and their parents are particularly difficult to interpret because no data on how many responded to each question and in what ways are reported.

The second study (Costa et al. 2015) was an uncontrolled, prospective observational study which assessed global functioning in adolescents with gender dysphoria using CGAS every 6 months, including during the first 6 months where statistically significant improvements were seen without GnRH analogues. The study is confounded by significant unexplained loss to follow-up (64.7%: from n=201 adolescents to n=71 after 18 months). Missing data for those lost to follow-up maybe more than sufficient to change the direction of effects seen in the study if the reasons for loss to follow-up are systematic (such as deriving little or no benefit from treatment). The study uses clustered data in its analysis, a single outcome (CGAS) measured in clusters (at different visits), and the analysis does not take account of the correlation of scores (data at different time points are not independent) as a significant change in scores early in the study means the successive changes measured against baseline were also significant. The study relies on multiple (>20) pairwise independent *t*-tests to examine change in CGAS between the 4 time points, increasing the possibility of type-I error (a false positive which occurs when a researcher incorrectly rejects a true null hypothesis) because the more tests performed the more likely a statistically significant result will be observed by chance alone.

The Costa et al. 2015 study compares immediately eligible and delayed eligible cohorts, however, it is highly likely that they are non-comparable groups because the immediately eligible group were those able to start GnRH analogues straight away whilst those in the delayed eligible group were either not ready to make a decision about starting treatment (no age comparison was made between the 2 groups so it is unclear if they were a younger cohort than the immediately eligible group) or had comorbid mental health or psychological difficulties. The authors report that those with concomitant problems (such as mental health

problems, substantial problems with peers, or conflicts with parents or siblings) were referred to local mental health services but no details are provided.

The third study (de Vries et al. 2011) was an uncontrolled, prospective observational study which assessed gender dysphoria and psychological functioning before and after puberty suppression in adolescents with gender dysphoria. Although the study mentions the DSM-IV-TR there is no explicit discussion of this, or any other criteria, being used as the diagnostic criteria for study entry. There are no details reported for how the outcomes in the study were assessed, and by whom. The length of follow-up for the outcomes in the model are questionable in relation to whether there was sufficient time for GnRH analogues to have a measurable effect. The time points used are start of GnRH analogues and start of gender-affirming hormones. Overall, the mean time between starting GnRH analogues and gender-affirming hormones was 1.88 (±1.05) years, but the range is as low as just 5 months between the 2 time points, which may be insufficient for any difference in outcome to have occurred in some individuals.

The fourth study (Joseph et al. 2019) was a retrospective, longitudinal observational single centre study which assessed bone mineral density in adolescents with gender dysphoria in the UK. For inclusion in the study, participants had to have been assessed by the Gender Identity Development Service multi-disciplinary psychosocial health team for at least 4 assessments over a minimum of 6 months. No other diagnostic criteria, such as the DSM-IV-TR, are discussed. Bone density was assessed using dual energy X-ray absorptiometry (DAXA) scan of the lumbar spine (L1-L4) and the femoral neck at baseline (n=70), 1 year (n=70) and 2 years after starting GnRH analogues (n=39). The results suggest a possible association between GnRH analogues and bone mineral apparent density. However, the evidence is of poor quality, and the results could be due to bias or chance. No concomitant treatments or comorbidities were reported.

The fifth study (Khatchadourian et al. 2014) was an uncontrolled retrospective observational study which describes patient characteristics at presentation, treatment, and response to treatment in 84 adolescents with gender dysphoria, of whom 27 received GnRH analogues. The study used clinical records to show outcomes for up to 13 years (continuing use of GnRH analogues, reasons for stopping GnRH analogues and onward care such as gender-affirming hormone use). The methods are well reported but the results for those taking GnRH analogues are poorly and incompletely reported, particularly for transfemales, and no analysis of data was undertaken. It is difficult to assess the results for stopping GnRH analogues due to incomplete reporting of this outcome.

The sixth study (Klink et al. 2015) was a retrospective longitudinal observational single centre study which assessed bone mineral density in adolescents with gender dysphoria, diagnosed with the DSM-IV-TR criteria. Bone density was assessed when starting GnRH analogues and then when starting gender-affirming hormones. Results are reported for transmales and transfemales separately and no results for the whole cohort are given. Statistical analyses were reported for all outcomes of interest but, because there was no comparator group and participants acted as their own controls, it is not known whether the findings are associated with GnRH analogues or due to changes over time. The authors reported z-scores which allows for comparison with the expected increase in bone density in the general population. However, because no concomitant treatments or comorbidities were

reported it is possible that the findings may not be because of GnRH analogues and there is another way in which the study population differs from the general population.

The seventh study (Schagen et al. 2016) was a prospective observational study of 116 adolescents which provided very low certainty non-comparative evidence on change in serum creatinine between starting GnRH analogues and 1 year, and liver function during treatment. Statistical analyses were reported for changes in serum creatinine but not for liver function. Because there was no comparator group and participants acted as their own controls, it is not known whether the findings are associated with GnRH analogues or due to changes over time, or concomitant treatments.

The eighth study (Staphorsius et al. 2015) was a cross-sectional study of 85 adolescents, 40 with gender dysphoria (of whom 20 were receiving GnRH analogues) and 45 matched controls (not further reported in this evidence review). The study includes 1 outcome of interest for clinical effectiveness (CBCL) and 1 outcome of interest for safety (cognitive development or functioning). The mean (±SD) CBCL, IQ test, reaction time and accuracy scores were given for each group, but the statistical analysis is unclear. It is not reported what analysis was used or which of the groups were compared, therefore it is difficult to interpret the results.

The ninth study (Vlot et al. 2017) was a retrospective observational study which assessed bone mineral apparent density in adolescents with DSM-IV-TR gender dysphoria. Measurements were taken at the start of GnRH analogues and at the start of gender-affirming hormones. Results are reported for young bone age and old bone age in transmales and transfemales separately, and no results for the whole cohort are given. Statistical analyses were reported for all outcomes of interest but, because there was no comparator group and participants acted as their own controls, it is not known whether the findings are associated with GnRH analogues or due to changes over time. The authors reported z-scores which allows for comparison with the expected increase in bone density in the general population. However, because no concomitant treatments or comorbidities were reported it is possible that the findings may not be because of GnRH analogues and there is another way in which the study population differs from the general population.

7. Conclusion

The results of the studies that reported impact on the critical outcomes of gender dysphoria and mental health (depression, anger and anxiety), and the important outcomes of body image and psychosocial impact (global and psychosocial functioning) in children and adolescents with gender dysphoria are of very low certainty using modified GRADE. They suggest little change with GnRH analogues from baseline to follow-up.

Studies that found differences in outcomes could represent changes that are either of questionable clinical value, or the studies themselves are not reliable and changes could be due to confounding, bias or chance. It is plausible, however, that a lack of difference in scores from baseline to follow-up is the effect of GnRH analogues in children and adolescents with gender dysphoria, in whom the development of secondary sexual characteristics might be expected to be associated with an increased impact on gender dysphoria, depression, anxiety, anger and distress over time without treatment. One study reported statistically significant reductions in the Child Behaviour Checklist/Youth Self-Report (CBCL/YSR) scores from

baseline to follow up, and given that the purpose of GnRH analogues is to reduce distress caused by the development of secondary sexual characteristics and the CBCL/YSR in part measures distress, this could be an important finding. However, as the studies all lack reasonable controls not receiving GnRH analogues, the natural history of the outcomes measured in the studies is not known and any positive changes could be a regression to mean.

The results of the studies that reported bone density outcomes suggest that GnRH analogues may reduce the increase in bone density which is expected during puberty. However, as the studies themselves are not reliable, the results could be due to confounding, bias or chance. While controlled trials may not be possible, comparative studies are needed to understand this association and whether the effects of GnRH analogues on bone density are seen after treatment is stopped. All the studies that reported safety outcomes provided very low certainty evidence.

No cost-effectiveness evidence was found to determine whether or not GnRH analogues are cost-effective for children and adolescents with gender dysphoria.

The results of the studies that reported outcomes for subgroups of children and adolescents with gender dysphoria, suggest there may be differences between sex assigned at birth males (transfemales) and sex assigned at birth females (transmales).

Appendix A PICO document

The review questions for this evidence review are:

1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
2. For children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
3. For children and adolescents with gender dysphoria, what is the cost-effectiveness of GnRH analogues compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?
4. From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may derive more (or less) advantage from treatment with GnRH analogues than the wider population of children and adolescents with gender dysphoria?
5. From the evidence selected,
   a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?
   b) what were the ages at which participants commenced treatment with GnRH analogues?
   c) what was the duration of treatment with GnRH analogues?

PICO table

P – Population and Indication	Children and adolescents aged 18 years or less who have gender dysphoria, gender identity disorder or gender incongruence of childhood as defined by study: The following subgroups of children and adolescents with gender dysphoria, gender identity disorder or gender incongruence of childhood need to be considered: • Sex assigned at birth males. • Sex assigned at birth females. • The duration of gender dysphoria: less than 6 months, 6-24 months, and more than 24 months. • The age of onset of gender dysphoria. • The age at which treatment was initiated. • The age of onset of puberty. • Tanner stage at which treatment was initiated. • Children and adolescents with gender dysphoria who have a pre-existing diagnosis of autistic spectrum disorder. • Children and adolescents with gender dysphoria who had a significant mental health symptom load at diagnosis including anxiety, depression (with or without a history of self-harm and suicidality), suicide attempts, psychosis, personality disorder, Attention Deficit Hyperactivity Disorder and eating disorders.
I – Intervention	Any GnRH analogue including: triptorelin*; buserelin; histrelin; goserelin (Zoladex); leuprorelin/leuprolide (Prostap); nafarelin.

	* Triptorelin (brand names Gonapeptyl and Decapeptyl) are used in Leeds Hospital, England. The search should include brand names as well as generic names.
C – Comparator(s)	One or a combination of: • Psychological support. • Social transitioning to the gender with which the individual identifies. • No intervention.
O – Outcomes	There are no known minimal clinically important differences and there are no preferred timepoints for the outcome measures selected. **All outcomes should be stratified by:** • The age at which treatment with GnRH analogues was initiated. • The length of treatment with GnRH analogues where possible. **A: Clinical Effectiveness** *Critical to decision making* • **Impact on Gender Dysphoria** This outcome is critical because gender dysphoria in adolescents and children is associated with significant distress and problems functioning. Impact on gender dysphoria may be measured by the Utrecht Gender Dysphoria Scale. Other measures as reported in studies may be used as an alternative to the stated measure. • **Impact on mental health** Examples of mental health problems include self-harm, thoughts of suicide, suicide attempts, eating disorders, depression/low mood and anxiety. These outcomes are critical because self-harm and thoughts of suicide have the potential to result in significant physical harm and for completed suicides the death of the young person. Disordered eating habits may cause significant morbidity in young people. Depression and anxiety are also critical outcomes because they may impact on social, occupational, or other areas of functioning of children and adolescents. The Child and Adolescent Psychiatric Assessment (CAPA) may be used to measure depression and anxiety. The impact on self-harm and suicidality (ideation and behaviour) may be measured using the Suicide Ideation Questionnaire Junior. Other measures may be used as an alternative to the stated measures. • **Impact on Quality of Life** This outcome is critical because gender dysphoria in children and adolescents may be associated with a significant reduction in health-related quality of life. Quality of Life may be measured by the KINDL questionnaire, Kidscreen 52. Other measures as reported in studies may be used as an alternative to the stated measure. *Important to decision making* • **Impact on body Image** This outcome is important because some transgender young people may desire to take steps to suppress features of their physical appearance associated with their sex assigned at birth or accentuate physical features of their desired gender. The Body Image Scale could be used as a measure. Other measures

	as reported in studies may also be used as an alternative to the stated measure. • **Psychosocial Impact** Examples of psychosocial impact are: coping mechanisms which may impact on substance misuse; family relationships; peer relationships. This outcome is important because gender dysphoria in adolescents and children is associated with internalising and externalising behaviours and emotional and behavioural problems which may impact on social and occupational functioning. The child behavioural check list (CBCL) may be used to measure the impact on psychosocial functioning. Other measures as reported in studies may be used as an alternative to the stated measure. • **Engagement with health care services** This outcome is important because patient engagement with healthcare services will impact on their clinical outcomes. Engagement with health care services may be measured using the Youth Health Care measure-satisfaction, utilization, and needs (YHC-SUN) questionnaire. Loss to follow up should also be ascertained as part of this outcome. Alternative measures to the YHC-SUN questionnaire may be used as reported in studies. • **Transitioning surgery – Impact on extent of and satisfaction with surgery** This outcome is important because some children and adolescents with gender dysphoria may proceed to transitioning surgery. Stated measures of the extent of transitioning surgery and satisfaction with surgery in studies may be reported. • **Stopping treatment** The proportion of patients who stop treatment with GnRH analogues and the reasons why. This outcome is important to patients because there is uncertainty about the short- and long-term safety and adverse effects of GnRH analogues in children and adolescents being treated for gender dysphoria. **B: Safety** • Short and long-term safety and adverse effects of taking GnRH analogues are important because GnRH analogues are not licensed for the treatment of adolescents and children with gender dysphoria. Aspects to be reported on should include: o Impact of the drug use such as its impact on bone density, arterial hypertension, cognitive development/functioning o Impact of withdrawing the drug such as, slipped upper femoral epiphysis, reversibility on the reproductive system, and any others as reported. **C: Cost effectiveness** Cost effectiveness studies should be reported.
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.

Language	English only
Patients	Human studies only
Age	18 years or less
Date limits	2000-2020
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines and pre-publication prints
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, the Cochrane Library, HTA and APA PsycInfo were searched on 23 July 2020, limiting the search to papers published in English language in the last 20 years. Conference abstracts and letters were excluded.

Database: Medline
Platform: Ovid
Version: Ovid MEDLINE(R) <1946 to July 21, 2020>
Search date: 23/7/2020
Number of results retrieved: 144
Search strategy:

1 Gender Dysphoria/ (485)
2 Gender Identity/ (18452)
3 "Sexual and Gender Disorders"/ (75)
4 Transsexualism/ (3758)
5 Transgender Persons/ (3143)
6 Health Services for Transgender Persons/ (136)
7 exp Sex Reassignment Procedures/ (836)
8 (gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)).tw. (7435)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (12678)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (102343)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (6974)
12 (male-to-female or m2f or female-to-male or f2m).tw. (114841)
13 or/1-12 (252702)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (1137479)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (852400)
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1913257)

17 Minors/ (2574)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (2361686)
19 exp pediatrics/ (58118)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (836269)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (2024207)
22 Puberty/ (13278)
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (424246)
24 Schools/ (38104)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (7199)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (468992)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (89353)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (887838)
29 or/14-28 (5534171)
30 13 and 29 (79263)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (7)
32 30 or 31 (79263)
33 Gonadotropin-Releasing Hormone/ (27588)
34 (pubert* adj3 block*).ti,ab. (78)
35 ((gonadotrophin or gonadotropin) and releasing).ti,ab. (17299)
36 (GnRH adj2 analog*).ti,ab. (2541)
37 GnRH*.ti,ab. (20991)
38 "GnRH agonist*".ti,ab. (4040)
39 Triptorelin Pamoate/ (1906)
40 triptorelin.ti,ab. (677)
41 arvekap.ti,ab. (1)
42 ("AY 25650" or AY25650).ti,ab. (1)
43 ("BIM 21003" or BIM21003).ti,ab. (0)
44 ("BN 52014" or BN52014).ti,ab. (0)
45 ("CL 118532" or CL118532).ti,ab. (0)
46 Debio.ti,ab. (83)
47 diphereline.ti,ab. (17)
48 moapar.ti,ab. (0)
49 pamorelin.ti,ab. (0)
50 trelstar.ti,ab. (3)
51 triptodur.ti,ab. (1)
52 ("WY 42422" or WY42422).ti,ab. (0)
53 ("WY 42462" or WY42462).ti,ab. (0)
54 gonapeptyl.ti,ab. (0)
55 decapeptyl.ti,ab. (210)
56 salvacyl.ti,ab. (0)
57 Buserelin/ (2119)
58 buserelin.ti,ab. (1304)

59 bigonist.ti,ab. (0)
60 ("hoe 766" or hoe-766 or hoe766).ti,ab. (69)
61 profact.ti,ab. (2)
62 receptal.ti,ab. (30)
63 suprecur.ti,ab. (4)
64 suprefact.ti,ab. (22)
65 tiloryth.ti,ab. (0)
66 histrelin.ti,ab. (55)
67 "LHRH-hydrogel implant".ti,ab. (1)
68 ("RL 0903" or RL0903).ti,ab. (1)
69 ("SPD 424" or SPD424).ti,ab. (1)
70 goserelin.ti,ab. (875)
71 Goserelin/ (1612)
72 ("ici 118630" or ici118630).ti,ab. (51)
73 ("ZD-9393" or ZD9393).ti,ab. (0)
74 zoladex.ti,ab. (379)
75 leuprorelin.ti,ab. (413)
76 carcinil.ti,ab. (0)
77 enanton*.ti,ab. (23)
78 ginecrin.ti,ab. (0)
79 leuplin.ti,ab. (13)
80 Leuprolide/ (2900)
81 leuprolide.ti,ab. (1743)
82 lucrin.ti,ab. (11)
83 lupron.ti,ab. (162)
84 provren.ti,ab. (0)
85 procrin.ti,ab. (3)
86 ("tap 144" or tap144).ti,ab. (40)
87 (a-43818 or a43818).ti,ab. (3)
88 Trenantone.ti,ab. (1)
89 staladex.ti,ab. (0)
90 prostap.ti,ab. (6)
91 Nafarelin/ (327)
92 nafarelin.ti,ab. (251)
93 ("76932-56-4" or "76932564").ti,ab. (0)
94 ("76932-60-0" or "76932600").ti,ab. (0)
95 ("86220-42-0" or "86220420").ti,ab. (0)
96 ("rs 94991 298" or rs94991298).ti,ab. (0)
97 synarel.ti,ab. (12)
98 deslorelin.ti,ab. (263)
99 gonadorelin.ti,ab. (201)
100 ("33515-09-2" or "33515092").ti,ab. (0)
101 ("51952-41-1" or "51952411").ti,ab. (0)
102 ("52699-48-6" or "52699486").ti,ab. (0)
103 cetrorelix.ti,ab. (463)
104 cetrotide.ti,ab. (41)
105 ("NS 75A" or NS75A).ti,ab. (0)
106 ("NS 75B" or NS75B).ti,ab. (0)

107 ("SB 075" or SB075).ti,ab. (0)
108 ("SB 75" or SB75).ti,ab. (63)
109 gonadoliberin.ti,ab. (143)
110 kryptocur.ti,ab. (6)
111 cetrorelix.ti,ab. (463)
112 cetrotide.ti,ab. (41)
113 antagon.ti,ab. (17)
114 ganirelix.ti,ab. (138)
115 ("ORG 37462" or ORG37462).ti,ab. (3)
116 orgalutran.ti,ab. (20)
117 ("RS 26306" or RS26306).ti,ab. (5)
118 ("AY 24031" or AY24031).ti,ab. (0)
119 factrel.ti,ab. (11)
120 fertagyl.ti,ab. (11)
121 lutrelef.ti,ab. (5)
122 lutrepulse.ti,ab. (3)
123 relefact.ti,ab. (10)
124 fertiral.ti,ab. (0)
125 (hoe471 or "hoe 471").ti,ab. (6)
126 relisorm.ti,ab. (4)
127 cystorelin.ti,ab. (18)
128 dirigestran.ti,ab. (5)
129 or/33-128 (42216)
130 32 and 129 (416)
131 limit 130 to english language (393)
132 limit 131 to (letter or historical article or comment or editorial or news or case reports) (36)
133 131 not 132 (357)
134 animals/ not humans/ (4686361)
135 133 not 134 (181)
136 limit 135 to yr="2000 -Current" (144)

Database: Medline in-process
Platform: Ovid
Version: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to July 21, 2020>
Search date: 23/7/2020
Number of results retrieved:
Search strategy: 42

1 Gender Dysphoria/ (0)
2 Gender Identity/ (0)
3 "Sexual and Gender Disorders"/ (0)
4 Transsexualism/ (0)
5 Transgender Persons/ (0)
6 Health Services for Transgender Persons/ (0)
7 exp Sex Reassignment Procedures/ (0)

8 (gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)).tw. (1645)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (2333)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (20884)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (968)
12 (male-to-female or m2f or female-to-male or f2m).tw. (15513)
13 or/1-12 (39905)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (0)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (80723)
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)
17 Minors/ (0)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (321871)
19 exp pediatrics/ (0)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (119783)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)
22 Puberty/ (0)
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (60264)
24 Schools/ (0)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (69233)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (10319)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (112800)
29 or/14-28 (525529)
30 13 and 29 (9196)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (3)
32 30 or 31 (9197)
33 Gonadotropin-Releasing Hormone/ (0)
34 (pubert* adj3 block*).ti,ab. (19)
35 ((gonadotrophin or gonadotropin) and releasing).ti,ab. (1425)
36 (GnRH adj2 analog*).ti,ab. (183)
37 GnRH*.ti,ab. (1695)
38 "GnRH agonist*".ti,ab. (379)
39 Triptorelin Pamoate/ (0)
40 triptorelin.ti,ab. (72)
41 arvekap.ti,ab. (0)
42 ("AY 25650" or AY25650).ti,ab. (0)
43 ("BIM 21003" or BIM21003).ti,ab. (0)
44 ("BN 52014" or BN52014).ti,ab. (0)
45 ("CL 118532" or CL118532).ti,ab. (0)

46 Debio.ti,ab. (11)
47 diphereline.ti,ab. (6)
48 moapar.ti,ab. (0)
49 pamorelin.ti,ab. (0)
50 trelstar.ti,ab. (0)
51 triptodur.ti,ab. (0)
52 ("WY 42422" or WY42422).ti,ab. (0)
53 ("WY 42462" or WY42462).ti,ab. (0)
54 gonapeptyl.ti,ab. (0)
55 decapeptyl.ti,ab. (8)
56 salvacyl.ti,ab. (0)
57 Buserelin/ (0)
58 buserelin.ti,ab. (59)
59 bigonist.ti,ab. (0)
60 ("hoe 766" or hoe-766 or hoe766).ti,ab. (3)
61 profact.ti,ab. (0)
62 receptal.ti,ab. (0)
63 suprecur.ti,ab. (1)
64 suprefact.ti,ab. (2)
65 tiloryth.ti,ab. (0)
66 histrelin.ti,ab. (9)
67 "LHRH-hydrogel implant".ti,ab. (0)
68 ("RL 0903" or RL0903).ti,ab. (0)
69 ("SPD 424" or SPD424).ti,ab. (0)
70 goserelin.ti,ab. (68)
71 Goserelin/ (0)
72 ("ici 118630" or ici118630).ti,ab. (0)
73 ("ZD-9393" or ZD9393).ti,ab. (0)
74 zoladex.ti,ab. (6)
75 leuprorelin.ti,ab. (47)
76 carcinil.ti,ab. (0)
77 enanton*.ti,ab. (1)
78 ginecrin.ti,ab. (0)
79 leuplin.ti,ab. (1)
80 Leuprolide/ (0)
81 leuprolide.ti,ab. (121)
82 lucrin.ti,ab. (4)
83 lupron.ti,ab. (10)
84 provren.ti,ab. (0)
85 procrin.ti,ab. (0)
86 ("tap 144" or tap144).ti,ab. (0)
87 (a-43818 or a43818).ti,ab. (0)
88 Trenantone.ti,ab. (1)
89 staladex.ti,ab. (0)
90 prostap.ti,ab. (0)
91 Nafarelin/ (0)
92 nafarelin.ti,ab. (5)
93 ("76932-56-4" or "76932564").ti,ab. (0)

94 ("76932-60-0" or "76932600").ti,ab. (0)
95 ("86220-42-0" or "86220420").ti,ab. (0)
96 ("rs 94991 298" or rs94991298).ti,ab. (0)
97 synarel.ti,ab. (0)
98 deslorelin.ti,ab. (14)
99 gonadorelin.ti,ab. (13)
100 ("33515-09-2" or "33515092").ti,ab. (0)
101 ("51952-41-1" or "51952411").ti,ab. (0)
102 ("52699-48-6" or "52699486").ti,ab. (0)
103 cetrorelix.ti,ab. (31)
104 cetrotide.ti,ab. (5)
105 ("NS 75A" or NS75A).ti,ab. (0)
106 ("NS 75B" or NS75B).ti,ab. (0)
107 ("SB 075" or SB075).ti,ab. (0)
108 ("SB 75" or SB75).ti,ab. (2)
109 gonadoliberin.ti,ab. (4)
110 kryptocur.ti,ab. (1)
111 cetrorelix.ti,ab. (31)
112 cetrotide.ti,ab. (5)
113 antagon.ti,ab. (0)
114 ganirelix.ti,ab. (8)
115 ("ORG 37462" or ORG37462).ti,ab. (0)
116 orgalutran.ti,ab. (3)
117 ("RS 26306" or RS26306).ti,ab. (0)
118 ("AY 24031" or AY24031).ti,ab. (0)
119 factrel.ti,ab. (2)
120 fertagyl.ti,ab. (1)
121 lutrelef.ti,ab. (0)
122 lutrepulse.ti,ab. (0)
123 relefact.ti,ab. (0)
124 fertiral.ti,ab. (0)
125 (hoe471 or "hoe 471").ti,ab. (0)
126 relisorm.ti,ab. (0)
127 cystorelin.ti,ab. (1)
128 dirigestran.ti,ab. (0)
129 or/33-128 (2332)
130 32 and 129 (45)
131 limit 130 to english language (45)
132 limit 131 to yr="2000 -Current" (42)

Database: Medline epubs ahead of print
Platform: Ovid
Version: Ovid MEDLINE(R) Epub Ahead of Print <July 21, 2020>
Search date: 23/7/2020
Number of results retrieved: 8
Search strategy:

1 Gender Dysphoria/ (0)

2 Gender Identity/ (0)
3 "Sexual and Gender Disorders"/ (0)
4 Transsexualism/ (0)
5 Transgender Persons/ (0)
6 Health Services for Transgender Persons/ (0)
7 exp Sex Reassignment Procedures/ (0)
8 (gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)).tw. (486)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (640)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (1505)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (178)
12 (male-to-female or m2f or female-to-male or f2m).tw. (2480)
13 or/1-12 (4929)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (0)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (15496)
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)
17 Minors/ (0)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (53563)
19 exp pediatrics/ (0)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (22796)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)
22 Puberty/ (0)
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (13087)
24 Schools/ (0)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (12443)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (1416)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (20166)
29 or/14-28 (88366)
30 13 and 29 (1638)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (1)
32 30 or 31 (1638)
33 Gonadotropin-Releasing Hormone/ (0)
34 (pubert* adj3 block*).ti,ab. (2)
35 ((gonadotrophin or gonadotropin) and releasing).ti,ab. (176)
36 (GnRH adj2 analog*).ti,ab. (30)
37 GnRH*.ti,ab. (223)
38 "GnRH agonist*".ti,ab. (49)
39 Triptorelin Pamoate/ (0)

40 triptorelin.ti,ab. (12)
41 arvekap.ti,ab. (0)
42 ("AY 25650" or AY25650).ti,ab. (0)
43 ("BIM 21003" or BIM21003).ti,ab. (0)
44 ("BN 52014" or BN52014).ti,ab. (0)
45 ("CL 118532" or CL118532).ti,ab. (0)
46 Debio.ti,ab. (2)
47 diphereline.ti,ab. (1)
48 moapar.ti,ab. (0)
49 pamorelin.ti,ab. (0)
50 trelstar.ti,ab. (0)
51 triptodur.ti,ab. (0)
52 ("WY 42422" or WY42422).ti,ab. (0)
53 ("WY 42462" or WY42462).ti,ab. (0)
54 gonapeptyl.ti,ab. (0)
55 decapeptyl.ti,ab. (0)
56 salvacyl.ti,ab. (0)
57 Buserelin/ (0)
58 buserelin.ti,ab. (7)
59 bigonist.ti,ab. (0)
60 ("hoe 766" or hoe-766 or hoe766).ti,ab. (0)
61 profact.ti,ab. (0)
62 receptal.ti,ab. (0)
63 suprecur.ti,ab. (0)
64 suprefact.ti,ab. (1)
65 tiloryth.ti,ab. (0)
66 histrelin.ti,ab. (2)
67 "LHRH-hydrogel implant".ti,ab. (0)
68 ("RL 0903" or RL0903).ti,ab. (0)
69 ("SPD 424" or SPD424).ti,ab. (0)
70 goserelin.ti,ab. (11)
71 Goserelin/ (0)
72 ("ici 118630" or ici118630).ti,ab. (0)
73 ("ZD-9393" or ZD9393).ti,ab. (0)
74 zoladex.ti,ab. (1)
75 leuprorelin.ti,ab. (13)
76 carcinil.ti,ab. (0)
77 enanton*.ti,ab. (1)
78 ginecrin.ti,ab. (0)
79 leuplin.ti,ab. (0)
80 Leuprolide/ (0)
81 leuprolide.ti,ab. (22)
82 lucrin.ti,ab. (0)
83 lupron.ti,ab. (2)
84 provren.ti,ab. (0)
85 procrin.ti,ab. (0)
86 ("tap 144" or tap144).ti,ab. (1)
87 (a-43818 or a43818).ti,ab. (0)

88 Trenantone.ti,ab. (0)
89 staladex.ti,ab. (0)
90 prostap.ti,ab. (0)
91 Nafarelin/ (0)
92 nafarelin.ti,ab. (4)
93 ("76932-56-4" or "76932564").ti,ab. (0)
94 ("76932-60-0" or "76932600").ti,ab. (0)
95 ("86220-42-0" or "86220420").ti,ab. (0)
96 ("rs 94991 298" or rs94991298).ti,ab. (0)
97 synarel.ti,ab. (0)
98 deslorelin.ti,ab. (3)
99 gonadorelin.ti,ab. (3)
100 ("33515-09-2" or "33515092").ti,ab. (0)
101 ("51952-41-1" or "51952411").ti,ab. (0)
102 ("52699-48-6" or "52699486").ti,ab. (0)
103 cetrorelix.ti,ab. (6)
104 cetrotide.ti,ab. (2)
105 ("NS 75A" or NS75A).ti,ab. (0)
106 ("NS 75B" or NS75B).ti,ab. (0)
107 ("SB 075" or SB075).ti,ab. (0)
108 ("SB 75" or SB75).ti,ab. (0)
109 gonadoliberin.ti,ab. (0)
110 kryptocur.ti,ab. (0)
111 cetrorelix.ti,ab. (6)
112 cetrotide.ti,ab. (2)
113 antagon.ti,ab. (1)
114 ganirelix.ti,ab. (1)
115 ("ORG 37462" or ORG37462).ti,ab. (0)
116 orgalutran.ti,ab. (0)
117 ("RS 26306" or RS26306).ti,ab. (0)
118 ("AY 24031" or AY24031).ti,ab. (0)
119 factrel.ti,ab. (0)
120 fertagyl.ti,ab. (0)
121 lutrelef.ti,ab. (0)
122 lutrepulse.ti,ab. (0)
123 relefact.ti,ab. (0)
124 fertiral.ti,ab. (0)
125 (hoe471 or "hoe 471").ti,ab. (0)
126 relisorm.ti,ab. (0)
127 cystorelin.ti,ab. (0)
128 dirigestran.ti,ab. (0)
129 or/33-128 (310)
130 32 and 129 (8)
131 limit 130 to english language (8)
132 limit 131 to yr="2000 -Current" (8)

Database: Medline daily update
Platform: Ovid

Version: Ovid MEDLINE(R) Daily Update <July 21, 2020>
Search date: 23/7/2020
Number of results retrieved: 1
Search strategy

1 Gender Dysphoria/ (4)
2 Gender Identity/ (38)
3 "Sexual and Gender Disorders"/ (0)
4 Transsexualism/ (2)
5 Transgender Persons/ (26)
6 Health Services for Transgender Persons/ (1)
7 exp Sex Reassignment Procedures/ (3)
8 (gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)).tw. (24)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (39)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (87)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (15)
12 (male-to-female or m2f or female-to-male or f2m).tw. (181)
13 or/1-12 (358)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (932)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (981)
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1756)
17 Minors/ (3)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (3672)
19 exp pediatrics/ (75)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (1658)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (2006)
22 Puberty/ (8)
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (732)
24 Schools/ (56)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (5)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (622)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (98)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (1301)
29 or/14-28 (6705)
30 13 and 29 (130)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (0)
32 30 or 31 (130)
33 Gonadotropin-Releasing Hormone/ (11)

34 (pubert* adj3 block*).ti,ab. (0)
35 ((gonadotrophin or gonadotropin) and releasing).ti,ab. (10)
36 (GnRH adj2 analog*).ti,ab. (2)
37 GnRH*.ti,ab. (14)
38 "GnRH agonist*".ti,ab. (4)
39 Triptorelin Pamoate/ (1)
40 triptorelin.ti,ab. (1)
41 arvekap.ti,ab. (0)
42 ("AY 25650" or AY25650).ti,ab. (0)
43 ("BIM 21003" or BIM21003).ti,ab. (0)
44 ("BN 52014" or BN52014).ti,ab. (0)
45 ("CL 118532" or CL118532).ti,ab. (0)
46 Debio.ti,ab. (1)
47 diphereline.ti,ab. (0)
48 moapar.ti,ab. (0)
49 pamorelin.ti,ab. (0)
50 trelstar.ti,ab. (0)
51 triptodur.ti,ab. (0)
52 ("WY 42422" or WY42422).ti,ab. (0)
53 ("WY 42462" or WY42462).ti,ab. (0)
54 gonapeptyl.ti,ab. (0)
55 decapeptyl.ti,ab. (0)
56 salvacyl.ti,ab. (0)
57 Buserelin/ (0)
58 buserelin.ti,ab. (0)
59 bigonist.ti,ab. (0)
60 ("hoe 766" or hoe-766 or hoe766).ti,ab. (0)
61 profact.ti,ab. (0)
62 receptal.ti,ab. (0)
63 suprecur.ti,ab. (0)
64 suprefact.ti,ab. (0)
65 tiloryth.ti,ab. (0)
66 histrelin.ti,ab. (0)
67 "LHRH-hydrogel implant".ti,ab. (0)
68 ("RL 0903" or RL0903).ti,ab. (0)
69 ("SPD 424" or SPD424).ti,ab. (0)
70 goserelin.ti,ab. (1)
71 Goserelin/ (2)
72 ("ici 118630" or ici118630).ti,ab. (0)
73 ("ZD-9393" or ZD9393).ti,ab. (0)
74 zoladex.ti,ab. (0)
75 leuprorelin.ti,ab. (0)
76 carcinil.ti,ab. (0)
77 enanton*.ti,ab. (0)
78 ginecrin.ti,ab. (0)
79 leuplin.ti,ab. (0)
80 Leuprolide/ (0)
81 leuprolide.ti,ab. (0)

82 lucrin.ti,ab. (0)
83 lupron.ti,ab. (0)
84 provren.ti,ab. (0)
85 procrin.ti,ab. (0)
86 ("tap 144" or tap144).ti,ab. (0)
87 (a-43818 or a43818).ti,ab. (0)
88 Trenantone.ti,ab. (0)
89 staladex.ti,ab. (0)
90 prostap.ti,ab. (0)
91 Nafarelin/ (0)
92 nafarelin.ti,ab. (0)
93 ("76932-56-4" or "76932564").ti,ab. (0)
94 ("76932-60-0" or "76932600").ti,ab. (0)
95 ("86220-42-0" or "86220420").ti,ab. (0)
96 ("rs 94991 298" or rs94991298).ti,ab. (0)
97 synarel.ti,ab. (0)
98 deslorelin.ti,ab. (0)
99 gonadorelin.ti,ab. (0)
100 ("33515-09-2" or "33515092").ti,ab. (0)
101 ("51952-41-1" or "51952411").ti,ab. (0)
102 ("52699-48-6" or "52699486").ti,ab. (0)
103 cetrorelix.ti,ab. (0)
104 cetrotide.ti,ab. (0)
105 ("NS 75A" or NS75A).ti,ab. (0)
106 ("NS 75B" or NS75B).ti,ab. (0)
107 ("SB 075" or SB075).ti,ab. (0)
108 ("SB 75" or SB75).ti,ab. (0)
109 gonadoliberin.ti,ab. (0)
110 kryptocur.ti,ab. (0)
111 cetrorelix.ti,ab. (0)
112 cetrotide.ti,ab. (0)
113 antagon.ti,ab. (0)
114 ganirelix.ti,ab. (0)
115 ("ORG 37462" or ORG37462).ti,ab. (0)
116 orgalutran.ti,ab. (0)
117 ("RS 26306" or RS26306).ti,ab. (0)
118 ("AY 24031" or AY24031).ti,ab. (0)
119 factrel.ti,ab. (0)
120 fertagyl.ti,ab. (0)
121 lutrelef.ti,ab. (0)
122 lutrepulse.ti,ab. (0)
123 relefact.ti,ab. (0)
124 fertiral.ti,ab. (0)
125 (hoe471 or "hoe 471").ti,ab. (0)
126 relisorm.ti,ab. (0)
127 cystorelin.ti,ab. (0)
128 dirigestran.ti,ab. (0)
129 or/33-128 (23)

130 32 and 129 (1)
131 limit 130 to english language (1)
132 limit 131 to yr="2000 -Current" (1)

Database: Embase
Platform: Ovid
Version: Embase <1974 to 2020 July 22>
Search date: 23/7/2020
Number of results retrieved: 367
Search strategy:

1 exp Gender Dysphoria/ (5399)
2 Gender Identity/ (16820)
3 "Sexual and Gender Disorders"/ (24689)
4 Transsexualism/ (3869)
5 exp Transgender/ (6597)
6 Health Services for Transgender Persons/ (158848)
7 exp Sex Reassignment Procedures/ or sex transformation/ (3058)
8 (gender* adj3 (dysphori* or affirm* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (13005)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (22509)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (154446)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (10327)
12 (male-to-female or m2f or female-to-male or f2m).tw. (200166)
13 or/1-12 (582812)
14 exp juvenile/ or Child Behavior/ or Child Welfare/ or Child Health/ or infant welfare/ or "minor (person)"/ or elementary student/ (3437324)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (1186161)
16 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (3586795)
17 exp pediatrics/ (106214)
18 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (1491597)
19 exp adolescence/ or exp adolescent behavior/ or adolescent health/ or high school student/ or middle school student/ (105108)
20 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (641660)
21 school/ or high school/ or kindergarten/ or middle school/ or primary school/ or nursery school/ or day care/ (103791)
22 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (687437)
23 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (138908)
24 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (1562903)

25 or/14-24 (7130881)
26 13 and 25 (182161)
27 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (17)
28 26 or 27 (182161)
29 gonadorelin/ (37580)
30 (pubert* adj3 block*).ti,ab. (142)
31 ((gonadotrophin or gonadotropin) and releasing).ti,ab. (21450)
32 (GnRH adj2 analog*).ti,ab. (4013)
33 GnRH*.ti,ab. (29862)
34 "GnRH agonist*".ti,ab. (6719)
35 exp gonadorelin agonist/ or gonadorelin derivative/ or gonadorelin acetate/ (23304)
36 Triptorelin/ (5427)
37 triptorelin.ti,ab. (1182)
38 arvekap.ti,ab. (3)
39 ("AY 25650" or AY25650).ti,ab. (1)
40 ("BIM 21003" or BIM21003).ti,ab. (0)
41 ("BN 52014" or BN52014).ti,ab. (0)
42 ("CL 118532" or CL118532).ti,ab. (0)
43 Debio.ti,ab. (185)
44 diphereline.ti,ab. (51)
45 moapar.ti,ab. (0)
46 pamorelin.ti,ab. (0)
47 trelstar.ti,ab. (5)
48 triptodur.ti,ab. (1)
49 ("WY 42422" or WY42422).ti,ab. (0)
50 ("WY 42462" or WY42462).ti,ab. (0)
51 gonapeptyl.ti,ab. (10)
52 decapeptyl.ti,ab. (307)
53 salvacyl.ti,ab. (1)
54 buserelin acetate/ or buserelin/ (5164)
55 buserelin.ti,ab. (1604)
56 bigonist.ti,ab. (1)
57 ("hoe 766" or hoe-766 or hoe766).ti,ab. (89)
58 profact.ti,ab. (4)
59 receptal.ti,ab. (37)
60 suprecur.ti,ab. (8)
61 suprefact.ti,ab. (30)
62 tiloryth.ti,ab. (0)
63 histrelin/ (446)
64 histrelin.ti,ab. (107)
65 "LHRH-hydrogel implant".ti,ab. (1)
66 ("RL 0903" or RL0903).ti,ab. (1)
67 ("SPD 424" or SPD424).ti,ab. (1)
68 goserelin.ti,ab. (1487)
69 Goserelin/ (7128)
70 ("ici 118630" or ici118630).ti,ab. (49)
71 ("ZD-9393" or ZD9393).ti,ab. (0)

72 zoladex.ti,ab. (501)
73 leuprorelin/ (11312)
74 leuprorelin.ti,ab. (727)
75 carcinil.ti,ab. (0)
76 enanton*.ti,ab. (38)
77 ginecrin.ti,ab. (1)
78 leuplin.ti,ab. (26)
79 leuprolide.ti,ab. (2788)
80 lucrin.ti,ab. (47)
81 lupron.ti,ab. (361)
82 provren.ti,ab. (0)
83 procrin.ti,ab. (11)
84 ("tap 144" or tap144).ti,ab. (63)
85 (a-43818 or a43818).ti,ab. (3)
86 Trenantone.ti,ab. (7)
87 staladex.ti,ab. (0)
88 prostap.ti,ab. (11)
89 nafarelin acetate/ or nafarelin/ (1441)
90 nafarelin.ti,ab. (324)
91 ("76932-56-4" or "76932564").ti,ab. (0)
92 ("76932-60-0" or "76932600").ti,ab. (0)
93 ("86220-42-0" or "86220420").ti,ab. (0)
94 ("rs 94991 298" or rs94991298).ti,ab. (0)
95 synarel.ti,ab. (28)
96 deslorelin/ (452)
97 deslorelin.ti,ab. (324)
98 gonadorelin.ti,ab. (338)
99 ("33515-09-2" or "33515092").ti,ab. (0)
100 ("51952-41-1" or "51952411").ti,ab. (0)
101 ("52699-48-6" or "52699486").ti,ab. (0)
102 cetrorelix/ (2278)
103 cetrorelix.ti,ab. (717)
104 cetrotide.ti,ab. (113)
105 ("NS 75A" or NS75A).ti,ab. (0)
106 ("NS 75B" or NS75B).ti,ab. (0)
107 ("SB 075" or SB075).ti,ab. (1)
108 ("SB 75" or SB75).ti,ab. (76)
109 gonadoliberin.ti,ab. (152)
110 kryptocur.ti,ab. (6)
111 cetrorelix.ti,ab. (717)
112 cetrotide.ti,ab. (113)
113 antagon.ti,ab. (32)
114 ganirelix/ (1284)
115 ganirelix.ti,ab. (293)
116 ("ORG 37462" or ORG37462).ti,ab. (4)
117 orgalutran/ (1284)
118 orgalutran.ti,ab. (68)
119 ("RS 26306" or RS26306).ti,ab. (6)

120 ("AY 24031" or AY24031).ti,ab. (0)
121 factrel.ti,ab. (14)
122 fertagyl.ti,ab. (20)
123 lutrelef.ti,ab. (7)
124 lutrepulse.ti,ab. (6)
125 relefact.ti,ab. (10)
126 fertiral.ti,ab. (0)
127 (hoe471 or "hoe 471").ti,ab. (4)
128 relisorm.ti,ab. (6)
129 cystorelin.ti,ab. (26)
130 dirigestran.ti,ab. (5)
131 or/29-130 (80790)
132 28 and 131 (988)
133 limit 132 to english language (940)
134 133 not (letter or editorial).pt. (924)
135 134 not (conference abstract or conference paper or conference proceeding or "conference review").pt. (683)
136 nonhuman/ not (human/ and nonhuman/) (4649157)
137 135 not 136 (506)
138 limit 137 to yr="2000 -Current" (420)
139 elsevier.cr. (25912990)
140 138 and 139 (372)
141 remove duplicates from 140 (367)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL
Platform: Wiley
Version:
CDSR – Issue 7 of 12, July 2020
CENTRAL – Issue 7 of 12, July 2020
Search date: 23/7/2020
Number of results retrieved: CDSR – 1; CENTRAL - 8.

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#6 [mh ^"health services for transgender persons"] 0
#7 [mh "sex reassignment procedures"] 4
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#10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*):ti,ab 3915
#11 ((sex or gender*) NEAR/3 (reassign* or chang* or transform* or transition*)):ti,ab 493
#12 (male-to-female or m2f or female-to-male or f2m):ti,ab 489

#13 {or #1-#12} 6142
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#17 [mh ^minors] 8
#18 (child* or minor or minors or boy* or girl* or kid or kids or young*):ti,ab 175826
#19 [mh pediatrics]661
#20 (pediatric* or paediatric* or peadiatric*):ti,ab 30663
#21 [mh ^adolescent] or [mh ^"adolescent behavior"] or [mh ^"adolescent health"] 102154
#22 [mh ^puberty] 295
#23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*):ti,ab 34139
#24 [mh ^schools] 1914
#25 [mh ^"Child Day Care Centers"] or [mh nurseries] or [mh ^"schools, nursery"] 277
#26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*):ti,ab 54723
#27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") NEAR/2 (year or years or age or ages or aged)):ti,ab 6710
#28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") NEAR/2 (year or years or age or ages or aged)):ti,ab 196881
#29 {or #14-#28} 469351
#30 #13 and #29 2146
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#32 #30 or #31 2146
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#35 ((gonadotrophin or gonadotropin) and releasing):ti,ab 2095
#36 (GnRH NEAR/2 analog*):ti,ab 493
#37 GnRH*:ti,ab 3764
#38 "GnRH agonist*":ti,ab 1399
#39 [mh ^"Triptorelin Pamoate"] 451
#40 triptorelin:ti,ab 451
#41 arvekap:ti,ab 4
#42 ("AY 25650" or AY25650):ti,ab 0
#43 ("BIM 21003" or BIM21003):ti,ab 0
#44 ("BN 52014" or BN52014):ti,ab 0
#45 ("CL 118532" or CL118532):ti,ab 0
#46 Debio:ti,ab 301
#47 diphereline:ti,ab 25
#48 moapar:ti,ab 0
#49 pamorelin:ti,ab 5
#50 trelstar:ti,ab 3

#51 triptodur:ti,ab 0
#52 ("WY 42422" or WY42422):ti,ab 0
#53 ("WY 42462" or WY42462):ti,ab 0
#54 gonapeptyl:ti,ab 11
#55 decapeptyl:ti,ab 135
#56 salvacyl:ti,ab 0
#57 [mh ^Buserelin] 290
#58 Buserelin:ti,ab 339
#59 bigonist:ti,ab 0
#60 ("hoe 766" or hoe-766 or hoe766):ti,ab 11
#61 profact:ti,ab 1
#62 receptal:ti,ab 4
#63 suprecur:ti,ab 0
#64 suprefact:ti,ab 28
#65 tiloryth:ti,ab 0
#66 histrelin:ti,ab 5
#67 "LHRH-hydrogel implant":ti,ab 0
#68 ("RL 0903" or RL0903):ti,ab 0
#69 ("SPD 424" or SPD424):ti,ab 0
#70 goserelin:ti,ab 761
#71 [mh ^goserelin] 568
#72 ("ici 118630" or ici118630):ti,ab 7
#73 ("ZD-9393" or ZD9393):ti,ab 1
#74 zoladex:ti,ab 318
#75 leuprorelin:ti,ab 248
#76 carcinil:ti,ab 0
#77 enanton*:ti,ab 21
#78 ginecrin:ti,ab 1
#79 leuplin:ti,ab 7
#80 [mh ^Leuprolide] 686
#81 leuprolide:ti,ab 696
#82 lucrin:ti,ab 21
#83 lupron:ti,ab 77
#84 provren:ti,ab 0
#85 procrin:ti,ab 2
#86 ("tap 144" or tap144):ti,ab 24
#87 (a-43818 or a43818):ti,ab 0
#88 Trenantone:ti,ab 3
#89 staladex:ti,ab 0
#90 prostap:ti,ab 9
#91 [mh ^Nafarelin] 77
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#93 ("76932-56-4" or "76932564"):ti,ab 0
#94 ("76932-60-0" or "76932600"):ti,ab 2
#95 ("86220-42-0" or "86220420"):ti,ab 0
#96 ("rs 94991 298" or rs94991298):ti,ab 0
#97 synarel:ti,ab 10
#98 deslorelin:ti,ab 16

#99 gonadorelin:ti,ab 11
#100 ("33515-09-2" or "33515092"):ti,ab 0
#101 ("51952-41-1" or "51952411"):ti,ab 0
#102 ("52699-48-6" or "52699486"):ti,ab 0
#103 cetrorelix:ti,ab 221
#104 cetrotide:ti,ab 111
#105 ("NS 75A" or NS75A):ti,ab 0
#106 ("NS 75B" or NS75B):ti,ab 0
#107 ("SB 075" or SB075):ti,ab 0
#108 ("SB 75" or SB75):ti,ab 10
#109 gonadoliberin:ti,ab 5
#110 kryptocur:ti,ab 0
#111 cetrorelix:ti,ab 221
#112 cetrotide:ti,ab 111
#113 antagon:ti,ab 12
#114 ganirelix:ti,ab 142
#115 ("ORG 37462" or ORG37462):ti,ab 4
#116 orgalutran:ti,ab 45
#117 ("RS 26306" or RS26306):ti,ab 0
#118 ("AY 24031" or AY24031):ti,ab 0
#119 factrel:ti,ab 1
#120 fertagyl:ti,ab 0
#121 lutrelef:ti,ab 0
#122 lutrepulse:ti,ab 1
#123 relefact:ti,ab 1
#124 fertiral:ti,ab 0
#125 (hoe471 or "hoe 471"):ti,ab 3
#126 relisorm:ti,ab 0
#127 cystorelin:ti,ab 0
#128 dirigestran:ti,ab 0
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#130 #32 and #129 27
#131 #130 with Cochrane Library publication date Between Jan 2000 and Jul 2020, in Cochrane Reviews 1
#132 #130 27
#133 "conference":pt or (clinicaltrials or trialsearch):so 492465
#134 #132 not #133 9
#135 #134 with Publication Year from 2000 to 2020, in Trials 8

Database: HTA
Platform: CRD
Version: HTA
Search date: 23/7/2020
Number of results retrieved: 26
Search strategy:

1 MeSH DESCRIPTOR Gender Dysphoria EXPLODE ALL TREES 0
2 MeSH DESCRIPTOR Gender Identity EXPLODE ALL TREES 14

3 MeSH DESCRIPTOR Sexual and Gender Disorders EXPLODE ALL TREES 2

4 MeSH DESCRIPTOR Transsexualism EXPLODE ALL TREES 12
5 MeSH DESCRIPTOR Transgender Persons EXPLODE ALL TREES 3
6 MeSH DESCRIPTOR Health Services for Transgender Persons EXPLODE ALL TREES 0
7 MeSH DESCRIPTOR Sex Reassignment Procedures EXPLODE ALL TREES 1

8 ((gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*))) 28
9 ((transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*)) 76
10 ((trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*)) 83
11 (((sex or gender*) adj3 (reassign* or chang* or transform* or transition*))) 24
12 (male-to-female or m2f or female-to-male or f2m) 86
13 ((transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*)) 0
14 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 262
15 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13) IN HTA 30

*26 results are from 200 onwards. Downloaded as a set to sift for drug terms rather than continuing with search strategy.

Database: APA PsycInfo
Search date: July 2020 (Week 2)
Search Strategy:
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1 Gender Dysphoria/ (936)
2 Gender Identity/ (8648)
3 Transsexualism/ (2825)
4 Transgender/ (5257)
5 exp Gender Reassignment/ (568)
6 (gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)).tw. (15471)
7 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (13028)
8 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (7679)
9 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (5796)
10 (male-to-female or m2f or female-to-male or f2m).tw. (63688)
11 or/1-10 (99560)
12 exp Infant Development/ (21841)
13 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (150219)

14 Child Characteristics/ or exp Child Behavior/ or Child Psychology/ or exp Child Welfare/ or Child Psychiatry/ (23423)
15 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (984230)
16 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (78962)
17 Adolescent Psychiatry/ or Adolescent Behavior/ or Adolescent Development/ or Adolescent Psychology/ or Adolescent Characteristics/ or Adolescent Health/ (62142)
18 Puberty/ (2753)
19 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (347604)
20 Schools/ or exp elementary school students/ or high school students/ or junior high school students/ or middle school students/ (113053)
21 Child Day Care/ or Nursery Schools/ (2836)
22 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (772814)
23 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (21475)
24 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (285697)
25 or/12-24 (1772959)
26 11 and 25 (49612)
27 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (14)
28 26 or 27 (49613)
29 exp Gonadotropic Hormones/ (4226)
30 (pubert* adj3 block*).ti,ab. (29)
31 ((gonadotrophin or gonadotropin) and releasing).ti,ab. (1060)
32 (GnRH adj2 analog*).ti,ab. (49)
33 GnRH*.ti,ab. (998)
34 "GnRH agonist*".ti,ab. (72)
35 triptorelin.ti,ab. (25)
36 arvekap.ti,ab. (0)
37 ("AY 25650" or AY25650).ti,ab. (0)
38 ("BIM 21003" or BIM21003).ti,ab. (0)
39 ("BN 52014" or BN52014).ti,ab. (0)
40 ("CL 118532" or CL118532).ti,ab. (0)
41 Debio.ti,ab. (7)
42 diphereline.ti,ab. (0)
43 moapar.ti,ab. (0)
44 pamorelin.ti,ab. (0)
45 trelstar.ti,ab. (0)
46 triptodur.ti,ab. (0)
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48 ("WY 42462" or WY42462).ti,ab. (0)
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50 decapeptyl.ti,ab. (3)
51 salvacyl.ti,ab. (1)

52 buserelin.ti,ab. (6)
53 bigonist.ti,ab. (0)
54 ("hoe 766" or hoe-766 or hoe766).ti,ab. (0)
55 profact.ti,ab. (0)
56 receptal.ti,ab. (0)
57 suprecur.ti,ab. (0)
58 suprefact.ti,ab. (0)
59 tiloryth.ti,ab. (0)
60 histrelin.ti,ab. (1)
61 "LHRH-hydrogel implant".ti,ab. (0)
62 ("RL 0903" or RL0903).ti,ab. (0)
63 ("SPD 424" or SPD424).ti,ab. (0)
64 goserelin.ti,ab. (30)
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66 ("ZD-9393" or ZD9393).ti,ab. (0)
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68 leuprorelin.ti,ab. (12)
69 carcinil.ti,ab. (0)
70 enanton*.ti,ab. (1)
71 ginecrin.ti,ab. (0)
72 leuplin.ti,ab. (0)
73 leuprolide.ti,ab. (79)
74 lucrin.ti,ab. (1)
75 lupron.ti,ab. (18)
76 provren.ti,ab. (0)
77 procrin.ti,ab. (0)
78 ("tap 144" or tap144).ti,ab. (1)
79 (a-43818 or a43818).ti,ab. (0)
80 Trenantone.ti,ab. (0)
81 staladex.ti,ab. (0)
82 prostap.ti,ab. (0)
83 nafarelin.ti,ab. (1)
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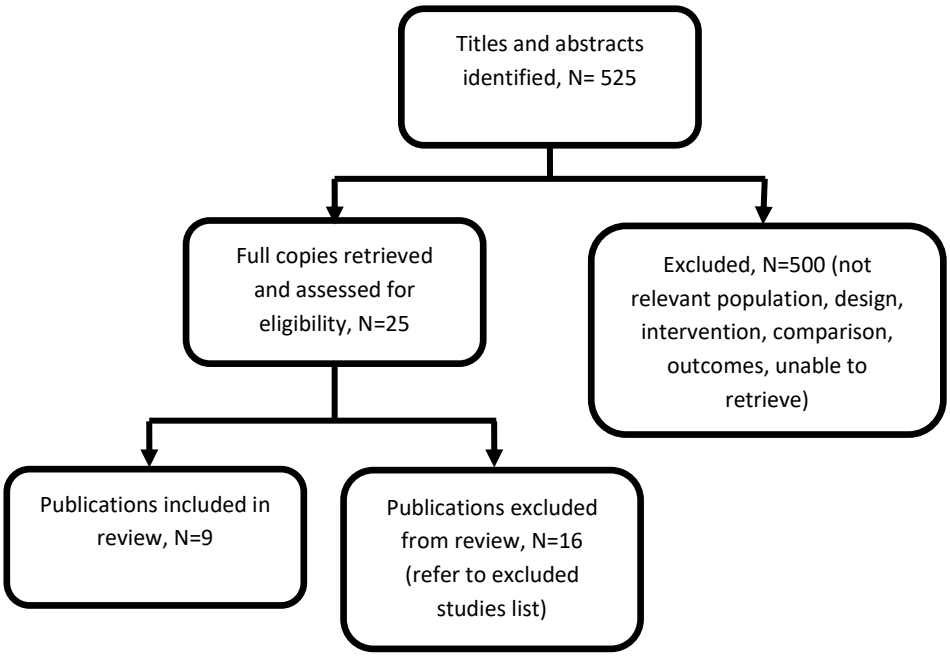
85 ("76932-60-0" or "76932600").ti,ab. (0)
86 ("86220-42-0" or "86220420").ti,ab. (0)
87 ("rs 94991 298" or rs94991298).ti,ab. (0)
88 synarel.ti,ab. (0)
89 deslorelin.ti,ab. (8)
90 gonadorelin.ti,ab. (3)
91 ("33515-09-2" or "33515092").ti,ab. (0)
92 ("51952-41-1" or "51952411").ti,ab. (0)
93 ("52699-48-6" or "52699486").ti,ab. (0)
94 cetrorelix.ti,ab. (9)
95 cetrotide.ti,ab. (0)
96 ("NS 75A" or NS75A).ti,ab. (0)
97 ("NS 75B" or NS75B).ti,ab. (0)
98 ("SB 075" or SB075).ti,ab. (0)
99 ("SB 75" or SB75).ti,ab. (1)

100 gonadoliberin.ti,ab. (1)
101 kryptocur.ti,ab. (0)
102 cetrorelix.ti,ab. (9)
103 cetrotide.ti,ab. (0)
104 antagon.ti,ab. (0)
105 ganirelix.ti,ab. (0)
106 ("ORG 37462" or ORG37462).ti,ab. (0)
107 orgalutran.ti,ab. (0)
108 ("RS 26306" or RS26306).ti,ab. (0)
109 ("AY 24031" or AY24031).ti,ab. (0)
110 factrel.ti,ab. (0)
111 fertagyl.ti,ab. (0)
112 lutrelef.ti,ab. (0)
113 lutrepulse.ti,ab. (0)
114 relefact.ti,ab. (0)
115 fertiral.ti,ab. (0)
116 (hoe471 or "hoe 471").ti,ab. (0)
117 relisorm.ti,ab. (0)
118 cystorelin.ti,ab. (0)
119 dirigestran.ti,ab. (0)
120 or/29-119 (4869)
121 28 and 120 (130)
122 limit 121 to english language (120)
123 limit 122 to yr="2000 -Current" (93)

Appendix C Evidence selection

The literature searches identified 525 references. These were screened using their titles and abstracts and 25 references were obtained and assessed for relevance. Of these, 9 references are included in the evidence review. The remaining 16 references were excluded and are listed in appendix D.

Figure 1 – Study selection flow diagram



References submitted with Preliminary Policy Proposal

There is no preliminary policy proposal for this policy.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Achille, C., Taggart, T., Eaton, N.R. et al. (2020) Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: Preliminary results. International Journal of Pediatric Endocrinology 2020(1): 8	Intervention – data for GnRH analogues not reported separately from other interventions
Bechard, Melanie, Vanderlaan, Doug P, Wood, Hayley et al. (2017) Psychosocial and Psychological Vulnerability in Adolescents with Gender Dysphoria: A "Proof of Principle" Study. Journal of sex & marital therapy 43(7): 678-688	Population – no GnRH analogues at time of study
Chew, Denise, Anderson, Jemma, Williams, Katrina et al. (2018) Hormonal Treatment in Young People With Gender Dysphoria: A Systematic Review. Pediatrics 141(4)	All primary studies included apart from 1 conference abstract
de Vries, Annelou L C, McGuire, Jenifer K et al. (2014) Young adult psychological outcome after puberty suppression and gender reassignment. Pediatrics 134(4): 696-704	Population – relevant population included in de Vries et al. 2011
Ghelani, Rahul, Lim, Cheryl, Brain, Caroline et al. (2020) Sudden sex hormone withdrawal and the effects on body composition in late pubertal adolescents with gender dysphoria. Journal of pediatric endocrinology & metabolism: JPEM 33(1): 107-112	Outcomes – not in the PICO

Study reference	Reason for exclusion
Giovanardi, G, Morales, P, Mirabella, M et al. (2019) Transition memories: experiences of trans adult women with hormone therapy and their beliefs on the usage of hormone blockers to suppress puberty. Journal of endocrinological investigation 42(10): 1231-1240	Population – adults only
Hewitt, Jacqueline K, Paul, Campbell, Kasiannan, Porpavai et al. (2012) Hormone treatment of gender identity disorder in a cohort of children and adolescents. The Medical journal of Australia 196(9): 578-81	Outcomes – no data reported for relevant outcomes
Jensen, R.K., Jensen, J.K., Simons, L.K. et al. (2019) Effect of Concurrent Gonadotropin-Releasing Hormone Agonist Treatment on Dose and Side Effects of Gender-Affirming Hormone Therapy in Adolescent Transgender Patients. Transgender Health 4(1): 300-303	Outcomes – not in the PICO
Klaver, Maartje, de Mutsert, Renee, Wiepjes, Chantal M et al. (2018) Early Hormonal Treatment Affects Body Composition and Body Shape in Young Transgender Adolescents. The journal of sexual medicine 15(2): 251-260	Outcomes – not in the PICO
Klaver, Maartje, de Mutsert, Renee van der Loos, Maria A T C et al. (2020) Hormonal Treatment and Cardiovascular Risk Profile in Transgender Adolescents. Pediatrics 145(3)	Outcomes – not in the PICO
Lopez, Carla Marisa, Solomon, Daniel, Boulware, Susan D et al. (2018) Trends in the use of puberty blockers among transgender children in the United States. Journal of pediatric endocrinology & metabolism : JPEM 31(6): 665-670	Outcomes – not in the PICO
Schagen, Sebastian E E, Lustenhouwer, Paul, Cohen-Kettenis, Peggy T et al. (2018) Changes in Adrenal Androgens During Puberty Suppression and Gender-Affirming Hormone Treatment in Adolescents With Gender Dysphoria. The journal of sexual medicine 15(9): 1357-1363	Outcomes – not in the PICO
Swendiman, Robert A, Vogiatzi, Maria G, Alter, Craig A et al. (2019) Histrelin implantation in the pediatric population: A 10-year institutional experience. Journal of pediatric surgery 54(7): 1457-1461	Population – less than 10% of participants had gender dysphoria; data not reported separately
Turban, Jack L, King, Dana, Carswell, Jeremi M et al. (2020) Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation. Pediatrics 145(2)	Intervention – data for GnRH analogues not reported separately from other interventions
Vrouenraets, Lieke Josephina Jeanne Johanna, Fredriks, A Miranda, Hannema, Sabine E et al. (2016) Perceptions of Sex, Gender, and Puberty Suppression: A Qualitative Analysis of Transgender Youth. Archives of sexual behavior 45(7): 1697-703	Outcomes – not in the PICO
Zucker, Kenneth J, Bradley, Susan J, Owen-Anderson, Allison et al. (2010) Puberty-blocking hormonal therapy for adolescents with gender identity disorder: A descriptive clinical study. Journal of Gay & Lesbian Mental Health 15(1): 58-82	Intervention – data for GnRH analogues not reported separately from other interventions

Appendix E Evidence tables

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Brik T, Vrouenraets L, de Vries M, et al. (2020) Trajectories of adolescents treated with gonadotropin-releasing hormone analogues for gender dysphoria. Archives of Sexual Behaviour https://doi.org/10.1007/s10508-020-01660-8 Netherlands Retrospective observational single-centre study To document trajectories after the initiation of GnRH analogue and explore reasons for extended use and discontinuation of GnRH analogues. Includes participants seen between November 2010 and January 1, 2018.	Inclusion criteria were adolescents with gender dysphoria, according to the DSM-5 criteria, seen at the single centre and treated with GnRH analogues between November 2010 and January 1, 2018. The study excluded adolescents without a diagnosis of gender dysphoria, those who had coexisting problems that interfered with the diagnostic process and/or might interfere with successful treatment (not further defined), those adolescents not wanting hormones, those with ongoing diagnostic evaluation and those who did not attend appointments. The sample consisted of 143 adolescents meeting the inclusion/exclusion criteria, 38 transfemales, 105 transmales, with median ages of 15.0 years (range 11.1 to 18.6 years) and 16.1 years	The study only reports that GnRH analogues were given, no specific drug, dose, route, or frequency of administration are reported. No comparator cohort was used in the study. Follow-up was at (up to) 9 years (last follow-up July 2019).	**Critical outcomes** No critical outcomes assessed. **Important outcomes** ***Psychosocial impact*** Not assessed. ***Engagement with health care services*** Not formally assessed but the study reported that out of 214 age and developmentally appropriate adolescents for potential inclusion in the study, 9 were excluded as they stopped attending appointments (4.2%). ***Stopping treatment*** Of the 143 adolescents, 9 (6.2%, 1 transfemale and 8 transmales) stopped taking GnRH analogues after a median duration of 0.8 years (range 0.1 to 3.0). Four adolescents (2.8%) discontinued GnRH analogues although they wanted to continue endocrine treatments for gender dysphoria: • 1 transmale stopped due to increase in mood problems, suicidal thoughts and confusion attributed to GnRH analogues (later had gender-affirming hormones at an adult gender clinic)[1] • 1 transmale experienced hot flushes, increased migraines, had a fear of injections, stress at school and unrelated medical issues, and	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection** 1. somewhat representative 2. no-non exposed cohort 3. secure record 4. yes **Domain 2: Comparability** 1. no comparator **Domain 3: Outcome** 1. record linkage 2. yes 3. complete follow-up **Overall quality is assessed as poor.** Other comments: Physical and psychological comorbidity was poorly reported, concomitant use of other medicines was not reported. Source of funding: not reported.

	(range 10.1 to 17.9 years), respectively at commencement of GnRH analogues. Of the 143 adolescents in the study, 125 (87%, 36 transfemales and 89 transmales) subsequently started treatment with gender-affirming hormones after median 1.0 (range 0.5 to 3.8) years and 0.8 (0.3 to 3.7) years, respectively. Median age at the start of gender-affirming hormones was 16.2 years (range 14.5 to 18.6 years) in transfemales and 17.1 years (range 14.9 to 18.8 years) in transmales. Five adolescents who used GnRH analogues had not started gender-affirming hormones at the time of data collection as they were not yet eligible for this treatment due to age. At the time of data collection, they had used GnRH analogues for a median duration of 2.1 years (range 1.6 to 2.8). Tanner stage was not reported. Six adolescents had been referred to a gender clinic elsewhere for further		temporarily discontinued treatment (after 4 months)[2] • 1 transmale experienced mood swings 4 months after commencing GnRH analogues. After 2.2 years he developed unexplained severe nausea and rapid weight loss and due to his general condition discontinued GnRH analogues after 2.4 years[3] • 1 transmale stopped GnRH analogues as his parents were unable to regularly collect medication from the pharmacy and take him to appointments for the injections[4] Five adolescents (3.5%) stopped treatment as they no longer wished to continue with gender-affirming treatment. • 1 adolescent had been very distressed about breast development at the start of GnRH analogues and later thought that she might want to live as a woman without breasts. She did not want to live as a boy and discontinued GnRH analogues, although dreaded breast development and menstruation. • 1 adolescent experienced concurrent psychosocial problems interfering with the exploration of gender identity and did not currently want treatment.[5] • 1 adolescent felt more in between male and female and therefore did not want to continue with GnRH analogues.[6] • 1 adolescent made a social transition while using GnRH	

	treatment, including 1 who had prolonged use.		analogues and shortly after decided to discontinue treatment.[7] • 1 adolescent discontinued after using GnRH analogues as the treatment allowed them to feel who they were.[8]	

[1] The adolescent later indicated "I was already fully matured when I started GnRH analogues, menstruations were already suppressed by contraceptives. For me, it had no added value" (transmale, age 19 years).
[2] The adolescent restarted endocrine treatment (testosterone) 5 months later.
[3] The adolescent recovered over the next 2 years and subsequently started lynestrenol and testosterone treatment.
[4] The adolescent subsequently started lynestrenol to suppress menses, he was not yet eligible for testosterone treatment.
[5] The adolescent later reflected that "The decision to stop GnRH analogues to my mind was made by the gender team, because they did not think gender dysphoria was the right diagnosis. I do still feel like a man, but for me it is okay to be just me instead of a he or a she, so for now I do not want any further treatment" (adolescent assigned female sex at birth, age 16 years).
[6] The adolescent stated "At the moment, I feel more like 'I am' instead of 'I am a woman' or 'I am a man'" (adolescent assigned female sex at birth, age 16 years).
[7] The adolescent stated that "he had fallen in love with a girl and had never had such feelings, which made him question his gender identity. At subsequent visits, he indicated that he was happy living as a man.
[8] The adolescent stated "After using GnRH analogues for the first time, I could feel who I was without the female hormones, this gave me peace of mind to think about my future. It was an inner feeling that said I am a woman" (adolescent assigned female sex at birth, age 18 years).

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Costa R, Dunsford M, Skagerberg E, et al. (2015) Psychological support, puberty suppression, and psychosocial functioning in adolescents with gender dysphoria. Journal of Sexual Medicine 12(11):2206-14. United Kingdom Prospective longitudinal observational single centre cohort study Includes participants referred to the service between 2010 and 2014.	Adolescents with gender dysphoria who completed a 6-month diagnostic process using DSM-IV-TR criteria for gender dysphoria (comprising the gender dysphoria assessment and psychological interventions) either immediately eligible for treatment with GnRH analogues or delayed eligible for treatment with GnRH analogues (received psychological support without any physical intervention). No exclusion criteria were reported. The sample consisted of 201 adolescents (sex assigned at birth male to female ratio 1:1.6)	**Intervention** 101 individuals were assessed as being immediately eligible for use of GnRH analogues (no specific treatment, dose or route, or frequency of administration reported but all received psychological support). **Comparison** The analyses were between the immediately eligible	**Critical outcomes** ***Impact on gender dysphoria*** The Utrecht gender dysphoria scale (UGDS) was used to assess adolescents' gender dysphoria related discomfort. The Cronbach's alpha (α) for the study was reported as 0.76 to 0.88, suggesting good internal consistency. UGDS was only reported once, for 160 adolescents (50 sex assigned at birth males and 110 sex assigned at birth females). The assessment time point is not reported (baseline or follow-up) and the comparison for gender related discomfort was between sex assigned at birth males and sex assigned at birth females. Sex assigned at birth males had a mean (±SD) UGDS score of 51.6 [±9.7] versus sex assigned at birth	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection** 1. somewhat representative 2. drawn from the same community as the exposed cohort. 3. secure record 4. no **Domain 2: Comparability** 1. partial comparator **Domain 3: Outcome** 1. independent assessment (unclear if blinded) 2. yes 3. incomplete follow-up

	mean (±SD) age 15.52±1.41 years) from a sampling frame of 436 consecutive adolescents referred to the service between 2010 and 2014. The mean (±SD) age (n=201) at the start of GnRH analogues was 16.48 [±1.26], range 13 to 17 years. The interval from the start of the diagnostic procedure to the start of puberty suppression took approximately 1.5 years [±0.63] from baseline. None of the delayed eligible individuals received puberty suppression at the time of this study. Tanner stage was not reported.	and delayed eligible (n=100) adolescents, Baseline assessment (following diagnostic procedure) was followed by follow-up at 6 months from baseline (T1), 12 months from baseline (T2) and 18 months from baseline (T3).	females score of 56.1 [±4.3], *t*-test 4.07; p<0.001. ***Impact on mental health*** Not assessed. ***Impact on quality of life*** Not assessed. **Important outcomes** ***Psychosocial impact*** The Children's Global Assessment Scale (CGAS) was used to assess adolescents' psychosocial functioning. The CGAS was administered by psychologists, psychotherapists, and psychiatrists (intra-class correlation assessment was 0.76 ≤ Cronbach's α ≤0.94). At baseline, CGAS scores were not associated with any demographic variable, in both sex assigned at birth males and sex assigned at birth females (all p>0.1). In comparison with sex assigned at birth females, sex assigned at birth males had statistically significantly lower mean (±SD) baseline CGAS scores (55.4 [±12.7] versus 59.2 [11.8]; *t*-test 2.15; p=0.03). There was no statistically significant difference in mean (±SD) CGAS scores at baseline (T0) between immediately eligible adolescents and delayed eligible adolescents (n=201, 58.72 [±11.38] versus 56.63 [±13.14]; *t*-test 1.21; p=0.23). **Immediately eligible compared with delayed eligible participants** At follow-up, there was no statistically significant difference in mean (±SD)	**Overall quality is assessed as poor.** Other comments: Physical and psychological comorbidity was poorly reported, concomitant use of other medicines was not reported. Large unexplained loss to follow-up (64.7%) at T3. Source of funding: not reported.

			CGAS scores at any follow-up time point (T1, T2 or T3) between immediately eligible adolescents and delayed eligible adolescents: • T1, n=201, 60.89 [±12.17] versus 60.29 [±12.81]; *t*-test 0.34; p=0.73 • T2, n=121, 64.70 [±13.34] versus 62.97 [±14.10]; *t*-test 0.69; p=0.49 • T3, n=71, 67.40 [±13.93] versus 62.53 [±13.54]; *t*-test 1.49; p=0.14. **All participants** There was a statistically significant increase in mean (±SD) CGAS scores at any follow-up time point (T1, T2 or T3) compared with baseline (T0) for the all adolescents group: • T0 (n=201) versus T1 (n=201), 57.73 [±12.27] versus 60.68 [±12.47]; *t*-test 4.87; p<0.001 • T0 (n=201) versus T2 (n=121), 57.73 [±12.27] versus 63.31 [±14.41]; *t*-test 3.70; p<0.001 • T0 (n=201) versus T3 (n=71), 57.73 [±12.27] versus 64.93 [±13.85]; *t*-test 4.11; p<0.001 There was a statistically significant increase in mean (±SD) CGAS scores when comparing the follow-up period T1 to T3 but not for the periods T1 to T2 and T2 to T3, for all adolescents: • T1 (n=201) versus T2 (n=121), 60.68 [±12.47] versus 63.31 [±14.41]; *t*-test 1.73; p<0.08 • T1 (n=201) versus T3 (n=71), 60.68 [±12.47] versus 64.93 [±13.85], *t*-test 2.40; p<0.02 • T2 (n=121) versus T3 (n=71), 63.31 [±14.41] versus 64.93 [±13.85], *t*-test 0.76; p=0.45	

			There were no statistically significant differences in CGAS scores between sex assigned at birth males and sex assigned at birth females with gender dysphoria in all the follow-up evaluations (all p>0.1). Delayed eligible and immediately eligible adolescents with gender dysphoria were not statistically significantly different for demographic variables (all p>0.1). **Immediately eligible participants** There was a statistically significant increase in mean (±SD) CGAS scores at follow-up times T2 and T3 compared with baseline (T0) but not for T0 versus T1, for the immediately eligible adolescents: • T0 (n=101) versus T1 (n=101), 58.72 [±11.38] versus 60.89 [±12.17]; *t*-test 1.31; p=0.19 • T0 (n=101) versus T2 (n=60), 58.72 [±11.38] versus 64.70 [±13.34]; *t*-test 3.02; p=0.003 • T0 (n=101) versus T3 (n=35), 58.72 [±11.38] versus 67.40 [±13.93]; *t*-test 3.66; p<0.001 There was a statistically significant increase in mean (±SD) CGAS scores when comparing the follow-up period T1 to T3 with each other but not for the periods T1 to T2 and T2 to T3, for the immediately eligible adolescents: • T1 (n=101) versus T2 (n=60), 60.89 [±12.17] versus 64.70 [±13.34]; *t*-test 1.85; p=0.07 • T1 (n=101) versus T3 (n=35), 60.89 [±12.17] versus 67.40 [±13.93], *t*-test 2.63; p<0.001	

			• T2 (n=60) versus T3 (n=35), 64.70 [±13.34] versus 67.40 [±13.93], *t*-test 0.94; p=0.35 The immediately eligible adolescents had a CGAS score which was not statistically significantly different compared to the sample of children/ adolescents without observed psychological /psychiatric symptoms after 12 months of puberty suppression (T3, *t*=0.01, *p*=0.99).	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
de Vries A, Steensma T, Doreleijers T, et al. (2011) Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. The Journal of Sexual Medicine 8 (8):2276-83. Netherlands Prospective longitudinal observational single centre before and after study.	The sample size was 70 adolescents receiving GnRH analogues (mean age [±SD] at assessment 13.6±1.8 years) from a sampling frame of 196 consecutive adolescents referred to the service between 2000 and 2008. Inclusion criteria were if they subsequently started gender-affirming hormones between 2003 and 2009 (mean [±SD] age at start of GnRH analogues was 14.75 [±1.92] years)[1]. No specific exclusion criteria were described. No diagnostic criteria or concomitant treatments were reported. Tanner stage of the included adolescents was not reported.	**Intervention** 70 adolescents were assessed at baseline (T0) before the start of GnRH analogues (no specific treatment, dose or route of administration reported). **Comparison** The same 70 adolescents were assessed again at follow-up (T1), shortly before starting gender-affirming hormones. Not all adolescents completed all assessments for all items[2].	**Critical outcomes** ***Impact on gender dysphoria*** Impact on gender dysphoria was assessed using the Utrecht Gender Dysphoria Scale (UGDS). • There was no statistically significant difference in UGDS scores between T0 and T1 (n=41). There was a statistically significant difference between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting more gender dysphoria, *F* (*df, errdf*), *P*: 15.98 (1,39), p<0.001. ***Impact on mental health*** Depressive symptoms were assessed using the Beck Depression Inventory (BDI-II). • There was a statistically significant reduction in BDI score between T0 and T1, n=41, 8.31 [±7.12] versus 4.95 [±6.72], *F* (*df, errdf*), *P*: 9.28 (1,39), p=0.004. • There was no statistically significant difference between sex assigned at	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection** 1. somewhat representative of children and adolescents who have gender dysphoria 2. no non-exposed cohort 3. no description 4. no **Domain 2: Comparability** 1. study controls for age, age at start of treatment, IQ, and parental factors **Domain 3: Outcome** 1. no description 2. no/unclear 3. complete **Overall quality is assessed as poor**. Other comments: Physical and psychological comorbidity was not reported, concomitant use of

			birth males and sex assigned at birth females, *F* (*df, errdf*), *P*: 3.85 (1,39), p=0.057. Anger and anxiety were assessed using Trait Anger and Anxiety (TPI and STAI, respectively) Scales of the State-Trait Personality Inventory. • There was no statistically significant difference in anger (TPI) scale scores between T0 and T1 (n=41). There was a statistically significant difference between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting increased anger compared with sex assigned at birth males, *F* (*df, errdf*), *P*: 5.70 (1,39), p=0.022. • Similarly, there was no statistically significant difference in anxiety (STAI) scale scores between T0 and T1 (n=41). There was a statistically significant difference between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting increased anxiety compared with sex assigned at birth males, *F* (*df, errdf*), *P*: 16.07 (1,39), p<0.001. ***Impact on quality of life*** Not assessed. **Important outcomes** ***Impact on body image*** Impact on body image was assessed using the Body Image Scale to measure body satisfaction (BIS).	other medicines was not reported. Source of funding: This study was supported by a personal grant awarded to the first author by the Netherlands Organization for Health Research and Development.

			There was no statistically significant difference between T0 and T1 for any of the 3 BIS scores (primary sex characteristics, secondary sex characteristics or neutral characteristics, n=57). There were statistically significant differences between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting more dissatisfaction, for: • primary sexual characteristics, *F* (*df, errdf*), *P*: 4.11 (1,55), p=0.047. • secondary sexual characteristics, *F* (*df, errdf*), *P*: 11.57 (1,55), p=0.001. But no statistically significant difference between sex assigned at birth males and sex assigned at birth females was found for neutral characteristics. However, there was a significant interaction effect between sex assigned at birth sex and the changes of gender dysphoria between T0 and T1; sex assigned at birth females became more dissatisfied with their secondary sex characteristics compared with sex assigned at birth males, *F* (*df, errdf*), *P*: 14.59 (1,55), p<0.001) and neutral characteristics, *F* (*df, errdf*), *P*: 15.26 (1,55), p<0.001). ***Psychosocial impact*** Psychosocial impact was assessed using both the Child Behaviour Checklist (CBCL) and the Youth Self-Report (YSR) to parents and adolescents, respectively. The Children's Global Assessment Scale was also reported. There was a statistically significant decrease in mean (±SD) total, internalising, and externalising[3] parental	

			CBCL scores between T0 and T1[4] for all adolescents (n=54): • Total score (T0 – T1) 60.70 [±12.76] versus 54.46 [±11.23], *F* (*df, errdf*), *P*: 26.17 (1,52), p<0.001. • Internalising score (T0 – T1) 61.00 [±12.21] versus 54.56 [±10.22], *F* (*df, errdf*), *P*: 22.93 (1,52), p<0.001. • Externalising score (T0 – T1) 58.04 [±12.99] versus 53.81 [±11.86], *F* (*df, errdf*), *P*: 12.04 (1,52), p=0.001. There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for total and internalising CBCL score but there was a significant difference for the externalising score: • Externalising score, *F* (*df, errdf*), *P*: 6.29 (1,52), p=0.015. There was a statistically significant decrease in mean (±SD) total, internalising, and externalising[3] YSR scores between T0 and T1 for all adolescents (n=54): • Total score (T0 – T1) 55.46 [±11.56] versus 50.00 [±10.56], *F* (*df, errdf*), *P*: 16.24 (1,52), p<0.001. • Internalising score (T0 – T1) 56.04 [±12.49] versus 49.78 [±11.63], *F* (*df, errdf*), *P*: 15.05 (1,52), p<0.001. • Externalising score (T0 – T1) 53.30 [±11.87] versus 49.98 [±9.35], *F* (*df, errdf*), *P*: 7.26 (1,52), p=0.009. There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for total and internalising YSR score but there was a significant difference for the externalising score:	

			• Externalising score, *F* (*df, errdf*), *P*: 9.14 (1,52), p=0.004. There was a statistically significant increase in CGAS mean (±SD) score between T0 and T1 (n=41), 70.24 [±10.12] versus 73.90 [±9.63], *F* (*df, errdf*), *P*: 8.76 (1,39), p=0.005. There was a statistically significant difference between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting lower score for global functioning compared with sex assigned at birth males, *F* (*df, errdf*), *P*: 5.77 (1,52), p=0.021. The proportion of adolescents scoring in the clinical range significantly decreased between T0 and T1, on the CBCL total problem scale (44.4% versus 22.2%, X^2[1] = 6.00, p=0.001), and the internalising scale (29.6% versus 11.1%, X^2[1] = 5.71, p=0.017) of the YSR.	

[1] There were statistically significant mean age [±SD] differences between sex assigned at birth males and sex assigned at birth females for age at assessment (13.14 [±1.55] versus 14.10 [±1.99] years, p=0.028), age at start of GnRH analogues (14.25 [±1.79] versus 15.21 [±1.95] years, p=0.036) and age at the start of gender-affirming hormones (16.24 [±1.21] versus 16.99 [±1.09] years, p=0.008). No statistically significant differences were seen for other baseline characteristics, time between GnRH analogue and gender-affirming hormones, full scale IQ, parental marital status, education, and sexual attraction to own, other or both sexes.
[2] Independent t-tests between mean scores on the CBCL, YSR, BDI, TPI, STAI, CGAS, UGS, and BIS of adolescents who completed both assessments and mean scores of adolescents who completed only one of the assessments revealed no significant differences on all used measures, at neither T0 or at T1.
[3] The CBCL/YSR has 2 components: Internalising score which sums the anxious/depressed, withdrawn-depressed, and somatic complaints scores; externalising score which sums rule-breaking and aggressive behaviour. The total problems score is the sum of the scores of all the problem items. The YSR is a child self-report version of the CBCL.
[4] A repeated measures ANOVA (analysis of variance) was used.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Joseph T, Ting J, Butler G. (2019) The effect of GnRH analogue treatment on bone mineral density in young adolescents with gender dysphoria: findings from a large national cohort. Journal of pediatric endocrinology & metabolism 32(10): 1077-1081	Adolescents (12 to 14 years) with gender dysphoria (no diagnostic criteria described), n=70, including 31 transfemales and 39 transmales.	Treatment with a GnRH analogue for at least 1 year or ongoing until they reached 16 years. No specific treatment, dose or route of	**Critical outcomes** No critical outcomes assessed. **Important outcomes** ***Bone density: lumbar[1]*** **Lumbar spine bone mineral apparent density (BMAD)[2] 0 to 1 year** Transfemales (mean [±SD]):	This study was appraised using the Newcastle-Ottawa quality assessment checklist for cohort studies. **Domain 1: Selection**

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
United Kingdom Retrospective longitudinal observational single centre study To investigate whether there is any significant loss of bone mineral density (BMD) and bone mineral apparent density (BMAD) for up to 3 years of GnRH analogues. To investigate whether there was a significant drop after 1 year of treatment following abrupt withdrawal. 2011 to 2016	All had been seen and assessed by a Gender Identity Development Service multi-disciplinary psychosocial health team for at least 4 assessments over a minimum of 6 months. All participants had entered puberty and all but 2 of the transmales were postmenarchal. 57% of the transfemales were in early puberty (G2–3 and testicular volume >4 mL) and 43% were in late puberty (G4–5). Details of the sampling frame were not reported. Further details of how the sample was drawn are not reported.	administration reported. No concomitant treatments were reported. No comparator.	0.235 (0.030) g/cm3 at baseline, 0.233 g/cm3 (0.029) at 1 year (p=0.459); z-score 0.859 (0.154) at baseline, −0.228 (1.027) at 1 year (p=0.000) Transmales (mean [±SD]): 0.196 (0.035) g/cm3 at baseline, 0.201 (0.033) g/cm3 at 1 year (p=0.074); z-score −0.186 (1.230) at baseline, −0.541 (1.396) at 1 year (p=0.006) **Lumbar spine BMAD 0 to 2 years** Transfemales (mean [±SD]): 0.240 (0.027) g/cm3 at baseline, 0.240 (0.030) g/cm3 at 2 years (p=0.865); z-score 0.486 (0.809) at baseline, −0.279 (0.930) at 2 years (p=0.000) Transmales (mean [±SD]): 0.195 (0.058) g/cm3 at baseline, 0.198 (0.055) at 2 years (p=0.433); z-score −0.361 (1.439) at baseline, −0.913 (1.318) at 2 years (p=0.001) **Lumbar spine bone mineral density (BMD) 0 to 1 year** Transfemales (mean [±SD]): 0.860 (0.154) kg/m2 at baseline, 0.859 (0.129) kg/m2 at 1 year (p=0.962); z-score −0.016 (1.106) at baseline, −0.461 (1.121) at 1 year (p=0.003) Transmales (mean [±SD]): 0.694 (0.149) kg/m2 at baseline, 0.718 (0.124) kg/m2 at 1 year (p=0.006); z-score −0.395 (1.428) at baseline, −1.276 (1.410) at 1 year (p=0.000) **Lumbar spine BMD 0 to 2 years** Transfemales (mean [±SD]): 0.867 (0.141) kg/m2 at baseline, 0.878 (0.130) kg/m2 at 2 years (p=0.395); z-score 0.130 (0.972) at baseline, −0.890 (1.075) at 2 years (p=0.000) Transmales (mean [±SD]):	1. Somewhat representative of children and adolescents who have gender dysphoria 2. Not applicable 3. Via routine clinical records 4. No **Domain 2: Comparability** 1. No control group **Domain 3: Outcome** 1. Via routine clinical records 2. Yes 3. No statement **Overall quality is assessed as poor**. Other comments: although the evidence is of poor quality, the results suggest a possible association between GnRH analogues and BMAD. However, the results are not reliable and could be due to bias or chance. Further details of how the sample was drawn are not reported. No concomitant treatments were reported. Source of funding: None disclosed

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			0.695 (0.220) kg/m2 at baseline, 0.731 (0.209) kg/m2 at 2 years (p=0.058); z-score −0.715 (1.406) at baseline, −2.000 (1.384) at 2 years (p=0.000) ***Bone density: femoral*** **Femoral neck (hip) BMD 0 to 1 year** Transfemales (mean [±SD]): 0.894 (0.118) kg/m2 at baseline, 0.905 (0.104) kg/m2 at 1 year (p=0.571); z-score 0.157 (0.905) at baseline, −0.340 (0.816) at 1 year (p=0.002) Transmales (mean [±SD]): 0.772 (0.137) kg/m2 at baseline, 0.785 (0.120) kg/m2 at 1 year (p=0.797); z-score −0.863 (1.215) at baseline, −1.440 (1.075) at 1 year (p=0.000) **Femoral neck (hip) BMD 0 to 2 years** Transfemales (mean [±SD]): 0.920 (0.116) kg/m2 at baseline, 0.910 (0.125) kg/m2 at 2 years (p=0.402); z-score 0.450 (0.781) at baseline, −0.600 (1.059) at 2 years (p=0.002) Transmales (mean [±SD]): 0.766 (0.215) kg/m2 at baseline, 0.773 (0.197) at 2 years (p=0.604); z-score −1.075 (1.145) at baseline, −1.779 (0.816) at 2 years (p=0.001)	

[1] Lumbar spine (L1-L4) BMD was measured by yearly dual energy X-ray absorptiometry (DXA) scans at baseline (n=70), 1 year (n=70), and 2 years (n=31).
[2] BMAD is a size adjusted value of BMD incorporating body size measurements using UK norms in growing adolescents. Reported as g/cm3 and z-scores. Hip BMAD z-scores were not calculated as there were no available reference ranges.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Khatchadourian K, Shazhan A, Metzger D. (2014) Clinical management of youth with gender dysphoria in	27 young people with gender dysphoria who started GnRH analogues (at mean age [±SD] 14.7±1.9 years) out of 84 young	**Intervention** 84 young people with gender dysphoria were included. For GnRH analogues no	**Critical Outcomes** No critical outcomes assessed. **Important outcomes** ***Stopping treatment***	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection**

Vancouver. The Journal of Pediatrics 164 (4): 906-11.
 	
Canada
 	
Retrospective observational chart review single centre study
	people seen at the unit between 1998 and 2011.
	Note: the transmale and transfemale subgroups reported in the paper is discrepant, 15 transmales and 11 transfemales (n=26) reported in the outcomes section rather than the n=27 stated in the paper; complete outcome reporting is also incomplete for the transfemale group.
	Inclusion criteria were at least Tanner stage 2 pubertal development, previous assessment by a mental health professional and a confirmed diagnosis of gender dysphoria (diagnostic criteria not specified). No exclusion criteria are specified.
		specific treatment, dose or route of administration reported.
		Comparison
		No comparator.
			The authors report that of 15 transmales taking GnRH analogues:
			• 14 transitioned to testosterone treatment during the observation period
			• 7 continued taking GnRH analogues after starting testosterone
			• 7 discontinued GnRH analogues after a median of 3.0 years (range 0.2 to 9.2 years), of which:
			  ○ 5 discontinued after hysterectomy and salpingo-oophorectomy
			  ○ 1 discontinued after 2.2 years (transitioned to gender-affirming hormone)
			  ○ 1 discontinued after <2 months due to mood and emotional lability
			The authors report that of 11 transfemales taking GnRH analogues:
			• 5 received oestrogen treatment during the observation period
			• 4 continued taking GnRH analogues during oestrogen treatment
			• 1 discontinued GnRH analogues during oestrogen treatment (no reason reported)
			• 1 stopped GnRH analogues after a few months due to emotional lability
			• 1 stopped GnRH analogues before oestrogen treatment (the following year delayed due to heavy smoking)
			• 1 discontinued GnRH analogues after 13 months due to choosing not to pursue transition
			
			Safety
			Of the 27 patients treated with GnRH analogues:
				1. not reported
				2. no non-exposed cohort
				3. secure record
				4. no
				Domain 2: Comparability
				1. not applicable
				Domain 3: Outcome
				1. record linkage
				2. yes
				3. in complete missing data
				
				Overall quality is assessed as poor.
				
				Other comments: mental health comorbidity was reported for all participants but not for the GnRH analogue cohort separately. Concomitant use of other medicines was not reported.
				
				Source of funding: No source of funding identified.

			• 1 transmale participant developed sterile abscesses; they were switched from leuprolide acetate to triptorelin, and this was well tolerated. • 1 transmale participant developed leg pains and headaches on GnRH analogues, which eventually resolved without treatment. • 1 participant gained 19 kg within 9 months of initiating GnRH analogues, although their body mass index was >85 percentile before GnRH analogues.	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Klink D, Caris M, Heijboer A et al. (2015) Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. The Journal of clinical endocrinology and metabolism 100(2): e270-5 Netherlands Retrospective longitudinal observational single centre study To assess BMD development during GnRH analogues and at age 22 years in adolescents with gender dysphoria who started treatment for gender dysphoria during adolescence.	34 adolescents (mean age ±SD 14.9±1.9 for transfemales and 15.0±2.0 for transmales at start of GnRH analogues). Participants were included if they met DSM-IV-TR criteria for gender identity disorder of adolescence and had been treated with GnRH analogues and gender-affirming hormones during their pubertal years. No concomitant treatments were reported.	The intervention was GnRH analogue monotherapy (triptorelin pamoate 3.75 mg subcutaneously every 4 weeks) followed by gender-affirming hormones from 16 years with discontinuation of GnRH analogue after gonadectomy. Median duration of GnRH analogue monotherapy in transfemales was 1.3 years (range, 0.5 to 3.8 years), and in transmales was 1.5 years	**Critical outcomes** No critical outcomes assessed. **Important outcomes** ***Bone density: lumbar*** **Lumbar spine bone mineral apparent density (BMAD)[1]** Change from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales (mean [±SD]): GnRH analogue: 0.22 (0.03) g/cm3, gender-affirming hormones: 0.22 (0.02) g/cm3 (NS); z-score GnRH analogue: −0.44 (1.10), gender-affirming hormones: −0.90 (0.80) (p=NS) Change from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales (mean [±SD]: GnRH analogue: 0.25 (0.03) g/cm3, gender-affirming hormones: 0.24 (0.02) g/cm3 (NS);	This study was appraised using the Newcastle-Ottawa quality assessment checklist for cohort studies. **Domain 1: Selection** 1. somewhat representative of children and adolescents who have gender dysphoria 2. not applicable 3. via routine clinical records 4. no **Domain 2: Comparability** 1. no control group **Domain 3: Outcome** 1. via routine clinical records 2. yes 3. follow-up rate variable across timepoints and no description of those lost **Overall quality is assessed as poor**.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
1998 to 2012		(range, 0.25 to 5.2 years).	z-score GnRH analogue: 0.28 (0.90), gender-affirming hormones: −0.50 (0.81) (p=0.004) **Lumbar spine bone mineral density (BMD)[1]** Change from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales (mean [±SD]): GnRH analogue: 0.84 (0.13) g/m2, gender-affirming hormones: 0.84 (0.11) g/m2 (NS); z-score GnRH analogue: −0.77 (0.89), gender-affirming hormones: −1.01 (0.98) (NS) Change from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales (mean [±SD]): GnRH analogue: 0.95 (0.12) g/m2, gender-affirming hormones: 0.91 (0.10) g/m2 (p=0.006); z-score GnRH analogue: 0.17 (1.18), gender-affirming hormones: −0.72 (0.99) (p<0.001) ***Bone density; femoral*** **Femoral area BMAD[1]** Change from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales (mean [±SD]), GnRH analogue: 0.28 (0.04) g/cm3, gender-affirming hormones: 0.26 (0.04) g/cm3 (NS); z-score GnRH analogue: −0.93 (1.22), gender-affirming hormones: −1.57 (1.74) (p=NS) Change from starting GnRH analogue	Other comments: Within person comparison. Small numbers of participants in each subgroup. No concomitant treatments or comorbidities were reported. Source of funding: None disclosed

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			(mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales (mean [±SD]), GnRH analogue: 0.32 (0.04) g/cm3, gender-affirming hormones: 0.31 (0.04) (NS); z-score GnRH analogue: 0.01 (0.70), gender-affirming hormones: −0.28 (0.74) (NS) **Femoral area BMD[1]** Change from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales (mean [±SD]), GnRH analogue: 0.88 (0.12) g/m2, gender-affirming hormones: 0.87 (0.08) (NS); z-score GnRH analogue: −0.66 (0.77), gender-affirming hormones: −0.95 (0.63) (NS) Change from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales (mean [±SD]), GnRH analogue: 0.92 (0.10) g/m2, gender-affirming hormones: 0.88 (0.09) (p=0.005); z-score GnRH analogue: 0.36 (0.88), gender-affirming hormones: −0.35 (0.79) (p=0.001)	

[1] BMD and BMAD of the lumbar spine and femoral region (nondominant side) measured by DXA scans at start of GnRH analogues, (n=32), start of gender-affirming hormones (n=34), and at 22 years (n=34).

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Schagen SEE, Cohen-Kettenis PT, Delemarre-van de Waal HA et al. (2016)	Adolescents with gender dysphoria (n=116), median age (range) 13.6 years (11.6 to 17.9) in transfemales and 14.2 years (11.1 to	GnRH analogue monotherapy (triptorelin pamoate 3.75 mg at 0, 2 and 4	**Critical outcomes** No critical outcomes assessed. **Important outcomes**	This study was appraised using the Newcastle-Ottawa quality assessment checklist for cohort studies.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Efficacy and Safety of Gonadotropin-Releasing Hormone Agonist Treatment to Suppress Puberty in Gender Dysphoric Adolescents. The journal of sexual medicine 13(7): 1125-32 Netherlands Prospective longitudinal study To describe the changes in Tanner stage, testicular volume, gonadotropins, and sex steroids during GnRH analogues of adolescents with gender dysphoria to evaluate the efficacy. To report on liver enzymes, renal function and changes in body composition. 1998 to 2009	18.6) in transmales during first year of GnRH analogues. Participants were included if they met DSM-IV-TR criteria for gender dysphoria, had lifelong extreme gender dysphoria, were psychologically stable and were living in a supportive environment. No concomitant treatments were reported.	weeks followed by injections every 4 weeks, route of administration not described) for at least 3 months.	***Other safety outcomes: liver function*** Glutamyl transferase was not elevated at baseline or during treatment in any subject. Mild elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) above the reference range were present at baseline but were not more prevalent during treatment than at baseline. Glutamyl transferase, AST, and ALT levels did not significantly change from baseline to 12 months of treatment. No values or statistical analyses were reported. ***Other safety outcomes: kidney function*** **Change in serum creatinine between 0 and 1 year** Transfemales (mean [±SD]): 70 (12) micromol/l at baseline, 66 (13) micromol/l at 1 year (p=0.20) Transmales (mean [±SD]): 73 (8) micromol/l at baseline, 68 (13) micromol/l at 1 year (p=0.01)	**Domain 1: Selection** 1. somewhat representative of children and adolescents who have gender dysphoria 2. not applicable 3. via routine clinical records 4. no **Domain 2: Comparability** 1. no control group **Domain 3: Outcome** 1. via routine clinical records 2. yes 3. no statement **Overall quality is assessed as poor**. Other comments: Within person comparison. No concomitant treatments or comorbidities were reported. Source of funding: Ferring pharmaceuticals (triptorelin manufacturer)

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Staphorsius A, Baudewijntje P, Kreukels P, et al. (2015) Puberty suppression and executive functioning: an fMRI-study	The inclusion criteria were diagnosed with Gender Identity Disorder according to the DSM-IV-TR and at least 12 years old and Tanner stage of at least B2 or G2 to G3 with	**Intervention** GnRH analogues (triptorelin pamoate 3.75 mg every 4 weeks	**Critical Outcomes** No critical outcomes assessed. **Important outcomes** ***Psychosocial impact***	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain**

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
in adolescents with gender dysphoria. Psychoneuroendocrinology 565:190-9. Netherlands Cross-sectional (single time point) assessment single centre study	measurable oestradiol and testosterone levels in girls and boys, respectively. For all group's exclusion criteria were an insufficient command of the Dutch language (how assessed not reported), unadjusted endocrine disorders, neurological or psychiatric disorders that could lead to deviant test results (details not reported) use of psychotropic medication, and contraindications for an MRI scan. Additionally, adolescents receiving puberty delaying medication or any form of hormones besides oral contraceptives were excluded as controls. The sample size was 85 of whom 41 were adolescents (the numbers are discrepant with the number for whom outcomes are reported n=40) with gender dysphoria (20 of whom were being treated with GnRH analogues); 24 girls and 21 boys without gender dysphoria acted as controls (not further reported here). Details of the sampling frame are not reported. The ages at which GnRH analogues were started was not reported. The mean duration of treatment was 1.6 years (SD 1.0) Mean (±SD) Tanner stage for each group was reported: • Transfemales 3.9 [±1.1] • Transfemales on GnRH analogues 4.1 [±1.0]	subcutaneously or intramuscularly). **Comparison** The comparison was between adolescents with gender dysphoria receiving GnRH analogues and those without GnRH analogues.	The Child Behaviour Checklist (CBCL) was used to assess psychosocial impact. The CBCL was administered once during the study. The reported outcomes for each group were (n, mean [±SD]): • Transfemales (all, n=18) 57.8 [±9.2] • Transfemales on GnRH analogues (n=8) 57.4 [±9.8] • Transfemales without GnRH analogues (n=10) 58.2 [±9.3] • Transmales (all, n=22) 60.4 [±10.2] • Transmales on GnRH analogues (n=12) 57.5 [±9.4] • Transmales without GnRH analogues (n=10) 63.9 [±10.5] The analysis of the CBCL data is not discussed, and statistical analysis is unclear. ***Cognitive development or functioning*** **IQ[1]** • Transfemales (mean [±SD]) on GnRH analogues: 94.0 (10.3) • Transfemales (mean [±SD]) without GnRH analogues: 109.4 (21.2) • Transmales (mean [±SD]) on GnRH analogues: 95.8 (15.6) • Transmales (mean [±SD]) without GnRH analogues: 98.5 (15.9) **Reaction time[2]** • Transfemales (mean [±SD]) on GnRH analogues: 10.9 (4.1) • Transfemales (mean [±SD]) without GnRH analogues: 9.9 (3.1)	1. somewhat representative of children and adolescents who have gender dysphoria 2. drawn from the same community as the exposed cohort 3. via routine clinical records 4. no **Domain 2: Comparability** 1. study controls for age and diagnosis **Domain 3: Outcome** 1. via clinical assessment 2. yes 3. unclear **Overall quality is assessed as poor.** Other comments: Physical and psychological comorbidity was not reported, concomitant use of other medicines was not reported. Source of funding: This work was supported by an educational grant from the pharmaceutical firm Ferring BV, and by a VICI grant (453-08-003) from the Dutch Science Foundation. The authors state that funding sources did not play a role in any component of this study.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
	• Transfemales without GnRH analogues 3.8 [±1.1] • Transmales 4.5 [±0.9] • Transmales on GnRH analogues 4.1 [±1.1] Transmales without GnRH analogues 4.9 [±0.3]		• Transmales (mean [±SD]) on GnRH analogues: 9.9 (3.1) • Transmales (mean [±SD]) without GnRH analogues: 10.0 (2.0) **Accuracy[3]** • Transfemales (mean [±SD]) on GnRH analogues: 73.9 (9.1) • Transfemales (mean [±SD]) without GnRH analogues: 83.4 (9.5) • Transmales (mean [±SD]) on GnRH analogues: 85.7 (10.5) • Transmales (mean [±SD]) without GnRH analogues: 88.8 (9.7)	

[1] Estimated with 4 subscales (arithmetic, vocabulary, picture arrangement, and block design) of the Wechsler Intelligence Scale for Children, third edition (WISC-III®, Wechsler 1991) or the Wechsler Adult Intelligence Scale, third edition (WAIS-III®, Wechsler 1997), depending on the participant's age.
[2] Reaction time in seconds in the Tower of London task
[3] Percentage of correct trials in the Tower of London task

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Vlot, Mariska C, Klink, Daniel T, den Heijer, Martin et al. (2017) Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. Bone 95: 11-19 Netherlands Retrospective observational data analysis study	Adolescents with gender dysphoria, n=70. Median age (range) 15.1 years (11.7 to 18.6) for transmales and 13.5 years (11.5 to 18.3) for transfemales at start of GnRH analogues. Participants were included if they had a diagnosis of gender dysphoria according to DSM-IV-TR criteria who were treated with GnRH analogues and then gender-affirming hormones. No concomitant treatments were reported. The study categorised	GnRH analogues (triptorelin pamoate 3.75 mg every 4 weeks subcutaneously).	**Critical outcomes** No critical outcomes reported **Important outcomes** ***Bone density: lumbar*** **Lumbar spine bone mineral apparent density (BMAD)** Change from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of <15 years; median [range]), GnRH analogue: 0.21 (0.17 to 0.25) g/cm3, gender-affirming hormones: 0.20 (0.18 to 0.24) g/cm3 (NS); z-score GnRH analogue: −0.20 (−1.82 to 1.18), gender-affirming hormones: −1.52 (−2.36 to 0.42) (p=0.001)	This study was appraised using the Newcastle-Ottawa quality assessment checklist for cohort studies. **Domain 1: Selection** 1. Somewhat representative of children and adolescents who have gender dysphoria 2. Not applicable 3. Via routine clinical records 4. No **Domain 2: Comparability** 1. No control group **Domain 3: Outcome** 1. Via routine clinical records 2. Yes

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
To investigate the course of 3 bone turnover markers in relation to bonemineral density, in adolescents with gender dysphoria during GnRH analogue and gender-affirming hormones. 2001 to 2011	participants into a young and old pubertal group, based on their bone age. The young transmales had a bone age of <14 years and the old transmales had a bone age of ≥14 years. The young transfemales group had a bone age of <15 years and the old transfemales group ≥15 years.		Change from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of ≥15; median [range]), GnRH analogue: 0.22 (0.18 to 0.25) g/cm3, gender-affirming hormones: 0.22 (0.19 to 0.24) g/cm3 (NS); z-score GnRH analogue: −1.18 (−1.78 to 1.09), gender-affirming hormones: −1.15 (−2.21 to 0.08) (p≤0.1) Change from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of <15 years; median [range]), GnRH analogue: 0.23 (0.20 to 0.29) g/cm3, gender-affirming hormones: 0.23 (0.19 to 0.28) g/cm3 (NS); z-score GnRH analogue: −0.05 (−0.78 to 2.94), gender-affirming hormones: −0.84 (−2.20 to 0.87) (p=0.003) Change from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of ≥15; median [range]), GnRH analogue: 0.26 (0.21 to 0.29) g/cm3, gender-affirming hormones: 0.24 (0.20 to 0.28) g/cm3 (p≤0.01); z-score GnRH analogue: 0.27 (−1.60 to 1.80), gender-affirming hormones: −0.29 (−2.28 to 0.90) (p≤ 0.0001) ***Bone density; femoral*** **Femoral neck BMAD** Change from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of <15 years; median [range]), GnRH analogue: 0.29 (0.20 to 0.33) g/cm3, gender-affirming hormones: 0.27 (0.20 to 0.33) g/cm3 (p≤0.1); z-score GnRH analogue: −0.71 (−3.35 to	3. Follow-up rate variable across outcomes and no description of those lost **Overall quality is assessed as poor**. Other comments: Within person comparison. No concomitant treatments were reported. Source of funding: grant from Abbott diagnostics

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			0.37), gender-affirming hormones: −1.32 (−3.39 to 0.21) (p≤0.1) Change from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of ≥15; median [range]), GnRH analogue: 0.30 (0.26 to 0.36) g/cm3, gender-affirming hormones: 0.30 (0.26 to 0.34) g/cm3 (NS); z-score GnRH analogue: −0.44 (−1.37 to 0.93), gender-affirming hormones: −0.36 (−1.50 to 0.46) (NS) Change from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of <15 years; median [range]), GnRH analogue: 0.31 (0.26 to 0.36) g/cm3, gender-affirming hormones: 0.30 (0.22 to 0.35) g/cm3 (NS); z-score GnRH analogue: −0.01 (−1.30 to 0.91), gender-affirming hormones: −0.37 (−2.28 to 0.47) (NS) Change from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of ≥15; median [range]), GnRH analogue: 0.33 (0.25 to 0.39) g/cm3, gender-affirming hormones: 0.30 (0.23 to 0.41) g/cm3 (p≤0.01); z-score GnRH analogue: 0.27 (−1.39 to 1.32), gender-affirming hormones: −0.27 (−1.91 to 1.29) (p=0.002)	

Appendix F Quality appraisal checklists

Newcastle-Ottawa tool for cohort studies

Question	
Domain: Selection	
1. Representativeness of the exposed cohort	Truly representative of the average [describe] in the community Somewhat representative of the average [describe] in the community Selected group of users e.g. nurses, volunteers No description of the derivation of the cohort
2. Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort Drawn from a different source No description of the derivation of the non-exposed cohort
3. Ascertainment of exposure	Secure record (e.g. surgical records) Structured interview Written self-report No description
4. Demonstration that outcome of interest was not present at start of study	Yes / No
Domain: Comparability	
1. Comparability of cohorts on the basis of the design or analysis	Study controls for [select most important factor] Study controls for any additional factor [this criteria could be modified to indicate specific control for a second important factor]
Domain: Outcome	
1. Assessment of outcome	Independent blind assessment Record linkage Self-report No description
2. Was follow-up long enough for outcomes to occur	Yes [select and adequate follow up period for outcome of interest] No
3. Adequacy of follow up of cohorts	Complete follow up (all subjects accounted for) Subjects lost to follow up unlikely to introduce bias (small number lost to follow up [select an adequate %] follow up or description provided of those lost) Follow up rate [select an adequate %] and no description of those lost No statement

Appendix G Grade profiles

Table 2: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – gender dysphoria

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on gender dysphoria									
Mean±SD Utrecht Gender Dysphoria Scale[1] (version(s) not reported), time point at baseline (before GnRH analogues) versus follow-up (before gender-affirming hormones, higher scores indicate more gender dysphoria)									
1 cohort study de Vries et al 2011	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 53.20±7.91 GnRH analogue: 53.9±17.42 *P*=0.333	Critical	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; *P*, P-value; SD, Standard deviation.

1 The UGDS is a validated screening tool for both adolescents and adults to assess gender dysphoria. It consists of 12 items, to be answered on a 1- to 5-point scale, resulting in a sum score between 12 and 60. The higher the UGDS score the greater the gender dysphoria.
2 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

Table 3: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – mental health

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on mental health									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Mean±SD Beck Depression Inventory-II, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones). (Lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 8.31±7.12 GnRH analogue: 4.95±6.72 *P*=0.004	Critical	VERY LOW
Mean±SD Trait Anger (TPI), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 18.29±5.54 GnRH analogue: 17.88±5.24 *P*=0.503	Critical	VERY LOW
Mean±SD Trait Anxiety (STAI), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 39.43±10.07 GnRH analogue: 37.95±9.38 *P*=0.276	Critical	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; *P*, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

Table 4: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – body image

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on body image									
Mean±SD Body Image Scale (primary sexual characteristics), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=57	None	Baseline: 4.10±0.56 GnRH analogue: 3.98±0.71 *P*=0.145	Important	VERY LOW
Mean±SD Body Image Scale (secondary sexual characteristics), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=57	None	Baseline: 2.74±0.65 GnRH analogue: 2.82±0.68 *P*=0.569	Important	VERY LOW
Mean±SD Body Image Scale (neutral characteristics), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=57	None	Baseline: 2.41±0.63 GnRH analogue: 2.47±0.56 *P*=0.620	Important	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; *P*, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

Table 5: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – psychosocial impact

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Psychosocial impact									
Mean [±SD] Children's Global Assessment Scale score, at baseline, higher scores indicate benefit)									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	n=101 58.72 [±11.38]	n=100 56.63 [±13.14]	*P*=0.23	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, at 6 months[2] (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	n=101 60.89 [±12.17]	n=100 60.29 [±12.81]	*P*=0.73	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, at 12 months[3] (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	n=60 64.70 [±13.34]	n=61 62.97 [±14.10]	*P*=0.49	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, at 18 months[4] (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	n=35 67.40 [±13.93]	n=36 62.53 [±13.54]	*P*=0.14	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 6 months compared to baseline (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=101	None	Baseline: 58.72±11.38 6 months: 60.89±12.17 *P*=0.19	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 12 months compared to baseline (higher scores indicate benefit).									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=60	None	Baseline: 58.72±11.38 12 months: 64.70±13.34 *P*=0.003	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 18 months compared to baseline (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=35	None	Baseline: 58.72±11.38 18 months: 67.40±13.93 *P*<0.001	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 12 months compared to 6 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=60	None	6 months: 60.89±12.17 12 months: 64.70±13.34 *P*=0.07	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 18 months compared to 6 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=35	None	6 months: 60.89±12.17 18 months: 67.40±13.93 *P*<0.001	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 18 months compared to 12 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=60 N=35	None	12 months: 64.70±13.34 18 months: 67.40±13.93 *P*=0.35	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 6 months[2] compared to baseline (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=201	None	Baseline: 57.73±12.27 6 months: 60.68±12.47 *P*<0.001	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 12 months[3] compared to baseline (higher scores indicate benefit).									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=201 N=121	None	Baseline: 57.73±12.27 12 months: 63.31±14.41 *P*<0.001	Important	VERY LOW
Mean±SD Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 18 months[4] compared to baseline (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=201 N=71	None	Baseline: 57.73±12.27 18 months: 64.93±13.85 *P*<0.001	Important	VERY LOW
Mean±SD Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 12 months compared to 6 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=201 N=121	None	6 months: 60.68±12.47 12 months: 63.31±14.41 *P*<0.08	Important	VERY LOW
Mean±SD Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 18 months compared to 6 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=201 N=71	None	6 months: 60.68±12.47 18 months: 64.93±13.85 *P*<0.02	Important	VERY LOW
Mean±SD Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 18 months compared to 12 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=121 N=71	None	12 months: 63.31±14.41 18 months: 64.93±13.85 *P*<0.45	Important	VERY LOW
Mean±SD Children's Global Assessment Scale score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, higher scores indicate benefit).									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 70.24±10.12 GnRH analogue: 73.90±9.63 *P*=0.005	Important	VERY LOW
Mean±SD Child Behaviour Checklist (total T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 60.70±12.76 GnRH analogue: 54.46±11.23 *P*<0.001	Important	VERY LOW
Mean±SD Child Behaviour Checklist (internalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 61.00±12.21 GnRH analogue: 52.1±9.81 *P*<0.001	Important	VERY LOW
Mean±SD Child Behaviour Checklist (externalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 58.04±12.99 GnRH analogue: 53.81±11.86 *P*=0.001	Important	VERY LOW
Proportion of adolescents scoring in the clinical range Child Behaviour Checklist total problem scale, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 44.4% GnRH analogue: 22,2% *P*=0.001	Important	VERY LOW
Mean±SD Youth Self-Report (total T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormone, lower scores indicate benefit).									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 55.46±11.56 GnRH analogue: 50.00±10.56 *P*<0.001	Important	VERY LOW
Mean±SD Youth Self-Report (internalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 56.04±12.49 GnRH analogue: 49.78±11.63 *P*<0.001	Important	VERY LOW
Mean±SD Youth Self-Report (externalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 53.30±11.87 GnRH analogue: 49.98±9.35 *P*=0.009	Important	VERY LOW
Proportion of adolescents scoring in the clinical range Youth Self-Report (internalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 29.6% GnRH analogue: 11.1% *P*=0.017	Important	VERY LOW
Mean±SD Child Behaviour Checklist score, transfemales (lower scores indicate benefit									
1 cross-sectional study Staphorsius et al 2015	Serious limitations[6]	No serious indirectness	Not applicable	Not calculable	N=8	N=10	GnRH analogue: 57.4 [±9.8] No GnRH analogue: 58.2 [±9.3]	Important	VERY LOW
Mean±SD Child Behaviour Checklist score, transmales (lower scores indicate benefit)									
1 cross-sectional study	Serious limitations[6]	No serious indirectness	Not applicable	Not calculable	N=12	N=10	GnRH analogues: 57.5 [±9.4] No GnRH analogue: 63.9 [±10.5]	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Staphorsius et al 2015									

Abbreviations: GnRH, gonadotrophin releasing hormone; *P*, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by Costa et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).
2 6 months from baseline (after 6 months of psychological support – both groups).
3 12 months from baseline (delayed eligible gender dysphoria [GD] adolescents, after 12 months of psychological support; immediately eligible GD adolescents, after 12 months of psychological support + 6 months of puberty suppression).
4 18 months from baseline (delayed eligible gender dysphoria [GD] adolescents, after 12 months of psychological support; immediately eligible GD adolescents, after 12 months of psychological support + 6 months of puberty suppression).
5 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).
6 Downgraded 1 level - the cohort study by Staphorsius et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding and no randomisation).

Table 6: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – engagement with healthcare services

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Engagement with healthcare services									
Number (proportion) failing to engage with health care services (did not attend clinic), at (up to) 9 years follow-up									
1 cohort study Brik et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	9/214 (4.2%)	None	9 adolescents out of 214 failed to attend clinic and were excluded from the study (4.2%)	Important	VERY LOW
Loss to follow-up									
1 cohort study	Serious limitations[2]	No serious indirectness	Not applicable		201	None	The sample size at baseline and 6 months was 201, which dropped by 39.8% to 121 after	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Costa et al 2015				Not calculable			12 months and by 64.7% to 71 at 18 months follow-up. No explanation of the reasons for loss to follow-up are reported.		

Abbreviations: GnRH, gonadotrophin releasing hormone.

1 Downgraded 1 level - the cohort study by Brik et al. (2018) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).
2 Downgraded 1 level - the cohort study by Costa et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

Table 7: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – stopping treatment

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Stopping treatment									
Number (proportion) stopping GnRH analogues, at (up to) 9 years follow-up									
1 cohort study Brik et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	9/143 (6.2%)	None	9/143 adolescents stopped GnRH analogues (6.2%)[2]	Important	VERY LOW
Number (proportion) stopping from GnRH analogues, at (up to) 13 years follow-up									
1 cohort study Khatchadourian et al 2014	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	11/27 (42%)	None	11/26 stopped GnRH analogues (42%)[4]	Important	VERY LOW
Number (proportion) stopping GnRH analogues but who wished to continue endocrine treatment, at (up to) 9 years follow-up									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 cohort study Brik et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	4/143 (2.8%)	None	4/143 adolescents stopped GnRH analogues but wished to continue treatment (2.8%)	Important	VERY LOW
Number (proportion) stopping GnRH analogues who no longer wished gender-affirming treatment, at (up to) 9 years follow-up									
1 cohort study Brik et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	5/143 (3.5%)	None	5/143 adolescents stopped GnRH analogues and no longer wished to continue gender-affirming treatment (3.5%)	Important	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone.

1 Downgraded 1 level - the cohort study by Brik et al. (2018) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

2 Median duration of 0.8 years (range 0.1 to 3.0). Five adolescents stopped treatment because they no longer wished to receive gender-affirming treatment for various reasons. In 4 adolescents (all transmales), although they wanted to continue treatments for gender dysphoria, GnRH analogues were stopped mainly because of adverse effects (such as mood and emotional lability).

3 Downgraded 1 level - the cohort study by Khatchadourian et al. (2014) was assessed as at high risk of bias (poor quality overall; lack of blinding, no control group and high number of participants lost to follow-up).

4 Because of transitioning to gender-affirming hormones or gender-affirming surgery, adverse effects (such as mood and emotional lability) or no longer wishing to pursue transition.

Table 8. Question 2. For children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – bone density

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Bone density: change in lumbar BMAD									
Change in lumbar spine BMAD from baseline to 1 year in transfemales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=31	None	Mean (SD), g/cm^3 Baseline: 0.235 (0.030) 1 year: 0.233 (0.029) p=0.459 z-score Baseline: 0.859 (0.154) 1 year: −0.228 (1.027) p=0.000	IMPORTANT	VERY LOW
Change in lumbar spine BMAD from baseline to 1 year in transmales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=39	None	Mean (SD), g/cm^3 Baseline: 0.196 (0.035) 1 year: 0.201 (0.033) p=0.074 z-score Baseline: −0.186 (1.230) 1 year: −0.541 (1.396) p=0.006	IMPORTANT	VERY LOW
Change in lumbar spine BMAD from baseline to 2 years in transfemales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=10	None	Mean (SD), g/cm^3 Baseline: 0.240 (0.027) 2 years: 0.240 (0.030) p=0.865 z-score Baseline: 0.486 (0.809) 2 years: −0.279 (0.930) p=0.000	IMPORTANT	VERY LOW
Change in lumbar spine BMAD from baseline to 2 years in transmales									
1 observational study	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=21	None	Mean (SD), g/cm^3 Baseline: 0.195 (0.058) 2 years: 0.198 (0.055) p=0.433	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Joseph et al. (2019)							z-score Baseline: −0.361 (1.439) 2 years: −0.913 (1.318) p=0.001		
Change in lumbar BMAD from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=11 N=12	None	Mean (SD), g/cm^3 GnRH analogue: 0.22 (0.03) Gender-affirming hormones: 0.22 (0.02) NS z-score GnRH analogue: −0.44 (1.10) Gender-affirming hormones: −0.90 (0.80) p-value: NS	IMPORTANT	VERY LOW
Change in lumbar BMAD from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=18	None	Mean (SD), g/cm^3 GnRH analogue: 0.25 (0.03) Gender-affirming hormones: 0.24 (0.02) NS z-score GnRH analogue: 0.28 (0.90) Gender-affirming hormones: −0.50 (0.81) p-value: 0.004	IMPORTANT	VERY LOW
Change in lumbar BMAD from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of <15 years)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=15	None	Median (range), g/cm^3 GnRH analogue: 0.21 (0.17 to 0.25) Gender-affirming hormones: 0.20 (0.18 to 0.24)	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							NS z-score GnRH analogue: −0.20 (−1.82 to 1.18) Gender-affirming hormones: −1.52 (−2.36 to 0.42) p-value: <0.01		
Change in lumbar BMAD from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of ≥15)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=5	None	Median (range), g/cm^3 GnRH analogue: 0.22 (0.18 to 0.25) Gender-affirming hormones: 0.22 (0.19 to 0.24) NS z-score GnRH analogue: −1.18 (−1.78 to 1.09) Gender-affirming hormones: −1.15 (−2.21 to 0.08) p-value: p≤0.1	IMPORTANT	VERY LOW
Change in lumbar BMAD from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of <14 years)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=11	None	Median (range), g/cm^3 GnRH analogue: 0.23 (0.20 to 0.29) Gender-affirming hormones: 0.23 (0.19 to 0.28) NS z-score GnRH analogue: −0.05 (−0.78 to 2.94) Gender-affirming hormones: −0.84 (−2.20 to 0.87) p-value: ≤0.01	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Change in lumbar BMAD from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of ≥14)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=23	None	Median (range), g/cm3 GnRH analogue: 0.26 (0.21 to 0.29) Gender-affirming hormones: 0.24 (0.20 to 0.28) p≤0.01 z-score GnRH analogue: 0.27 (−1.60 to 1.80) Gender-affirming hormones: −0.29 (−2.28 to 0.90) p-value: p ≤ 0.01)	IMPORTANT	VERY LOW
Bone density: change in lumbar BMD									
Change in lumbar spine BMD from baseline to 1 year in transfemales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=31	None	Mean (SD), kg/m2 Baseline: 0.860 (0.154) 1 year: 0.859 (0.129) p=0.962 z-score Baseline: −0.016 (1.106) 1 year: −0.461 (1.121) p=0.003	IMPORTANT	VERY LOW
Change in lumbar spine BMD from baseline to 1 year in transmales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=39	None	Mean (SD), kg/m2 Baseline: 0.694 (0.149) 1 year: 0.718 (0.124) p=0.006 z-score Baseline: −0.395 (1.428) 1 year: −1.276 (1.410) p=0.000	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Change in lumbar spine BMD from baseline to 2 years in transfemales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=10	None	Mean (SD), kg/m2 Baseline: 0.867 (0.141) 2 years: 0.878 (0.130) p=0.395 z-score Baseline: 0.130 (0.972) 2 years: −0.890 (1.075) p=0.000	IMPORTANT	VERY LOW
Change in lumbar spine BMD from baseline to 2 years in transmales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=21	None	Mean (SD), kg/m2 Baseline: 0.695 (0.220) 2 years: 0.731 (0.209) p=0.058 z-score Baseline: −0.715 (1.406) 2 years: −2.000 (1.384) p=0.000	IMPORTANT	VERY LOW
Change in lumbar BMD from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=12 N=11	None	Mean (SD), g/m2 GnRH analogue: 0.84 (0.13) Gender-affirming hormones: 0.84 (0.11) NS z-score GnRH analogue: −0.77 (0.89) Gender-affirming hormones: −1.01 (0.98) NS	IMPORTANT	VERY LOW
Change in lumbar BMD from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=18	None	Mean (SD), g/m2 GnRH analogue: 0.95 (0.12) Gender-affirming hormones: 0.91 (0.10) p-value: 0.006 z-score GnRH analogue: 0.17 (1.18) Gender-affirming hormones: −0.72 (0.99) p-value: <0.001	IMPORTANT	VERY LOW
Bone density: change in femoral neck (hip) BMD									
Change in femoral neck BMD from baseline to 1 year in transfemales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=31	None	Mean (SD), kg/m2 Baseline: 0.894 (0.118) 1 year: 0.905 (0.104) p=0.571 z-score Baseline: 0.157 (0.905) 1 year: −0.340 (0.816) p=0.002	IMPORTANT	VERY LOW
Change from baseline to 1 year in femoral neck BMD in transmales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=39	None	Mean (SD), kg/m2 Baseline: 0.772 (0.137) 1 year: 0.785 (0.120) p=0.797 z-score Baseline: −0.863 (1.215) 1 year: −1.440 (1.075) p=0.000	IMPORTANT	VERY LOW
Change from baseline to 2 years in femoral neck BMD in transfemales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=10	None	Mean (SD), kg/m2 Baseline: 0.920 (0.116) 2 years: 0.910 (0.125) p=0.402 z-score Baseline: 0.450 (0.781) 2 years: −0.600 (1.059) p=0.002	IMPORTANT	VERY LOW
Change from baseline to 2 years in femoral neck BMD in transmales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=21	None	Mean (SD), kg/m2 Baseline: 0.766 (0.215) 2 years: 0.773 (0.197) p=0.604 z-score Baseline: −1.075 (1.145) 2 years: −1.779 (0.816) p=0.001	IMPORTANT	VERY LOW
Bone density: change in femoral neck (hip) BMAD									
Change from starting GnRH analogue to starting gender-affirming hormones in femoral neck BMAD in transfemales (bone age of <15 years)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=16	None	Median (range), g/cm3 GnRH analogue: 0.29 (0.20 to 0.33) Gender-affirming hormones: 0.27 (0.20 to 0.33) p≤0.1 z-score GnRH analogue: −0.71 (−3.35 to 0.37) Gender-affirming hormones: −1.32 (−3.39 to 0.21) p≤0.1	IMPORTANT	VERY LOW
Change in femoral neck BMAD from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of ≥15)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=6	None	Median (range), g/cm3 GnRH analogue: 0.30 (0.26 to 0.36) Gender-affirming hormones: 0.30 (0.26 to 0.34) NS z-score GnRH analogue: −0.44 (−1.37 to 0.93) Gender-affirming hormones: −0.36 (−1.50 to 0.46) NS	IMPORTANT	VERY LOW
Change in femoral neck BMAD from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of <14 years)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=10	None	Median (range), g/cm3 GnRH analogue: 0.31 (0.26 to 0.36) Gender-affirming hormones: 0.30 (0.22 to 0.35) NS z-score GnRH analogue: −0.01 (−1.30 to 0.91) Gender-affirming hormones: −0.37 (−2.28 to 0.47) NS	IMPORTANT	VERY LOW
Change in femoral neck BMAD from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of ≥14)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=23	None	Median (range), g/cm3 GnRH analogue: 0.33 (0.25 to 0.39) Gender-affirming hormones: 0.30 (0.23 to 0.41) p-value: ≤0.01 z-score	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							GnRH analogue: 0.27 (−1.39 to 1.32) Gender-affirming hormones: −0.27 (−1.91 to 1.29) p-value: ≤0.01		
Bone density: change in femoral area BMD									
Change in femoral BMD from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=14 N=6	None	Mean (SD), g/m2 GnRH analogue: 0.88 (0.12) Gender-affirming hormones: 0.87 (0.08) NS z-score GnRH analogue: −0.66 (0.77) Gender-affirming hormones: −0.95 (0.63) NS	IMPORTANT	VERY LOW
Change in femoral BMD from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=18 N=13	None	Mean (SD), g/m2 GnRH analogue: 0.92 (0.10) Gender-affirming hormones: 0.88 (0.09) p-value: 0.005 z-score GnRH analogue: 0.36 (0.88) Gender-affirming hormones: −0.35 (0.79) p-value: 0.001	IMPORTANT	VERY LOW
Bone density: change in femoral area BMAD									
Change in femoral BMAD from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=12 N=10	None	Mean (SD), g/cm3 GnRH analogue: 0.28 (0.04) Gender-affirming hormones: 0.26 (0.04) NS z-score GnRH analogue: −0.93 (1.22) Gender-affirming hormones: −1.57 (1.74) p-value: NS	IMPORTANT	VERY LOW
Change in femoral BMAD from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=18 N=18	None	Mean (SD), g/cm3 GnRH analogue: 0.32 (0.04) Gender-affirming hormones: 0.31 (0.04) NS z-score GnRH analogue: 0.01 (0.70) Gender-affirming hormones: −0.28 (0.74) NS	IMPORTANT	VERY LOW

Abbreviations: BMAD, bone mineral apparent density; BMD, bone mineral density; GnRH, gonadotrophin releasing hormone; NS, not significant; SD, standard deviation.

1 Downgraded 1 level - the cohort study by Joseph et al. (2019) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

2 Downgraded 1 level - the cohort study by Klink et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding, no randomisation, no control group and high number of participants lost to follow-up).

3 Downgraded 1 level - the cohort study by Vlot et al. (2017) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control).

Table 9 Question 2: For children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – cognitive development or functioning

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Cognitive development or functioning (1 cross-sectional study)									
IQ (4 subscales: arithmetic, vocabulary, picture arrangement, and block design) at a single time point between GnRH analogue treated and untreated transfemales									
1 Cross-sectional study Staphorsius et al. 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=8 Mean (SD) 94.0 (10.3)	N=10 Mean (SD) 109.4 (21.2)	NR	IMPORTANT	VERY LOW
IQ (4 subscales: arithmetic, vocabulary, picture arrangement, and block design) at a single time point between GnRH analogue treated and untreated transmales									
1 Cross-sectional study Staphorsius et al. 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=12 Mean (SD) 95.8 (15.6)	N=10 Mean (SD) 98.5 (15.9)	NR	IMPORTANT	VERY LOW
Reaction time at a single time point between GnRH analogue treated and untreated transfemales									
1 Cross-sectional study Staphorsius et al. 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=8 Mean (SD) 10.9 (4.1)	N=10 Mean (SD) 9.9 (3.1)	NR	IMPORTANT	VERY LOW
Reaction time at a single time point between GnRH analogue treated and untreated transmales									
1 Cross-sectional study	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=12 Mean (SD) 9.9 (3.1)	N=10 Mean (SD) 10.0 (2.0)	NR	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Staphorsius et al. 2015									
Accuracy at a single time point between GnRH analogue treated and untreated transfemales									
1 cohort study Staphorsius et al. 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=8 Mean (SD) 73.9 (9.1)	N=10 Mean (SD) 83.4 (9.5)	NR	IMPORTANT	VERY LOW
Accuracy at a single time point between GnRH analogue treated and untreated transmales									
1 cohort study Staphorsius et al. 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=12 Mean (SD) 85.7 (10.5)	N=10 Mean (SD) 88.8 (9.7)	NR	IMPORTANT	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; NR, not reported; *P*, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by Staphorsius et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding and no randomisation).

Table 10: Question 2: In children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – other safety outcomes

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Other safety outcomes: change in serum creatinine									
Change in serum creatinine (micromol/l) between baseline and 1 year in transfemales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 observational study Schagen et al. 2016	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=28	None	Mean (SD) Baseline: 70 (12) 1 year: 66 (13) p-value: 0.20	IMPORTANT	VERY LOW
Change in serum creatinine (µmol/l) between baseline and 1 year in transmales									
1 observational study Schagen et al. 2016	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=29	None	Mean (SD) Baseline: 73 (8) 1 year: 68 (13) p-value: 0.01	IMPORTANT	VERY LOW
Other safety outcomes: liver enzymes									
Presence of elevated liver enzymes (AST, ALT, and glutamyl transferase) between baseline and during treatment									
1 observational study Schagen et al. 2016	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	39	None	Glutamyl transferase was not elevated at baseline or during treatment in any subject. Mild elevations of AST and ALT above the reference range were present at baseline but were not more prevalent during treatment than at baseline. Glutamyl transferase, AST, and ALT levels did not significantly change from baseline to 12 months of treatment.	IMPORTANT	VERY LOW
Other safety outcomes: adverse effects									
Proportion of patients reporting adverse effects									
1 cohort study Khatchadourian et al 2014	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable[2]	27	None	3/27 adolescents[3]	Important	VERY LOW

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GnRH, gonadotrophin releasing hormone; P, P-value; SD, standard deviation.

1 Downgraded 1 level - the cohort study by Schagen et al. (2016) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control).

2 Downgraded 1 level - the cohort study by Khatchadourian et al. (2014) was assessed as at high risk of bias (poor quality overall; lack of blinding, no control group and high number of participants lost to follow-up).

3 1 transmale developed sterile abscesses; they were switched from leuprolide acetate to triptorelin, and this was well tolerated. 1 transmale developed leg pains and headaches, which eventually resolved without treatment. 1 participant gained 19 kg within 9 months of initiating GnRH analogues.

Table 11: Question 4. From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may derive more (or less) advantage from treatment with GnRH analogues than the wider population of children and adolescents with gender dysphoria? – critical outcomes

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result		
Subgroups: sex assigned at birth males compared with sex assigned at birth females									
Impact on gender dysphoria									
Mean [±SD] Utrecht Gender Dysphoria Scale (version(s) not reported), time point at baseline (before GnRHa) versus follow-up (just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[2] score at T0 47.95 [±9.70] score at T1 49.67 [±9.47]	n-NR[2] score at T0 56.57 [±3.89] score at T1 56.62 [±4.0]	*F*-ratio 15.98 (*df, errdf*: 1,39), *P*<0.001	Critical	VERY LOW
Impact on mental health									
Mean [±SD] Beck Depression Inventory-II, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result		
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[2] score at T0 5.71 [±4.31] score at T1 3.50 [±4.58]	n-NR[2] score at T0 10.34 [±8.24] score at T1 6.09 [±7.93]	*F*-ratio 3.85 (*df, errdf*: 1,39), *P*=0.057	Critical	VERY LOW
Mean [±SD] Trait Anger (TPI), time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[2] score at T0 5.22 [±2.76] score at T1 5.00 [±3.07]	n-NR[2] score at T0 6.43 [±2.78] score at T1 6.39 [±2.59]	*F*-ratio 5.70 (*df, errdf*: 1,39), *P*=0.022	Critical	VERY LOW
Mean [±SD] Trait Anxiety (STAI), time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[2] score at T0 4.33 [±2.68] score at T1 4.39 [±2.64]	n-NR[2] score at T0 7.00 [±2.36] score at T1 6.17 [±2.69]	*F*-ratio 16.07 (*df, errdf*: 1,39), *P*<0.001	Critical	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; NR, not reported; *P*, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).
2 The overall sample size completing the outcome at both time points was 41.

Table 11: Question: 4. From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may derive more (or less) advantage from treatment with GnRH analogues than the wider population of children and adolescents with gender dysphoria? – important outcomes

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result		
Subgroups: sex assigned at birth males compared with sex assigned at birth females									
Impact on body image									
Mean [±SD] Body Image Scale (primary sexual characteristics), time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[2] score at T0 4.02 [±0.16] score at T1 3.74 [±0.78]	n-NR[2] score at T0 4.16 [±0.52] score at T1 4.17 [±0.58]	*F*-ratio 4.11 (*df, errdf*: 1,55), *P*=0.047	Important	VERY LOW
Mean [±SD] Body Image Scale (secondary sexual characteristics), time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[2] score at T0 2.66 [±0.50] score at T1 2.39 [±0.69]	n-NR[2] score at T0 2.81 [±0.76] score at T1 3.18 [±0.42]	*F*-ratio 11.57 (*df, errdf*: 1,55), *P*=0.001[3]	Important	VERY LOW
Mean [±SD] Body Image Scale (neutral characteristics), time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Sex assigned at birth males**	**Sex assigned at birth females**	**Result**		
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[2] score at T0 2.60 [±0.58] score at T1 2.32 [±0.59]	n-NR[2] score at T0 2.24 [±0.62] score at T1 2.61 [±0.50]	*F*-ratio 0.081 (*df, errdf*: 1,55), *P*=0.777[3]	Important	VERY LOW
Psychosocial impact									
Mean [±SD] Children's Global Assessment Scale score, at baseline.									
1 cohort study Costa et al 2015	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	n=not reported 55.4 [±12.7]	n=not reported 59.2 [±11.8]	*t*-test 2.15; *P*=0.03[5]	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[6] score at T0 73.10 [±8.84] score at T1 77.33 [±8.69]	n-NR[6] score at T0 67.25 [±11.06] score at T1 70.30 [±9.44]	*F*-ratio 5.77 (*df, errdf*: 1,39), *P*=0.021	Important	VERY LOW
Mean [±SD] Child Behaviour Checklist (total T) score, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[7] score at T0 59.42 [±11.78] score at T1 50.38	n-NR[7] score at T0 61.73 [±13.60]	*F*-ratio 2.64 (*df, errdf*: 1,52), *P=0.110*	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result		
					[±10.57]	score at T1 57.73 [±10.82]			
Mean [±SD] Child Behaviour Checklist (internalising T) score, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[7] score at T0 60.00 [±9.51] score at T1 52.17 [±9.81]	n-NR[7] score at T0 61.80 [±14.12] score at T1 56.30 [±10.33]	*F*-ratio 1.16 (*df, errdf*: 1,52), *P*=0.286	Important	VERY LOW
Mean [±SD] Child Behaviour Checklist (externalising T) score, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[7] score at T0 54.71 [±12.91] score at T1 48.75 [±10.22]	n-NR[7] score at T0 60.70 [±12.64] score at T1 57.87 [±11.66]	*F*-ratio 6.29 (*df, errdf*: 1,52), *P*=0.015	Important	VERY LOW
Mean [±SD] Youth Self-Report (total T) score, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[7] score at T0 53.56 [±12.26] score at T1 47.84 [±10.86]	n-NR[7] score at T0 57.10 [±10.87] score at T1 51.86 [±10.11]	*F*-ratio 1.99 (*df, errdf*: 1,52), *P*=0.164	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result		
Mean [±SD] Youth Self-Report (internalising T) score, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[7] score at T0 55.88 [±11.81] score at T1 49.24 [±12.24]	n-NR[7] score at T0 56.17 [±13.25] score at T1 50.24 [±11.28]	*F*-ratio 0.049 (*df, errdf*: 1,52), *P*=0.825	Important	VERY LOW
Mean [±SD] Youth Self-Report (externalising T) score, time point at baseline (T0 before GnRHa) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[7] score at T0 48.72 [±11.83] score at T1 46.52 [±9.23]	n-NR[7] score at T0 57.24 [±10.59] score at T1 52.97 [±8.51]	*F*-ratio 9.14 (*df, errdf*: 1,52), *P*=0.004	Important	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; NR, not reported; *P*, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).
2 The overall sample size completing the outcome at both time points was 57.
3 There was a significant interaction effect between sex assigned at birth and BDI between T0 and T1; sex assigned at birth females became more dissatisfied with their secondary F (df, errdf), P: 14.59 (1,55), P<0.001) and neutral F (df, errdf), P: 15.26 (1,55), P<0.001) sex characteristics compared with sex assigned at birth males.
4 Serious limitations – the cohort study by Costa et al. 2015 was assessed as at high risk of bias (poor quality).
5 At baseline, CGAS scores were not associated with any demographic variable, in both sex assigned at birth males and females. There were no statistically significant differences in CGAS scores between gender dysphoric sex assigned at birth males and females in all follow-up evaluations (P>0.1; full data not reported).
6 The overall sample size completing the outcome at both time points was 41
7 The overall sample size completing the outcome at both time points was 54.

Glossary

Beck Depression Inventory-II (BDI-II)	The BDI-II is a tool for assessing depressive symptoms. There are no specific scores to categorise depression severity, but it is suggested that 0 to 13 is minimal symptoms, 14 to 19 is mild depression, 20 to 28 is moderate depression, and severe depression is 29 to 63.
Body Image Scale (BIS)	The BIS is used to measure body satisfaction. The scale consists of 30 body features, which the person rates on a 5-point scale. Each of the 30 items falls into one of 3 basic groups based on its relative importance as a gender-defining body feature: primary sex characteristics, secondary sex characteristics, and neutral body characteristics. A higher score indicates more dissatisfaction.
Bone mineral apparent density (BMAD)	BMAD is a size adjusted value of bone mineral density (BMD) incorporating body size measurements using UK norms in growing adolescents.
Child Behaviour Checklist (CBCL)	CBCL is a checklist parents complete to detect emotional and behavioural problems in children and adolescents.
Children's Global Assessment Scale (CGAS)	The CGAS tool is a validated measure of global functioning on a single rating scale from 1 to 100. Lower scores indicate poorer functioning.
Gender	The roles, behaviours, activities, attributes, and opportunities that any society considers appropriate for girls and boys, and women and men.
Gender dysphoria	Discomfort or distress that is caused by a discrepancy between a person's gender identity (how they see themselves regarding their gender) and that person's sex assigned at birth (and the associated gender role, and/or primary and secondary sex characteristics).
Gonadotrophin releasing hormone (GnRH) analogues	GnRH analogues competitively block GnRH receptors to prevent the spontaneous release of 2 gonadotropin hormones, Follicular Stimulating Hormone (FSH) and Luteinising Hormone (LH) from the pituitary gland. The reduction in FSH and LH secretion reduces oestradiol secretion from the ovaries in those whose sex assigned at birth was female and testosterone secretion from the testes in those whose sex assigned at birth was male.
Sex assigned at birth	Sex assigned at birth (male or female) is a biological term and is based on genes and how external and internal sex and reproductive organs work and respond to hormones. Sex is the label that is recorded when a baby's birth is registered.
Tanner stage	Tanner staging is a scale of physical development.
Trait Anger Spielberger scales of the State-Trait Personality Inventory (TPI)	The TPI is a validated 20-item inventory tool which measures the intensity of anger as the disposition to experience angry feelings as a personality trait. Higher scores indicate greater anger.
Transgender (including transmale and transfemale)	Transgender is a term for someone whose gender identity is not congruent with their birth-registered sex. A transmale is a person who identifies as male and a transfemale is a person who identifies as female.

Utrecht Gender Dysphoria Scale (UGDS)	The UGDS is a validated screening tool for both adolescents and adults to assess gender dysphoria. It consists of 12 items, to be answered on a 1- to 5-point scale, resulting in a sum score between 12 and 60. The higher the UGDS score the greater the impact on gender dysphoria.
Youth Self-Report (YSR)	The self-administered YSR is a checklist to detect emotional and behavioural problems in children and adolescents. It is self-completed by the child or adolescent. The scales consist of a Total problems score, which is the sum of the scores of all the problem items. An internalising problem scale sums the anxious/depressed, withdrawn-depressed, and somatic complaints scores while the externalising problem scale combines rule-breaking and aggressive behaviour.

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Evidence review: Gender-affirming hormones for children and adolescents with gender dysphoria

This document will help inform Dr Hilary Cass' independent review into gender identity services for children and young people. It was commissioned by NHS England and Improvement who commissioned the Cass review. It aims to assess the evidence for the clinical effectiveness, safety and cost-effectiveness of gender-affirming hormones for children and adolescents aged 18 years or under with gender dysphoria.

The document was prepared by NICE in October 2020.

The content of this evidence review was up to date on 21 October 2020. See summaries of product characteristics (SPCs), British National Formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites for up-to-date information.

Contents

1. Introduction

This review aims to assess the evidence for the clinical effectiveness, safety and cost-effectiveness of gender-affirming hormones for children and adolescents aged 18 years or under with gender dysphoria. The review follows the NHS England Specialised Commissioning process and template and is based on the criteria outlined in the PICO framework (see appendix A). This document will help inform Dr Hilary Cass' independent review into gender identity services for children and young people.

Gender dysphoria in children, also known as gender identity disorder or gender incongruence of childhood (World Health Organisation 2020), refers to discomfort or distress that is caused by a discrepancy between a person's gender identity (how they see themselves[1] regarding their gender) and that person's sex assigned at birth and the associated gender role, and/or primary and secondary sex characteristics (Diagnostic and Statistical Manual of Mental Disorders 2013).

Gender-affirming hormones are oestradiol for sex assigned at birth males (transfemales) and testosterone for sex assigned at birth females (transmales). The aim of gender-affirming hormones is to induce the development of the physical sex characteristics congruent with the individual's gender expression while aiming to improve mental health and quality of life outcomes.

No oestradiol-containing products are licensed for gender dysphoria and therefore any use for children and adolescents with gender dysphoria is off-label.

The only testosterone-containing product licensed for gender dysphoria is Sustanon 250 mg/ml solution for injection, which is indicated as supportive therapy for transmales, use of all other testosterone-containing products for children and adolescents with gender dysphoria is off-label.

For children and adolescents with gender dysphoria it is recommended that management plans are tailored to the needs of the individual and aim to ameliorate the potentially negative impact of gender dysphoria on general developmental processes, to support young people and their families in managing the uncertainties inherent in gender identity development and to provide ongoing opportunities for exploration of gender identity. The plans may also include psychological support and exploration and, for some individuals, the use of gonadotrophin releasing hormone (GnRH) analogues in adolescence to suppress puberty; this may be followed later with gender-affirming hormones of the desired sex (NHS England 2013).

Currently NHS England, as part of the Gender Identity Development Service for Children and Adolescents, routinely commissions gender-affirming hormones for young people with continuing gender dysphoria from around their 16th birthday subject to individuals meeting the eligibility and readiness criteria (Clinical Commissioning Policy 2016).

[1] Gender refers to the roles, behaviours, activities, attributes and opportunities that any society considers appropriate for girls and boys, and women and men (World Health Organisation, Health Topics: Gender).

2. Executive summary of the review

Ten observational studies were included in the evidence review. Seven studies were retrospective observational studies (Allen et al. 2019, Kaltiala et al. 2020, Khatchadourian et al. 2014, Klaver et Al. 2020, Klink et al. 2015, Stoffers et al. 2019, Vlot et al. 2017) and 3 studies were prospective longitudinal observational studies (Achille et al. 2020, Kuper et al. 2020, Lopez de Lara et al. 2020). No studies directly compared gender-affirming hormones to a control group (either placebo or active comparator). Follow-up was relatively short across all studies, with an average duration of treatment with gender-affirming hormones between around 1 year and 5.8 years.

The terminology used in this topic area is continually evolving and is different depending on stakeholder perspectives. In this evidence review we have used the phrase 'people's assigned sex at birth' rather than saying natal or biological sex and 'cross sex hormones' are now referred to as 'gender-affirming hormones'. The research studies may use historical terms which are no longer considered appropriate.

In children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Critical outcomes

The critical outcomes for decision making are impact on gender dysphoria, impact on mental health and quality of life. The quality of evidence for all these outcomes was assessed as very low certainty using modified GRADE.

Impact on gender dysphoria
The study by Lopez de Lara et al. 2020 in 23 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, gender dysphoria (measured using the Utrecht Gender Dysphoria Scale [UGDS]) was statistically significantly reduced (improved) from a mean [±SD] score of 57.1 (±4.1) points at baseline to 14.7 (±3.2) points at 12 months, which is below the threshold (40 points) for gender dysphoria ($p<0.001$).

Impact on mental health
Depression
The study by Lopez de Lara et al. 2020 in 23 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, depression (measured using the Beck Depression Inventory-II [BDI-II]) was statistically significantly reduced from a mean [±SD] score of 19.3 (±5.5) points at baseline to 9.7 (±3.9) points at 12 months ($p<0.001$).

The study by Achille et al. 2020 in 50 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, depression was statistically significantly reduced from baseline to about 12 months follow-up:

- The Center for Epidemiologic Studies Depression (CESD-R) improved from a mean score of 21.4 points at baseline to 13.9 points ($p<0.001$).
- The Patient Health Questionnaire (PHQ 9) Modified for Teens improved, although absolute scores were not reported numerically ($p<0.001$).

The study by Kuper et al. 2020 in 148 adolescents with gender dysphoria (of whom 123 received gender-affirming hormones) found that during treatment with gender-affirming hormones for an average of 10.9 months, the impact on depression (measured using the Quick Inventory of Depressive Symptoms [QIDS]) was unclear as no statistical analysis was reported. The mean (±SD) self-reported score was 9.6 points (±5.0) at baseline and 7.4 (±4.5) at follow-up. The mean (±SD) clinician-reported score was 5.9 points (±4.1) at baseline and 6.0 (±3.8).

The study by Kaltiala et al. 2020 in 52 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, statistically significantly fewer participants needed treatment for depression (54% at initial assessment compared with 15% at 12-month follow-up, p<0.001). No details of the treatments for depression are reported.

Anxiety

The study by Lopez de Lara et al. 2020 in 23 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, state anxiety (measured using the State-Trait Anxiety Inventory [STAI] – State subscale) was statistically significantly reduced from a mean (±SD) score of 33.3 points (±9.1) at baseline to 16.8 points (±8.1) at 12 months (p<0.001). Trait anxiety (measured using STAI – Trait subscale) was also statistically significantly reduced from a mean (±SD) score of 33.0 (±7.2) points at baseline to 18.5 (±8.4) points at 12 months (p<0.001).

The study by Kuper et al. 2020 in 148 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, small reductions were seen in anxiety, panic, generalised anxiety, social anxiety and separation anxiety symptoms and school avoidance (measured using the Screen for Child Anxiety Related Emotional Disorders [SCARED] questionnaire) from baseline to follow-up (mean duration of treatment 10.9 months). The statistical significance of these findings are unknown as no statistical analyses were reported.

The study by Kaltiala et al. 2020 in 52 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, statistically significantly fewer participants needed treatment for anxiety (48% at initial assessment compared with 15% at 12-month follow-up, p<0.001). No details of treatments for anxiety are reported.

Suicidality and self-injury

The study by Allen et al. 2019 in 47 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, suicide risk (measured using the Ask Suicide-Screening Questions [ASQ]) was statistically significantly reduced from an adjusted mean (±SE) score of 1.11 points (±0.22) at baseline to 0.27 points (±0.12) after about 12 months (p<0.001).

The study by Achille et al. 2020 in 50 adolescents with gender dysphoria (of whom 35 received gender-affirming hormones at follow-up) found that during treatment with gender-affirming hormones, the impact on suicidal ideation was unclear (measured using the PHQ 9_Modified for Teens with additional questions for suicidal ideation). At baseline 10%of participants had suicidal ideation and 6% had suicidal ideation after about 12 months, but it is unclear if these participants received gender-affirming hormones. No statistical analyses were reported.

The study by Kuper et al. 2020 in 148 adolescents with gender dysphoria reported the impact on suicidal ideation, suicide attempts and non-suicidal self-injury during treatment with gender-affirming hormones, after mean 10.9 months follow-up . The statistical significance of these findings are unknown as no statistical analyses were reported:

- Suicidal ideation was reported in 25% of participants 1 month before the initial assessment and in 38% of participants during follow-up.
- Suicide attempts were reported in 2% of participants at 3 months before the initial assessment and in 5% during follow-up.
- Self-injury was reported in 10% of participants at 3 months before the initial assessment and in 17% during follow-up.

The study by Kaltiala et al. 2020 in 52 adolescents with gender dysphoria reported that during treatment with gender-affirming hormones, statistically significantly fewer participants needed treatment for suicidal ideation or self-harm (35% at initial assessment compared with 4% at 12-month follow-up, p<0.001). No details of treatments for suicidal ideation or self-harm are reported.

Other related symptoms

The study by Kaltiala et al. 2020 in 52 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, there was no statistically significant difference in the number of people needing treatment for either psychotic symptoms or psychosis, conduct problems or antisocial behaviour, substance abuse, autism, attention deficit hyperactivity disorder (ADHD) or eating disorders during the 12-month 'real life' phase compared with before or during the assessment. No details of the treatments received are reported.

Impact on quality of life

The study by Achille et al. 2020 in 50 adolescents with gender dysphoria (of whom 35 were receiving gender-affirming hormones at follow-up) found that during treatment with gender-affirming hormones, quality of life (measured using the Quality of Life Enjoyment and Satisfaction Questionnaire [QLES-Q-SF]) was statistically significantly improved from baseline to about 12 months, but absolute scores were not reported numerically (p<0.001).

The study by Allen et al. 2019 in 47 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, quality of life (measured using the General Well-Being Scale [GWBS] of the Paediatric Quality of Life Inventory) was statistically significantly improved from an adjusted mean (±SE) score of 61.70 (±2.43) points at baseline to 70.23 (±2.15) points at about 12 months (p<0.002).

Important outcomes

The important outcomes for decision making are impact on body image, psychosocial impact, engagement with healthcare services, impact on extent of and satisfaction with surgery and de-transition. The quality of evidence for all these outcomes was assessed as very low certainty using modified GRADE.

Impact on body image

The study by Kuper et al. 2020 in 148 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, the impact on body image is unclear (measured using the Body Image Scale [BIS]). The mean (±SD) BIS score was 70.7 points (±15.2) at baseline and 51.4 points (±18.3) at follow-up (mean duration of treatment 10.9 months; no statistical analysis was reported).

Psychosocial impact
The study by Lopez de Lara et al. 2020 in 23 adolescents with gender dysphoria found that during treatment with gender affirming hormones, family functioning is unchanged (measured using the Family Adaptability, Partnership, Growth, Affection and Resolve [APGAR] test). The mean score was 17.9 points at baseline and 18.0 points at 12-month follow-up (no statistical analysis was reported).

The study by Lopez de Lara et al. 2020 in 23 adolescents with gender dysphoria found that during treatment with gender affirming hormones, behavioural problems (measured using the Strengths and Difficulties Questionnaire [SDQ]) were statistically significantly improved from a mean (±SD) of 14.7 (±3.3) points at baseline to 10.3 points (±2.9) at 12-month follow-up ($p<0.001$).

The study by Kaltiala et al. 2020 in 52 adolescents with gender dysphoria found that about 12-months after starting treatment with gender-affirming hormones:

- Statistically significantly fewer participants were living with parents or guardians (73% versus 40%, $p=0.001$) and statistically significantly fewer participants had normal peer contacts (89% versus 81%, $p<0.001$).
- There were no statistically significant differences in:
    - progress in school or work (64% versus 60%, $p=0.69$),
    - the number of participants who had been dating or in steady relationships (62% versus 58%, $p=0.51$)
    - the ability to cope with matters outside of the home (for example, shopping and travelling alone on local public transport; 81% versus 81%, $p=1.0$)

Engagement with health care services
No evidence was identified.

Impact on extent of and satisfaction with surgery
No evidence was identified.

De-transition
No evidence was identified.

In children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Important outcomes

The important outcomes for decision making are short- and long-term safety outcomes and adverse effects. The quality of evidence for all these outcomes was assessed as very low certainty using modified GRADE.

Bone density

The study by Klink et al. 2015 in 34 adolescents with gender dysphoria (who were previously treated with a GnRH analogue) found that gender-affirming hormones may increase lumbar spine and femoral neck bone density. However, not all results are statistically significant (particularly in transfemales). Z-scores suggest the average bone density at the end of follow-up was generally lower than in the equivalent cisgender population (transfemales compared with cis-males and transmales compared with cis-females). From starting gender-affirming hormones to age 22 years:

- There was no statistically significant difference in lumbar spine bone mineral apparent density (BMAD) z-score in transfemales, but this was statistically significantly higher in transmales (z-score [±SD]: start of hormones -0.50 [±0.81], age 22 years -0.033 [±0.95], p=0.002).
- There was no statistically significant difference in lumbar spine bone mineral density (BMD) z-score in transfemales or transmales.
- Actual lumbar spine BMAD and BMD values were statistically significantly higher in transfemales and transmales.
- There was no statistically significant difference in femoral neck BMD z-score in transfemales, but this was statistically significantly higher in transmales (z-score [SD]: start of hormones -0.35 [0.79], age 22 years -0.35 [0.74], p=0.006).
- There was no statistically significant difference in actual femoral neck BMAD values in transfemales, but this was statistically significantly higher in transmales.
- Actual femoral neck BMD values were statistically significantly higher in transfemales and transmales.

The study by Vlot et al. 2017 in 70 adolescents with gender dysphoria (who were previously treated with a GnRH analogue) found that gender-affirming hormones may increase lumbar spine and femoral neck bone density. However, not all results are statistically significant. Z-scores suggest the average bone density at the end of follow-up was generally lower than the equivalent cisgender population (transfemales compared with cis-males and transmales compared with cis-females). From starting gender-affirming hormones to 24-month follow-up:

- The z-score for lumbar spine BMAD was statistically significantly higher in transfemales with a bone age of less than 15 years (z-score [range]: start of hormones -1.52 [-2.36 to 0.42], 24-month follow-up -1.10 [-2.44 to 0.69], p≤ 0.05) and 15 years and older (z-score [range]: start of hormones -1.15 [-2.21 to 0.08], 24-month follow-up -0.66 [-1.66 to 0.54], p≤ 0.05).
- The z-score for lumbar spine BMAD was statistically significantly higher in transmales with a bone age of less than 14 years (z-score [range]: start of hormones -0.84 [-2.2 to 0.87], 24-month follow-up -0.15 [-1.38 to 0.94], p≤ 0.01) and 14 years and older (z-score [range]: start of hormones -0.29 [-2.28 to 0.90], 24-month follow-up -0.06 [-1.75 to 1.61], p≤ 0.01).
- Actual lumbar spine BMAD values were statistically significantly higher in transfemales and transmales of all bone ages.
- There was no statistically significant difference in femoral neck BMAD z-score in transfemales (all bone ages).

- The z-score for femoral neck BMAD was statistically significantly higher in transmales with a bone age of less than 14 years (z-score [range]: start of hormones -0.37 [-2.28 to 0.47], 24-month follow-up -0.37 [-2.03 to 0.85], p≤ 0.01) and 14 years and older (z-score [range]: start of hormones -0.27 [-1.91 to 1.29], 24-month follow-up 0.02 [-2.1 to 1.35], p≤0.05).
- There was no statistically significant difference in actual femoral neck BMAD values in transfemales (all bone ages), but this was statistically significantly higher in transmales (all bone ages).

The study by Stoffers et al. 2019 in 62 sex assigned at birth females (transmales) with gender dysphoria (who were previously treated with a GnRH analogue) found that during treatment with gender-affirming hormones there was no statistically significant difference in lumbar spine or femoral neck bone density (measured as BMD z-scores or actual values) from starting gender-affirming hormones to any timepoint (6, 12 and 24 months).

Change in clinical parameters

The study by Klaver et al. 2020 in 192 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, from starting treatment to age 22 years:

- Glucose levels, insulin levels and insulin resistance were largely unchanged in transfemales and transmales.
- Total cholesterol, HDL cholesterol and LDL cholesterol levels were unchanged in transfemales, and there was a statistically significant improvement in triglyceride levels.
- Total cholesterol, HDL cholesterol, LDL cholesterol and triglyceride levels significantly worsened in transmales, but mean levels were within the UK reference range at the end of treatment.
- Diastolic blood pressure was statistically significantly increased in transfemales and transmales. Systolic blood pressure was also statistically significantly increased in transmales, but not in transfemales. The absolute increases in blood pressure were small.
- Body mass index was statistically significantly increased in transfemales and transmales, although most participants were within the healthy weight range (18.5 to 24.9 kg/m).

The study by Stoffers et al. 2019 in 62 sex assigned at birth females (transmales) with gender dysphoria found that during treatment with gender affirming hormones, from starting treatment to 24-month follow-up:

- There was no statistically significant change in glycosylated haemoglobin (HbA1c).
- There was no statistically significant change in aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyltransferase (GCT).
- There was a statistically significant increase in alkaline phosphatase (ALP) at some timepoints, but the difference was not statistically significant by 24-months.
- There was a statistically significant increase in serum creatinine levels at all timepoints up to 24 months, but these were within the UK reference range. Serum urea levels were unchanged (follow-up duration not reported).

Treatment discontinuation and adverse effects

The study by Khatchadourian et al. 2014 in 63 adolescents (24 transfemales and 39 transmales) with gender dysphoria found that during treatment with gender affirming hormones (duration of treatment not reported):

- No participants permanently discontinued treatment.
- No transfemales temporarily discontinued treatment, but 3 transmales temporarily discontinued treatment due to mental health comorbidities (n=2) and androgenic alopecia (n=1). All 3 participants eventually resumed treatment, although timescales were not reported
- No severe complications were reported.
- No transfemales reported minor complications, but 12 transmales developed minor complications which were: severe acne (n=7), androgenic alopecia (n=1), mild dyslipidaemia (n=3) and significant mood swings (n=1).

In children and adolescents with gender dysphoria, what is the cost-effectiveness of gender-affirming hormones compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?

No cost-effectiveness evidence was found for gender-affirming hormones for children and adolescents with gender dysphoria.

From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria?

Some studies reported data separately for the following subgroups of children and adolescents with gender dysphoria:

- Sex assigned at birth males (transfemales).
- Sex assigned at birth females (transmales).
- Tanner stage at which GnRH analogue or gender-affirming hormones started.
- Diagnosis of a mental health condition.

Some direct comparisons of transfemales and transmales were included. No evidence was found for other specified subgroups.

Sex assigned at birth males (transfemales)
Impact on mental health
In the study by Kuper et al. 2020 in 33 to 45 (number varies by outcome) sex assigned at birth males (transfemales) with gender dysphoria found that during treatment with gender-affirming hormones changes were seen in depression, anxiety and anxiety-related symptoms from baseline to follow-up (mean duration of treatment 10.9 months). The authors did not report any statistical analyses, so it is unclear if any changes were statistically significant.

The study by Allen et al. 2019 in 47 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, suicide risk (measured using the ASQ) is not statistically significant different in transfemales compared with transmales, between baseline and the final assessment at about 12 months (p=0.79).

The study by Achille et al. 2020 in 17 transfemales with gender dysphoria found that during treatment with gender-affirming hormones, suicidal ideation (measured using the PHQ 9_Modified for Teens with additional questions for suicidal ideation) was reported in 11.8% (2/17) of transfemales at baseline compared with 5.9% (1/17) at about 12-months follow-up (no statistical analysis was reported).

Impact on quality of life

The study by Allen et al. 2019 in 47 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, quality of life (measured using the GWBS of the Paediatric Quality of Life Inventory) was not statistically significant different in transfemales compared with transmales, between baseline and the final assessment at about 12 months (p=0.32).

Bone density

The studies by Klink et al. 2015 and Vlot et al. 2017 provided evidence on bone density in transfemales; see above for details.

Change in clinical parameters

The study by Klaver et al. 2020 provided evidence on the following clinical parameters in transfemales:

- Glucose levels, insulin levels and insulin resistance.
- Total cholesterol, HDL cholesterol and LDL cholesterol and triglycerides.
- Blood pressure.
- Body mass index.

See above for details.

Treatment discontinuation and adverse effects

The study by Khatchadourian et al. 2014 provided evidence on treatment discontinuation and adverse effects in transfemales; see above for details.

Sex assigned at birth females (transmales)

Impact on mental health

In the study by Kuper et al. 2020 in 65 to 78 (number varies by outcome) sex assigned at birth females (transmales) with gender dysphoria found that during treatment with gender-affirming hormones, changes were seen in depression, anxiety and anxiety-related symptoms from baseline to 10.9 month follow-up. The authors did not report any statistical analyses, so it is unclear if any changes were statistically significant.

The study by Allen et al. 2019 in 47 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, suicide risk (measured using the ASQ) is not statistically significantly different in transmales compared with transfemales, between baseline and the final assessment (p=0.79).

The study by Achille et al. 2020 in 33 transmales with gender dysphoria found that during treatment with gender-affirming hormones, suicidal ideation (measured using the PHQ 9_Modified for Teens with additional questions for suicidal ideation) was reported in 9.1% (3/33) of transmales at baseline compared with 6.1% (2/33) at about 12-months follow-up (no statistical analysis reported).

Impact on quality of life
The study by Allen et al. 2019 in 47 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, quality of life (measured using the GWBS of the Paediatric Quality of Life Inventory) was not statistically significantly different in transmales compared with transfemales, between baseline and the final assessment at about 12 months (p=0.32).

Bone density
The studies by Klink et al. 2015, Stoffers et al. 2019 and Vlot et al. 2017 provided evidence on bone density in transmales; see above for details.

Change in clinical parameters
The study by Klaver et al. 2020 provided evidence on the following clinical parameters in transmales:

- Glucose levels, insulin levels and insulin resistance.
- Total cholesterol, HDL cholesterol and LDL cholesterol and triglycerides.
- Blood pressure.
- Body mass index.

See above for details.

The study by Stoffers et al. 2019 provided evidence on HbA1c, liver enzymes and renal function in transmales; see above for details.

Treatment discontinuation and adverse effects
The study by Khatchadourian et al. 2014 provided evidence on treatment discontinuation and adverse effects in transmales; see above for details.

Tanner stage at which GnRH analogues or gender-affirming hormones started
The study by Kuper et al. 2020 stated that the impact of Tanner stage on outcomes was considered, but it is unclear if this refers to Tanner stage at the initial assessment, at the start of GnRH analogue treatment or another timepoint. No results were reported.

Diagnosis of a mental health condition
Impact on mental health
The study by Achille et al. 2020 in 50 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, there was no statistically significant difference in depression (measured using the CESD-R and PHQ 9_Modified for Teens) when the results were adjusted for engagement in counselling and medicines for mental health problems, from baseline to about 12-months follow-up.

Impact on quality of life
The study by Achille et al. 2020 in 50 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, there was no statistically significant difference in quality of life (measured using the QLES-Q-SF) when the results were adjusted for engagement in counselling and medicines for mental health problems, from baseline to about 12-months follow-up.

From the evidence selected,

(a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?
(b) what were the ages at which participants commenced treatment with gender-affirming hormones?
(c) what was the duration of treatment with GnRH analogues?

The most commonly reported diagnostic criteria for gender dysphoria was the DSM criteria in use at the time (5/10 studies). In 3 studies (Klaver et al. 2020, Klink et al. 2015 and Vlot et al. 2017) DSM-IV-TR criteria was used. In 2 studies (Kuper et al. 2020 and Stoffers et al. 2019) DSM-V criteria was used. One study from Finland (Kaltiala et al. 2020) used the ICD-10 diagnosis of 'transexualism'. It was not reported how gender dysphoria was defined in the remaining 4 studies.

In the studies, treatment with gender-affirming hormones started at about 16 to 17 years, with a range of about 14 to 19 years. Most studies did not report the duration of treatment with GnRH analogues, but where this was reported there was a wide variation ranging from a few months up to about 5 years (Klaver et al. 2020, Klink et al. 2015 and Stoffers et al. 2019).

Discussion

The key limitation to identifying the effectiveness and safety of gender-affirming hormones for children and adolescents with gender dysphoria is the lack of reliable comparative studies.

All the studies included in the evidence review are uncontrolled observational studies, which are subject to bias and confounding and were of very low certainty using modified GRADE. A fundamental limitation of all the uncontrolled studies included in this review is that any changes in scores from baseline to follow-up could be attributed to a regression-to-the-mean.

The included studies have relatively short follow-up, with an average duration of treatment with gender-affirming hormones between around 1 year and 5.8 years. Further studies with a longer follow-up are needed to determine the long-term effect of gender-affirming hormones for children and adolescents with gender dysphoria.

Most studies included in this review did not report comorbidities (physical or mental health) and no study reported concomitant treatments in detail. Because of this it is not clear whether any changes seen were due to gender-affirming hormones or other treatments the participants may have received.

There is a degree of indirectness in some studies, with some participants included that fall outside of the population of this evidence review. Furthermore, participant numbers are poorly reported in some studies, with high numbers lost to follow-up or outcomes not reported for some participants. The authors provide no explanation for this incomplete reporting.

Details of the gender-affirming hormone treatment regimen are poorly reported in most of the included studies, with limited information provided about the medicines, doses and routes of administration used. It is not clear whether the interventions used in the studies are reflective of current UK practice for children and adolescents with gender dysphoria.

It is difficult to draw firm conclusions for many of the effectiveness and safety outcomes reported in the included studies because many different scoring tools and methods were used to assess the same outcome, often with conflicting results. In addition to this, most outcomes reported across the included studies do not have an accepted minimal clinically important difference (MCID), making it difficult the determine whether any statistically significant changes seen are clinically meaningful. However, the authors of some studies report thresholds to interpret the results of the scoring tools (for example, by linking scores to symptom severity), so some conclusions can be made.

Conclusion

Any potential benefits of gender-affirming hormones must be weighed against the largely unknown long-term safety profile of these treatments in children and adolescents with gender dysphoria.

Results from 5 uncontrolled, observational studies suggest that, in children and adolescents with gender dysphoria, gender-affirming hormones are likely to improve symptoms of gender dysphoria, and may also improve depression, anxiety, quality of life, suicidality, and psychosocial functioning. The impact of treatment on body image is unclear. All results were of very low certainty using modified GRADE.

Safety outcomes were reported in 5 observational studies. Statistically significant increases in some measures of bone density were seen following treatment with gender-affirming hormones, although results varied by bone region (lumber spine versus femoral neck) and by population (transfemales versus transmales). However, z-scores suggest that bone density remained lower in transfemales and transmales compared with an equivalent cisgender population. Results from 1 study of gender-affirming hormones started during adolescence reported statistically significant increases in blood pressure and body mass index, and worsening of the lipid profile (in transmales) at age 22 years, although longer term studies that report on cardiovascular event rates are required. Adverse events and discontinuation rates associated with gender-affirming hormones were only reported in 1 study, and no conclusions can be made on these outcomes.

This review did not identify sub-groups of patients who may benefit more from gender-affirming hormones.

No cost-effectiveness evidence was found to determine whether gender-affirming hormones are a cost-effective treatment for children and adolescents with gender dysphoria.

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

2. For children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
3. For children and adolescents with gender dysphoria, what is the cost-effectiveness of gender-affirming hormones compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?
4. From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria?
5. From the evidence selected,
   (a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?
   (b) what were the ages at which participants commenced treatment with gender-affirming hormones?
   (c) what was the duration of GnRH analogues treatment?

See appendix A for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO and were conducted on 21 July 2020.

See appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO framework. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See appendix C for evidence selection details and appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See appendix E and appendix F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See appendix G for GRADE Profiles.

4. Summary of included studies

Ten observational studies were included in the evidence review. Seven studies were retrospective observational studies (Allen et al. 2019, Kaltiala et al. 2020, Khatchadourian et al. 2014, Klaver et Al. 2020, Klink et al. 2015, Stoffers et al. 2019, Vlot et al. 2017) and three studies were prospective longitudinal observational studies (Achille et al. 2020, Kuper et al. 2020, Lopez de Lara et al. 2020).

The terminology used in this topic area is continually evolving and is different depending on stakeholder perspectives. In this evidence review we have used the phrase 'people's assigned sex at birth' rather than saying natal or biological sex and 'cross sex hormones' are now referred to as 'gender-affirming hormones'. The research studies may use historical terms which are no longer considered appropriate.

Table 1 provides a summary of these included studies and full details are given in appendix E.

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Achille et al. 2020 Prospective longitudinal study Single centre, New York, United States	50 children, adolescents and young adults with gender dysphoria; 17 transfemales and 33 transmales Mean age at baseline was 16.2 years (SD 2.2)	**Intervention** Endocrine interventions (the collective term used for puberty suppression and gender-affirming hormones) were introduced as per Endocrine Society and the World Professional Association for Transgender Health (WPATH) guidelines Puberty suppression was: • GnRH analogue and/or anti-androgens (transfemales) • GnRH analogue or medroxyprogesterone (transmales) Once eligible, gender-affirming hormones were offered, these were: • Oestradiol (transfemales)	**Critical Outcomes** *Impact on mental health* • Depression- The Center for Epidemiologic Studies Depression Scale (CESD-R) • Depression- The Patient Health Questionnaire Modified for Teens (PHQ 9_Modified for Teens) *Impact on quality of life* • Quality of Life Enjoyment and Satisfaction Questionnaire (QLES-Q-SF) **Important Outcomes** *None reported*

Study	Population	Intervention and comparison	Outcomes reported
		• Testosterone (transmales) Doses and formulations not reported After about 12-months treatment ('wave 3'): • 24 people (48%) were on gender-affirming hormones alone • 12 people (24%) were on puberty suppression alone • 11 people (22%) were on both gender-affirming hormones and puberty suppression • 3 people (6%) were on no endocrine intervention **Comparison** No comparison group. Change over time reported	
Allen et al. 2019 Retrospective longitudinal study Single centre, Kansas City, USA	47 adolescents and young adults with gender dysphoria: 14 transfemales and 33 transmales Mean age at administration (start of treatment) 16.5 years	**Intervention** 39 participants received gender-affirming hormones only 8 participants received hormones and a GnRH analogue Mean duration of treatment with gender-affirming hormones was 349 days (range 113 to 1,016) **Comparison** No comparison group. Comparison over time reported	**Critical Outcomes** *Impact on mental health* • Suicidality- Ask Suicide-Screening Questions (ASQ) instrument *Impact on quality of life* • General Well-Being Scale (GWBS) of the Pediatric Quality of Life Inventory **Important Outcomes** *None reported*
Kaltiala et al. 2020	52 adolescents with gender dysphoria: 11 transfemales and 41 transmales.	**Intervention** Hormonal sex assignment treatment – details of	**Critical Outcomes** *Impact on mental health*

Study	Population	Intervention and comparison	Outcomes reported
Retrospective chart review Single centre, Tampere, Finland	Mean age at diagnosis 18.1 years (range 15.2 to 19.9)	intervention not reported, although all patients received gender-affirming hormones. **Comparison** No comparison group. Comparison over time reported	• Need for mental health treatment **Important Outcomes** *Psychosocial Impact* Measure of functioning in different domains of adolescent development, which were: • Living with parent(s)/ guardians • Normative peer contacts • Progresses normatively in school/ work • Has been dating or had steady relationships • Is age-appropriately able to deal with matters outside of the home
Khatchadourian et al. 2014 Retrospective chart review Single centre, Vancouver, Canada	84 young people with gender dysphoria, of whom 63 received gender-affirming hormones. Median age at start of gender-affirming hormones was: • 17.3 years (range 13.7-19.8) for testosterone • 17.9 years (range 13.3-22.3) for oestrogen	**Intervention** Transfemales: Oestrogen (oral micronized 17β-oestradiol) Transmales: Testosterone (injectable testosterone enanthate and/or cypionate) 19 participants (30%) had previously received a GnRH analogue **Comparison** No comparison group. Comparison over time reported.	**Critical Outcomes** *None reported* **Important Outcomes** *Safety:* • Adverse events • Discontinuation rates
Klaver et al. 2020 Retrospective chart review Single centre, Amsterdam, Netherlands	192 people with gender dysphoria who started GnRH analogues before the age of 18 years, and started gender-affirming hormones within 1.5 years of their 22nd birthday.	**Intervention** Oral oestrogen or intramuscular (IM) testosterone **Comparison**	**Critical Outcomes** *None reported* **Important Outcomes** *Safety* • Body mass index (BMI)

Study	Population	Intervention and comparison	Outcomes reported
	Mean age at start of gender-affirming hormones: • Transfemale – 16.4 years (SD 1.1) • Transmale – 16.9 years (SD 1.9)	No comparison group. Comparison over time reported	• Systolic blood pressure • Diastolic blood pressure • Glucose • Insulin • HOMA-IR • Total cholesterol • HDL cholesterol • LDL cholesterol • Triglycerides
Klink et al. 2015 Retrospective longitudinal study Single centre, Amsterdam, Netherlands	34 young people with gender dysphoria who had received GnRH analogues, gender-affirming hormones and gonadectomy. The study included 15 transfemales and 19 transmales; mean age at start of gender-affirming hormones was 16.6 years (SD 1.4) and 16.4 years (SD 2.3) respectively. At the start of gender-affirming hormone treatment, in the transfemale subgroup the median Tanner P was 4 (IQR 2) and the median Tanner G was 12 (IQR 11) In the transmale subgroup the median Tanner B was 5 (IQR 2) and the median Tanner P was 5 (IQR 0)	**Intervention** Transfemales – oral 17-β oestradiol (incremental dosing) Transmales – IM testosterone (Sustanon 250 mg/ml; incremental dosing) Median duration of treatment with gender-affirming hormones for transfemales was 5.8 years (range 3.0 to 8.0) and for transmales was 5.4 years (range 2.8 to 7.8) The GnRH analogue was subcutaneous (SC) triptorelin 3.75 mg every 4 weeks No details of gonadectomy reported **Comparison** No comparison group. Comparison over time reported.	**Critical Outcomes** None **Important Outcomes** *Safety* • Bone mineral apparent density (BMAD) • Bone mineral density (BMD) Measures reported at 3 timepoints: start of GnRH analogue treatment, start of gender-affirming hormone treatment and age 22 years.
Kuper et al. 2020 Prospective longitudinal study	Children and adolescents with gender dysphoria (9 to18 years), n=148, of whom: • 25 received puberty suppression only	**Intervention** Gender-affirming hormones, guided by Endocrine Society Clinical Practice Guidelines	**Critical Outcomes** *Impact on mental health* • Depression- Quick Inventory of Depressive

Study	Population	Intervention and comparison	Outcomes reported
Single centre, Texas, USA	• 93 received gender-affirming hormone therapy only • 30 received both Mean age 14.9 years	**Comparison** No comparison group. Comparison over time reported.	Symptoms (QIDS), self-reported • Depression- QIDS, clinician-reported • Anxiety- Screen for Child Anxiety Related Emotional Disorders (SCARED) • Panic- specific questions from SCARED • Generalised anxiety-specific questions from SCARED • Social anxiety - specific questions from SCARED • Separation anxiety-specific questions from SCARED • School avoidance-specific questions from SCARED **Important Outcomes** *Impact on body image* • Body Image Scale (BIS)
Lopez de Lara et al. 2020 Prospective analytical study Single centre, Madrid, Spain	23 adolescents with gender dysphoria: 7 transfemales and 16 transmales. Mean age at baseline was 16 years (range 14 to 18)	**Intervention** Gender-affirming hormones: • Oral oestradiol • Intramuscular testosterone Participants had previously received GnRH analogues in the intermediate pubertal stages (Tanner 2 to 3). Participants were assessed twice: • pre-treatment (T0), • after 12 months treatment with gender-affirming hormones (T1)	**Critical Outcomes** *Impact on gender dysphoria* • Utrecht Gender Dysphoria Scale (UGDS) *Impact on mental health* • Depression- Beck Depression Inventory II (BDI-II) • Anxiety- State-Trait Anxiety Inventory **Important Outcomes** *Psychosocial Impact* • Family functioning-Family APGAR test • Patient strengths and difficulties-Strengths and Difficulties Questionnaire,

Study	Population	Intervention and comparison	Outcomes reported
		Comparison No comparison group. Comparison over time reported.	Spanish Version (SDQ-Cas).
Stoffers et al. 2019 Retrospective chart review Single centre, Leiden, Netherlands	62 transmales with gender dysphoria. Patients had received a GnRH analogue and more than 6 months of testosterone treatment. Median age at start of testosterone was 17.23 years (range 14.9 to 18.4) Median treatment duration was 12 months (range 5 to 33) Change over time	**Intervention** Testosterone intramuscular injections (Sustanon 250 mg). Dose was titrated to a maintenance dose of 125 mg every 2 weeks. Participants who started GnRH analogues at 16 years or older had their dose increased more rapidly. Some participants chose to receive testosterone every 3-4 weeks, and participants could switch to transdermal preparations if needed. **Comparison** No comparison group. Comparison over time reported.	**Critical Outcomes** None **Important Outcomes** *Safety* • Body mass index (BMI) • Blood pressure • BMD • Acne • Liver enzymes • Creatinine • Urea • HbA1c
Vlot et al. 2017 Retrospective chart review Single centre, Amsterdam, Netherlands	70 children and adolescents with gender dysphoria Median age at baseline – • 13.5 years (11.5-18.3) for transfemales • 15.1 years (range 11.7-18.6) for transmales Comparison is change over time. 24 month follow-up.	**Intervention** Oestrogen or testosterone (had previously received triptorelin for puberty suppression) **Comparison** No comparison group. Comparison over time reported.	**Critical Outcomes** None **Important Outcomes** *Safety* • Bone mineral apparent density (BMAD)

5. Results

In children and adolescents with gender dysphoria, what is the clinical effectiveness of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Outcome	Evidence statement
Clinical Effectiveness	

Critical outcomes	
Impact on gender dysphoria **Certainty of evidence: very low**	This is a critical outcome because gender dysphoria in children and adolescents is associated with significant distress and problems with functioning. One uncontrolled, prospective, observational study (Lopez de Lara et al. 2020) provided evidence relating to the impact on gender dysphoria, measured using the Utrecht Gender Dysphoria Scale (UGDS) score during the first year of treatment with gender-affirming hormones. The UGDS is a validated, screening tool for both adolescents and adults, used to assess gender dysphoria. It consists of 12 items, to be answered on a 1- to 5-point scale, resulting in a sum score between 12 and 60. The authors state that the cut-off point to identify gender dysphoria is 40 points. The higher the UGDS score the greater the gender dysphoria. In this study (n=23), the mean (±SD) UGDS score was statistically significantly reduced (improved) from 57.1 (±4.1) points at baseline to 14.7 points (±3.2) at 12 months (p<0.001). A UGDS score below 40 suggests an absence of gender dysphoria **(VERY LOW)**. **This study provides very low certainty evidence that gender-affirming hormones statistically significantly improve gender dysphoria from baseline to 12 months follow-up. The mean UGDS score was below the threshold for gender dysphoria at follow-up.**
Impact on mental health: depression **Certainty of evidence: very low**	This is a critical outcome because depression may impact on social, occupational, or other areas of functioning in children and adolescents. Four observational studies (Achille et al. 2020; Kaltiala et al. 2020; Kuper et al. 2020; Lopez de Lara et al. 2020) provided evidence relating to the impact on depression in children and adolescents with gender dysphoria, with follow-up of around 12 months. Five different outcome measures for depression were reported. **Beck Depression Inventory (BDI-II)** One uncontrolled, prospective, analytical study (Lopez de Lara et al. 2020) reported the change in BDI-II. The BDI-II is a valid, reliable, and widely used tool for assessing depressive symptoms. There are no specific scores to categorise depression severity, but it is suggested that 0 to 13 is minimal symptoms, 14 to 19 is mild depression, 20 to 28 is moderate depression, and severe depression is 29 to 63. In Lopez de Lara et al. 2020 (n=23) the mean (±SD) BDI-II score was statistically significantly reduced (improved) from 19.3 (±5.5) points at baseline to 9.7 (±3.9) points at 12 months (p<0.001) **(VERY LOW)**. **Center for Epidemiologic Studies Depression (CESD-R)** One uncontrolled, prospective, longitudinal study (Achille et al. 2020) reported the change in CESD-R scale. The CESD-R is a valid, widely used tool to assess depressive symptoms. Total score ranges from 0 to 60, with higher scores indicating more depressive symptoms. There are no specific scores to categorise depression severity, although the authors of the study suggest that a total CESD-R score less than 16 suggests no clinical depression.

	In Achille et al. 2020 (n=50), the mean CESD-R score statistically significantly reduced (improved) from 21.4 points at baseline to 13.9 points at about 12 months follow-up (p<0.001; standard deviation not reported) **(VERY LOW)**. **Patient Health Questionnaire (PHQ 9) Modified for Teens** One uncontrolled, prospective, longitudinal study (Achille et al. 2020) reported the change in PHQ 9_Modified for Teens score. The PHQ 9_Modified for Teens is a validated tool to assess depression, dysthymia and suicide risk. The tool consists of 9 questions scored from 0 to 3 (total score 0 to 27), plus an additional 4 questions that are not scored. A score of 0 to 4 suggests no or minimal depressive symptoms, 5 to 9 mild, 10 to 14 moderate, 15 to 19 moderately severe, and 20-27 severe symptoms. In Achille et al. 2020 (n=50), the mean PHQ 9_Modified for Teens score statistically significantly reduced (improved) from baseline to around 12 months follow-up, although absolute scores were not reported numerically (p<0.001). From the visual representation of results, the PHQ-9_Modified for Teens score is about 9 at baseline and about 5 at final follow-up **(VERY LOW)**. **Quick Inventory of Depressive Symptoms (QIDS)** One uncontrolled, prospective, longitudinal study (Kuper et al. 2020) reported the change in QIDS, clinician-reported and self-reported. Both the clinician-reported and self-reported QIDS are validated tools to assess depressive symptoms. The tool consists of 16 items, with the highest score for 9 domains (sleep, weight, psychomotor changes, depressed mood, decreased interest, fatigue, guilt, concentration, and suicidal ideation) added to give a total score ranging from 0 to 27. A score of 0 to 5 suggests no depression, 6 to 10 mild symptoms, 11 to 15 moderate symptoms, 16 to 20 severe symptoms, and 21 to 27 very severe symptoms. In Kuper et al. 2020 (n=105), the mean (±SD) QIDS self-reported score was 9.6 points (±5.0) at baseline and 7.4 (±4.5) after 10.9 months of treatment with gender-affirming hormones (no statistical analysis reported). The mean (±SD) QIDS clinician-reported score was 5.9 points (±4.1) at baseline and 6.0 (±3.8) after 10.9 months of treatment with gender-affirming hormones (no statistical analysis was reported) **(VERY LOW)**. **Participants needing treatment for depression** One observational study (Kaltiala et al. 2020) reported the proportion of participants needing treatment for depression before or during the initial assessment and during the 12-month follow-up period after starting gender-affirming hormones. In Kaltiala et al. 2020 (n=52), statistically significantly fewer participants needed treatment for depression during the 12-month 'real life' phase (15%, 8/52) compared with before or during the assessment (54%, 28/52; p<0.001). No details of what treatments for depression the participants received are reported **(VERY LOW)**.

	These studies provide very low certainty evidence that during treatment with gender-affirming hormones depression is reduced from baseline to about 12 months follow-up. However, most participants had mild symptoms at the start of treatment.
Impact on mental health: anxiety **Certainty of evidence: very low**	This is a critical outcome because anxiety may impact on social, occupational, or other areas of functioning in children and adolescents. Three observational studies (Kaltiala et al. 2020; Kuper et al. 2020; Lopez de Lara et al. 2020) provided evidence relating to the impact on anxiety in children and adolescents with gender dysphoria. **State-Trait Anxiety Inventory (STAI)** One uncontrolled, prospective, analytical study (Lopez de Lara et al. 2020) reported the change in STAI scores. STAI is a validated and commonly used measure of trait and state anxiety. It has 20 items and can be used in clinical settings to diagnose anxiety and to distinguish it from depressive illness. Higher scores indicate greater anxiety. In Lopez de Lara et al. 2020 (n=23), the mean (±SD) STAI-State subscale was statistically significantly reduced (improved) with gender-affirming hormones from 33.3 points (±9.1) at baseline to 16.8 points (±8.1) at 12 months (p<0.001). The mean STAI-Trait subscale scores also statistically significantly reduced (improved) from 33.0 points (±7.2) at baseline to 18.5 points (±8.4) at 12 months (p<0.001) **(VERY LOW)**. **Screen for Child Anxiety Related Emotional Disorders (SCARED)** One uncontrolled, prospective, longitudinal study (Kuper et al. 2020) reported anxiety symptoms using the SCARED questionnaire. Other anxiety-related symptoms using specific questions from the SCARED questionnaire were also reported: panic, generalised anxiety, social anxiety, separation anxiety and school avoidance. SCARED is a validated, 41-point questionnaire, with each item scored 0 to 2. A total score of 25 or more is suggestive of anxiety disorder, with scores above 30 being more specific. Certain scores for specific questions may indicate the presence of other anxiety-related disorders: • A score of 7 or more in questions related to panic disorder or significant somatic symptoms may indicate the presence of these. • A score of 9 or more in questions related to generalised anxiety disorder may indicate the presence of this. • A score of 5 or more in questions related to separation anxiety may indicate the presence of this. • A score of 8 or more in questions related to social anxiety disorder may indicate the presence of this. • A score of 3 or more in questions related to significant school avoidance may indicate the presence of this. In Kuper et al. 2020 (n=80 to 82, varies by outcome), small reductions were seen in anxiety, panic, generalised anxiety, social anxiety and separation anxiety and school avoidance symptoms (measured using the SCARED questionnaire) from baseline to follow-up (mean duration of treatment 10.9 months). The statistical significance of these findings are unknown as no statistical analyses were reported **(VERY LOW)**.

	Participants needing treatment for anxiety One observational study (Kaltiala et al. 2020) reported the proportion of participants needing treatment for anxiety before or during initial assessment and during the 12-month follow-up period after starting gender-affirming hormones. In Kaltiala et al. 2020 (n=52), statistically significantly fewer participants needed treatment for anxiety during the 12-month 'real life' phase (15%, 8/52) compared with before or during the assessment (48%, 25/52; p<0.001). No details of what treatments for anxiety the participants received are reported **(VERY LOW)**. **These studies provide very low certainty evidence that during treatment with gender-affirming hormones anxiety symptoms may be reduced from baseline to around 12 months follow-up.**
Impact on mental health: suicidality and self-injury **Certainty of evidence: very low**	These are critical outcomes because self-harm and thoughts of suicide have the potential to result in significant physical harm and, for completed suicides, the death of the young person. Four observational studies (Achille et al. 2020; Allen et al. 2019; Kaltiala et al. 2020; Kuper et al. 2020) provided evidence relating to suicidal ideation in children and adolescents with gender dysphoria, with an average follow-up of around 12 months. **Ask Suicide-Screening Questions (ASQ)** One uncontrolled, retrospective, longitudinal study (Allen et al. 2019) reported the change in ASQ. This is a 4-item dichotomous (yes/no) response measure designed to identify risk of suicide. The authors of Allen et al. 2019 amended 1 question in the ASQ ("*Have you ever tried to kill yourself?*") by prefacing it with "*In the past few weeks . . .*" as they were not investigating lifetime incidence. A response of 'no' is scored as 0 and a response of 'yes' is scored as 1; each item is summed to give an overall score for suicidal ideation ranging from 0 to 4. A person is considered to have screened positive if they answer 'yes' to any item with higher scores indicating higher levels of suicidal ideation. In Allen et al. 2019 (n=39), the adjusted mean (±SE) ASQ score statistically significantly reduced from 1.11 points (±0.22) at baseline to 0.27 points (±0.12) after a mean duration of treatment of about 12 months (p<0.001) **(VERY LOW)**. **PHQ 9_Modified for Teens (additional questions for suicidal ideation)** One uncontrolled, prospective, longitudinal study (Achille et al. 2020) reported the change in suicidal ideation measured using additional questions from the PHQ 9_Modified for Teens. This is a validated tool to assess depression, dysthymia and suicide risk (see above for detailed description). In addition to the 9 scored questions, the PHQ 9_Modified Teens asked 4 additional questions relating to suicidal ideation and difficulty dealing with problems of life. Responses to the PHQ 9_Modified for Teens were used to determine if the participant had suicidal ideation or not, but specific details of how this was determined are not reported.

	In Achille et al. 2020 (n=50), 10% (5/50) of participants had suicidal ideation at baseline and 6% (3/50) had suicidal ideation after about 12 months treatment with gender-affirming hormones (no statistical analysis reported) **(VERY LOW)**. **Suicidality and non-suicidal self-injury** One uncontrolled, prospective, longitudinal study (Kuper et al. 2020) reported on suicidal ideation, suicide attempts and non-suicidal self-injury, although it was unclear how and when this outcome was measured. In Kuper et al. 2020 (n=130), 25% of participants reported suicidal ideation 1 month before the initial assessment and 38% reported this during the follow-up period (no statistical analysis reported). Suicide attempts were reported in 2% of participants at 3 months before the initial assessment and 5% during follow-up. Self-injury was reported in 10% of participants at 3 months before the initial assessment and 17% during follow-up. No statistical analysis was reported for any outcomes. Mean duration of gender-affirming hormone treatment was 10.9 months **(VERY LOW)**. **Participants needing treatment for suicidality or self-harm** One observational study (Kaltiala et al. 2020) reported the proportion of participants requiring treatment for suicidality or self-harm before or during initial assessment and during the 12-month follow-up period after starting gender-affirming hormones. In Kaltiala et al. 2020 (n=52) statistically significantly fewer participants needed treatment for suicidality or self-harm during the 12-month 'real life' phase (4%, 2/52) compared with before or during the assessment (35%, 18/52; p<0.001). No details of what treatments for suicidal ideation or self-harm the participants received are reported **(VERY LOW)**. **These studies provide very low certainty evidence that gender-affirming hormones may reduce suicidality from baseline to about 12 months follow-up. However, results are inconsistent and it is difficult to draw conclusions.**
Impact on mental health: other **Certainty of evidence: very low**	This is a critical outcome because mental health problems may impact on social, occupational, or other areas of functioning in children and adolescents. One observational study (Kaltiala et al. 2020) reported the proportion of participants needing treatment for either psychotic symptoms or psychosis, substance abuse, autism, attention deficit hyperactivity disorder (ADHD) or eating disorders before or during initial assessment and during the 12-month follow-up period after starting gender-affirming hormones. In Kaltiala et al. 2020 (n=52) there was no statistically significant difference in the number of people needing treatment for either psychotic symptoms / psychosis, substance abuse, autism, attention deficit hyperactivity disorder (ADHD) or eating disorders during the 12-month 'real life' phase compared with before or during the assessment.

	No details of which specific treatments the participants received are reported **(VERY LOW)**. **This study provides very low certainty evidence on the need for treatment for either psychotic symptoms or psychosis, conduct problems or antisocial behaviour, substance abuse, autism, attention deficit hyperactivity disorder (ADHD) or eating disorders during treatment with gender-affirming hormones. No conclusions could be drawn.**
Impact on quality of life score **Certainty of evidence: very low**	This is a critical outcome because gender dysphoria in children and adolescents may be associated with a significant reduction in health-related quality of life. Two uncontrolled longitudinal studies Achille et al. 2020; Allen et al. 2019) provided evidence relating to quality of life in children and adolescents with gender dysphoria. **Quality of Life Enjoyment and Satisfaction Questionnaire (QLES-Q-SF)** One uncontrolled, prospective, longitudinal study (Achille et al. 2020) reported the change in QLES-Q-SF scores from baseline to about 12 months of treatment with gender-affirming hormones. QLES-Q-SF is a validated questionnaire, consisting of 15 questions that rate quality of life on a scale of 1 (poor) to 5 (very good). In Achille et al. 2020 (n=50), the mean QLES-Q-SF score was statistically significantly reduced from baseline to about 12 months ($p<0.001$). However, absolute scores are not reported numerically **(VERY LOW)**. **General Well-Being Scale (GWBS) of the Paediatric Quality of Life Inventory** One uncontrolled, retrospective, longitudinal study (Allen et al. 2019) reported the change in adjusted mean GWBS of the Paediatric Quality of Life Inventory score from baseline to about 12 months of treatment with gender-affirming hormones. The GWBS of the Paediatric Quality of Life Inventory contains 7 items that measure two dimensions: general wellbeing (6 items) and general health (1 item). Each item is scored from 0 to 4, and the total score is linearly transformed to a 0 to 100 scale. Higher scores reflect fewer perceived problems and greater well-being. In Allen et al. 2019 (n=47), the adjusted mean (±SE) GWBS of the Paediatric Quality of Life Inventory score was statistically significantly increased (improved) from 61.70 (±2.43) points at baseline to 70.23 (±2.15) points at about 12 months ($p<0.002$) **(VERY LOW)**. **This study provides very low certainty evidence that gender-affirming hormones statistically significantly improve quality of life and well-being from baseline to 12 months follow-up.**
Important outcomes	
Impact on body image	This is an important outcome because some children and adolescents with gender dysphoria may want to take steps to suppress features of

Certainty of evidence: very low	their physical appearance associated with their sex assigned at birth or accentuate physical features of their desired gender. One uncontrolled, prospective, longitudinal study (Kuper et al. 2020) provided evidence relating to the impact on body image in children and adolescents with gender dysphoria who started treatment with gender-affirming hormones (median duration 10.9 months; range 1 to 18), measured by the change in Body Image Scale (BIS) score. BIS is a validated 30-item scale covering 3 aspects: primary, secondary and neutral body characteristics. Higher scores represent a higher degree of body dissatisfaction. In Kuper et al. 2020 (n=86), the mean (±SD) BIS score was 70.7 points (±15.2) at baseline and 51.4 points (±18.3) at follow-up (no statistical analysis reported) **(VERY LOW)**. **This study provides very low certainty evidence on the effects of gender-affirming hormones on body image during treatment with gender-affirming hormones (mean duration of treatment 10.9 months). No conclusions could be drawn.**
Psychosocial impact **Certainty of evidence: very low**	This is an important outcome because gender dysphoria in children and adolescents is associated with internalising and externalising behaviours, and emotional and behavioural problems which may impact on social and occupational functioning. Two uncontrolled, observational studies (Kaltiala et al. 2020; Lopez de Lara et al. 2020) provided evidence related to psychosocial impact in children and adolescents with gender dysphoria. **Family APGAR (Adaptability, Partnership, Growth, Affection and Resolve) test** One uncontrolled, prospective, analytical study (Lopez de Lara et al. 2020) reported the Family APGAR test. The Family APGAR test is a 5-item questionnaire, with higher scores indicating better family functioning. The authors reported the following interpretation of the test: functional, 17 to 20 points; mildly dysfunctional, 16 to 13 points; moderately dysfunctional, 12 to 10 points; severely dysfunctional, <9 points. In Lopez de Lara et al. 2020 (n=23), the mean Family APGAR test score was unchanged from baseline (17.9 points) to 12-month follow-up (18.0 points; no statistical analysis or standard deviations reported) **(VERY LOW)**. **Strengths and Difficulties Questionnaire (SDQ)** One uncontrolled, prospective, analytical study (Lopez de Lara et al. 2020) reported on behaviour using the Strengths and Difficulties Questionnaire (SDQ, Spanish version). The SDQ includes 25-items covering emotional symptoms, conduct problems, hyperactivity/ inattention, peer relationship problems and prosocial behaviour. The authors state that a score of more than 20 suggests having a behavioural disorder (normal 0 to 15, borderline 16 to 19, abnormal 20 to 40).

	In Lopez de Lara et al. 2020 (n=23), the mean (±SD) SDQ score was statistically significantly reduced (improved) from 14.7 points (±3.3) at baseline to 10.3 points (±2.9) at 12-month follow-up (p<0.001) **(VERY LOW)**. **Psychosocial functioning** One uncontrolled, retrospective chart review (Kaltiala et al. 2020) reported various markers of functioning in adolescent development, covering living arrangements, peer contacts, school or work progress, relationships, and ability to cope with matters outside the home. These measures were reported during the gender identity assessment and at about 12 months after starting gender-affirming hormones (referred to as the 'real-life phase'). In Kaltiala et al. 2020 (n=52), from the gender identity assessment to the 12-month follow-up period: • statistically significantly fewer participants were living with parents or guardians (73% versus 40%, p=0.001) • statistically significantly fewer participants had normal peer contacts (89% versus 81%, p<0.001) • there was no statistically significant difference in progress in school or work (64% versus 60%, p=0.69) • there was no statistically significant difference in the number of participants who had been dating or in steady relationships (62% versus 58%, p=0.51) • there was no statistically significant difference in the participant's ability to cope with matters outside of the home (81% versus 81%, p=1.00) **(VERY LOW)**. **These studies provide very low certainty evidence that gender-affirming hormones statistically significantly improve behavioural problems (measured by SDQ score). However, the SDQ score was in the 'normal' range at baseline and at 12-month follow up. There was no significant impact on other measures of psychosocial functioning.**
Engagement with health care services	This is an important outcome because patient engagement with health care services will impact on their clinical outcomes. No evidence was identified.
Impact on extent of and satisfaction with surgery	This is an important outcome because some children and adolescents with gender dysphoria may proceed to transitioning surgery. No evidence was identified.
De-transition	This is an important outcome because there is uncertainty about the short- and long-term safety and adverse effects of gender-affirming hormones in children and adolescents with gender dysphoria No evidence was identified.

Abbreviations: APGAR: Adaptability, Partnership, Growth, Affection and Resolve; ASQ: Ask Suicide-Screening Questions; BDI-II: Beck Depression Inventory II; BIS: Body Image Scale; CESD-R: Center for Epidemiologic Studies Depression; GWBS: General Well-Being Scale; p: p-value; PHQ 9_Modified for Teens: Patient Health Questionnaire Modified for Teens; QIDS: Quick Inventory of Depressive Symptoms; QLES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire; SCARED: Screen for Child Anxiety Related Emotional Disorders;

SD: standard deviation; SE: standard error; SDQ: Strengths and Difficulties Questionnaire; STAI: State-Trait Anxiety Inventory; UGDS: Utrecht Gender Dysphoria Scale.

In children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Outcome	Evidence statement
Safety	
Change in bone density: lumbar spine **Certainty of evidence: very low**	This is an important outcome because childhood and adolescence is a key time for bone development and gender-affirming hormones may affect bone development, as shown by changes in lumbar spine bone density. Three uncontrolled, observational studies (2 retrospective and 1 prospective) provided evidence related to bone density: lumbar spine in children and adolescents with gender dysphoria. This was reported as either bone mineral density (BMD), bone mineral apparent density (BMAD), or both. One study reported change in bone density from start of treatment with gender-affirming hormones to age 22 years (Klink et al. 2015). Two studies reported change in bone density from start of gender-affirming hormones up to 24-month follow-up (Stoffers et al. 2019 and Vlot et al. 2017). All participants had previously been treated with a GnRH analogue. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. **Bone mineral apparent density (BMAD)** Two uncontrolled, observational studies reported change in lumbar BMAD (Klink et al. 2015; Vlot et al. 2017). BMAD is a size adjusted value of BMD, incorporating bone size measurements using a UK reference population of growing cis-gender adolescents (up to age 17 years). BMAD is used to correct for height and height gain and may provide a more accurate estimate of bone density in growing adolescents. BMAD was reported as g/cm^3 and as z-scores. Z-scores report how many standard deviations from the mean a measurement sits. A z-score of 0 is equal to the mean, a z-score of -1 is equal to 1 standard deviation below the mean, and a z-score of +1 is equal to 1 standard deviation above the mean. A cis-gender population was used to calculate the bone density z-score, meaning transfemales were compared with cis-males and transmales were compared with cis-females. In Klink et al. 2015 (n=34): • There was no statistically significant difference in lumbar spine BMAD z-score from starting gender-affirming hormones to age 22 years in transfemales. • The z-score for lumbar spine BMAD was statistically significantly higher at age 22 years compared with the start of gender-affirming hormones in transmales (z-score [±SD]: start of hormones -0.50 [±0.81], age 22 years -0.033 [±0.95], p=0.002).

- Actual lumbar spine BMAD values in g/cm^3 were statistically significantly higher at age 22 years compared with the start of gender-affirming hormones in transfemales and transmales **(VERY LOW)**.

In Vlot et al. 2017 (n=70):

- The z-score for lumbar spine BMAD in transfemales with a bone age of <15 years was statistically significantly higher at 24-month follow-up compared with start of gender-affirming hormones (z-score [range]: start of hormones -1.52 [-2.36 to 0.42], 24-month follow-up -1.10 [-2.44 to 0.69], p≤ 0.05). Statistically significant improvements in z-score for lumbar spine BMAD in transfemales with a bone age of ≥15 years were also seen (z-score [range]: start of hormones -1.15 [-2.21 to 0.08], 24-month follow-up -0.66 [-1.66 to 0.54], p≤ 0.05).
- The z-score for lumbar spine BMAD in transmales with a bone age of <14 years was statistically significantly higher at 24-month follow-up compared with start of gender-affirming hormones (z-score [range]: start of hormones -0.84 [-2.2 to 0.87], 24-month follow-up -0.15 [-1.38 to 0.94], p≤ 0.01). Statistically significant improvements in z-score for lumbar spine BMAD in transmales with a bone age of ≥14 years were also seen (z-score [range]: start of hormones -0.29 [-2.28 to 0.90], 24-month follow-up -0.06 [-1.75 to 1.61], p≤ 0.01).
- Actual lumbar spine BMAD values in g/cm^3 were statistically significantly higher at 24-month follow-up compared with start of gender-affirming hormones in transfemales and transmales of all bone ages **(VERY LOW)**.

Bone mineral density (BMD)

Two uncontrolled, observational studies reported change in lumbar BMD (Klink et al. 2015; Stoffers et al. 2019). BMD was determined using dual energy x-ray absorptiometry (DXA-scan; HologicQDR4500, Hologic). BMD was reported as g/cm^2 and as z-scores – see BMAD above for more details).

In Klink et al. 2015 (n=34):

- There was no statistically significant difference in lumbar spine BMD z-score from starting gender-affirming hormones to age 22 years in transfemales or transmales.
- Actual lumbar spine BMD values in g/cm^2 were statistically significantly higher at age 22 years compared with the start of gender-affirming hormones in transfemales and transmales **(VERY LOW)**.

In Stoffers et al. 2019 (n=62 at 6-month follow-up; n=15 at 24-month follow-up):

- There was no statistically significant difference in lumbar spine BMD z-score in transmales from starting gender-affirming hormones to any timepoint (6, 12 and 24 months).
- There was also no statistically significant difference in actual lumbar spine BMD values in g/cm^2 from starting gender-affirming hormones to any timepoint (6, 12 and 24 months) **(VERY LOW)**.

	These studies provide very low certainty evidence that lumber spine bone density (measured by BMAD) increases during treatment with gender-affirming hormones (from baseline to follow-up of 2 to 5 years). Z-scores at the end of follow-up suggest the average lumbar spine bone density was generally lower than the equivalent cisgender population (transfemales compared with cis-males and transmales compared with cis-females). The results for bone density (measured by BMD) were inconsistent.
Change in bone density: femoral neck **Certainty of evidence: very low**	This is an important outcome because childhood and adolescence is a key time for bone development and gender-affirming hormones may affect bone development, as shown by changes in femoral neck bone density. Three uncontrolled, observational studies (2 retrospective and 1 prospective) provided evidence related to bone density: femoral neck in children and adolescents with gender dysphoria. This was reported as either bone mineral density (BMD), bone mineral apparent density (BMAD), or both. One study reported change in bone density from start of gender-affirming hormones to age 22 years (Klink et al. 2015). Two studies reported change in bone density from start of gender-affirming hormones up to 24-month follow-up (Stoffers et al. 2019 and Vlot et al. 2017). All participants had previously been treated with a GnRH analogue. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. **Bone mineral apparent density (BMAD)** Two uncontrolled, observational studies reported change in femoral neck BMAD (Klink et al. 2015; Vlot et al. 2017). See above for more details on BMAD. In Klink et al. 2015 (n=34): • The z-score for femoral neck BMAD was reported for the start of gender-affirming hormones but not at age 22 years in transfemales or transmales. No statistical analysis reported. • In transfemales there was no statistically significant difference in actual femoral neck BMAD values in g/cm^3 at age 22 years compared with start of gender-affirming hormones. In transmales actual lumbar spine BMAD values in g/cm^3 were statistically significantly higher at age 22 years compared with start of gender-affirming hormones (mean [±SD]: start of hormones 0.31 [±0.04], age 22 years 0.33 [±0.05], p=0.010) **(VERY LOW)**. In Vlot et al. 2017 (n=70): • In transfemales (all bone ages), there was no statistically significant difference in femoral neck BMAD z-score from start of gender-affirming hormones to 24-month follow-up. • The z-score for femoral neck BMAD in transmales with a bone age of <14 years was statistically significantly higher at 24-month follow-up compared with start of gender-affirming hormones (z-score [range]: start of hormones -0.37 [-2.28 to 0.47], 24-month follow-up -0.37 [-2.03 to 0.85], p≤0.01). Statistically significant improvements in z-score for lumbar spine BMAD in transmales with a bone age of ≥14 years were also

	seen (z-score [range]: start of hormones -0.27 [-1.91 to 1.29], 24-month follow-up 0.02 [-2.1 to 1.35], p≤0.05). • In transfemales of all bone ages, there was no statistically significant change in actual femoral neck BMAD values in g/cm^3 from start of gender-affirming hormones to 24-month follow-up. In transmales of all bone ages, actual femoral neck BMAD values in g/cm^3 were statistically significantly higher at 24-month follow-up compared with start of gender-affirming hormones **(VERY LOW)**. **Bone mineral density (BMD)** Two uncontrolled, observational studies reported change in femoral neck BMD (Klink et al. 2015; Stoffers et al. 2019). See above for more details on BMD. In Klink et al. 2015 (n=34): • In transfemales, there was no statistically significant difference in femoral neck BMD z-score from start of gender-affirming hormones to age 22 years. In transmales, femoral neck BMD z-score was statistically significantly higher at age 22 years compared with start of gender-affirming hormones (z-score [SD]: start of hormones -0.35 [0.79], age 22 years -0.35 [0.74], p=0.006). • Actual femoral neck BMD values in g/cm^2 were statistically significantly higher at age 22 years compared with start of gender-affirming hormones in transfemales and transmales **(VERY LOW)**. In Stoffers et al. 2019 (n=62 at 6-month follow-up; n=15 at 24-month follow-up): • there was no statistically significant difference in right or left femoral neck BMD z-score in transmales, from the start of gender-affirming hormones to any timepoint (6, 12 and 24 months). • There was also no statistically significant difference in transmales in right or left actual femoral neck BMD values in g/cm^2 from start of gender-affirming hormones to any timepoint (6, 12 and 24 months) **(VERY LOW)**. **These studies provide very low certainty evidence that during treatment with gender-affirming hormones from baseline to follow-up of 2 to 5 years, femoral neck bone density (measured by BMAD) was unchanged in transfemales but was statistically significantly increased in transmales (although the absolute change was small). Z-scores at the end of follow-up suggest that average femoral neck bone density was lower in both transfemales and transmales than in the equivalent cisgender population (transfemales compared with cis-males and transmales compared with cis-females). The results for bone density (measured by BMD) were inconsistent.**
Change in clinical parameters: glucose, insulin and HbA1c	This is an important outcome because the effect of gender-affirming hormones on insulin sensitivity and cardiovascular risk in children and adolescents with gender dysphoria is unknown.

Certainty of evidence: very low	Two uncontrolled, retrospective chart reviews (Klaver et al. 2020; Stoffers et al. 2019) provided evidence on glucose, insulin and HbA1c. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. **Glucose levels, insulin levels and insulin resistance** One retrospective chart review (Klaver et al. 2020) reported non-comparative evidence on the change in glucose levels, insulin levels and insulin resistance (measured using Homeostatic Model Assessment of Insulin Resistance [HOMA-IR]) between starting gender-affirming hormones and age 22 years. In Klaver et al. 2020 (n=192): • There was no statistically significant change in glucose levels, insulin levels and insulin resistance in transfemales. • There was no statistically significant change in glucose levels in transmales. • There was a statistically significant decrease in insulin levels in transmales (mean change [95% CI] -2.1 mU/L [-3.9 to -0.3], p<0.05; mean insulin level at 22 years [95% CI] 8.6 mU/L [6.9 to 10.2]). • There was a statistically significant decrease in insulin resistance in transmales (HOMA-IR; mean change [95% CI] -0.5 [-1.0 to -0.1], p<0.05; mean HOMA-IR at 22 years [95% CI] 1.8 [1.4 to 2.2]) **(VERY LOW)**. **HbA1c** One retrospective chart review (Stoffers et al. 2019; n=62) reported non-comparative evidence on the change in HbA1c in transmales between starting gender-affirming hormones and 24-month follow-up. There was no statistically significant change in HbA1c **(VERY LOW)**. **These studies provide very low certainty evidence that gender-affirming hormones do not affect HbA1c, glucose levels, insulin levels and insulin resistance.**
Change in clinical parameters: lipids **Certainty of evidence: very low**	This is an important outcome because the effect of gender-affirming hormones on lipid profiles and cardiovascular risk in children and adolescents with gender dysphoria is unknown. One retrospective chart review (Klaver et al. 2020) provided non-comparative evidence on the change in lipids (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides) between starting gender-affirming hormones and age 22 years. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. In Klaver et al. 2020 (n=192): • There was no statistically significant change in total cholesterol, HDL cholesterol and LDL cholesterol in transfemales. • There was a statistically significant decrease (improvement) in triglycerides in transfemales (mean change [95% CI] +0.2 mmol/L [0.0 to 0.5], p<0.05; mean triglyceride level at 22 years [95% CI] 1.1 mmol/L [0.9 to 1.4]). • There was a statistically significant increase in total cholesterol in transmales (mean change [95% CI] +0.4 mmol/L [0.2 to 0.6],

	p<0.001; mean total cholesterol at 22 years [95% CI] 4.6 mmol/L [4.3 to 4.8]). • There was a statistically significant decrease (worsening) in HDL cholesterol (mean change in transmales [95% CI] -0.3 mmol/L [-0.4 to -0.1], p<0.001; mean HDL cholesterol at 22 years [95% CI] 1.3 mmol/L [1.2 to 1.3]). • There was a statistically significant increase (worsening) in LDL cholesterol in transmales (mean change [95% CI] +0.4 mmol/L [0.2 to 0.6], p<0.001; mean LDL cholesterol at 22 years [95% CI] 2.6 mmol/L [2.4 to 2.8]). • There was a statistically significant increase (worsening) in triglycerides in transmales (mean change [95% CI] +0.5 mmol/L [0.3 to 0.7], p<0.001; mean triglyceride level at 22 years [95% CI] 1.3 mmol/L [1.1 to 1.5]) **(VERY LOW)**. **This study provides very low certainty evidence that gender-affirming hormones do not affect lipid profiles in transfemales. In transmales, there was a small but statistically significant worsening in cholesterol levels from start of gender-affirming hormone treatment to age 22 years, but mean cholesterol and triglyceride levels were within the UK reference range at the end of treatment.**
Change in clinical parameters: blood pressure **Certainty of evidence: very low**	This is an important outcome because the effect of gender-affirming hormones on blood pressure and cardiovascular risk in children and adolescents with gender dysphoria is unknown. One retrospective chart review (Klaver et al. 2020) provided non-comparative evidence on the change in blood pressure between starting gender-affirming hormones and at age 22 years. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. In Klaver et al. 2020 (n=192): • There was no statistically significant change in systolic blood pressure (SBP) in transfemales. However, there was a statistically significant increase in diastolic blood pressure (DBP) in transfemales (mean change [95% CI] +6 mmHg [3 to 10], p<0.001; mean DBP at 22 years [95% CI] 75 [72 to 78]). • In transmales, there was a statistically significant increase in SBP (mean change [95% CI] +5 mmHg [1 to 9], p<0.05; mean SBP at 22 years [95% CI] 126 [122 to 130]), and DBP (mean change [95% CI] +6 mmHg [4 to 9], p<0.001; mean DBP at 22 years [95% CI] 74 [72 to 77]) **(VERY LOW)**. **This study provides very low certainty evidence that gender-affirming hormones statistically significantly increase blood pressure from start of treatment to age 22 years, although the absolute increase was small.**
Change in clinical parameters: body mass index (BMI)	This is an important outcome because the effect of gender-affirming hormones on weight gain and cardiovascular risk in children and adolescents with gender dysphoria is unknown. One retrospective chart review (Klaver et al. 2020) provided non-comparative evidence on the change in body mass index (BMI) between starting gender-affirming hormones and age 22 years. All

Certainty of evidence: very low	outcomes were reported separately for transfemales and transmales; also see subgroups table below. In Klaver et al. 2020 (n=192): • There was a statistically significant increase in BMI in transfemales from the start of gender-affirming hormones to age 22 years (mean change [95% CI] +1.9 [0.6 to 3.2], p<0.005; mean BMI at 22 years [95% CI] 23.2 [21.6 to 24.8]. At age 22 years, 9.9% of transfemales were obese, compared with 3.0% in a reference population of cisgender men. • There was a statistically significant increase in BMI in transmales from the start of gender-affirming hormones to age 22 years (mean change [95% CI] +1.4 [0.8 to 2.0], p<0.005; mean BMI at 22 years [95% CI] 23.9 [23.0 to 24.7]). At age 22 years, 6.6% of transmales were obese, compared with 2.2% in a reference population of cisgender women **(VERY LOW)**. **This study provides very low certainty evidence that gender-affirming hormones statistically significantly increase BMI from start of treatment to age 22 years, although most participants were within the healthy weight range.**
Change in clinical parameters: liver function **Certainty of evidence: very low**	This is an important outcome because if treatment-induced liver injury (raised liver enzymes are a marker of this) is suspected, gender-affirming hormones may need to be stopped. One retrospective chart review (Stoffers et al. 2019) provided non-comparative evidence on the change in liver enzymes in transmales between starting gender-affirming hormones and up to 24-months follow-up. In Stoffers et al. 2019 (n=62): • There was no statistically significant change in aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyltransferase (GCT) in transmales. • There was a statistically significant increase in alkaline phosphatase (ALP) levels from starting gender-affirming hormones to 6- and 12-months follow-up, although by 24-months the difference was not statistically significant (median [IQR]: start of hormones 102 [78 to 136], 6-month follow-up 115 [102 to 147] p<0.001, 12-month follow-up 112 [88 to 143] p<0.001) **(VERY LOW)**. **This study provides very low certainty evidence that gender-affirming hormones do not affect liver function in transmales from baseline to 24 months follow-up.**
Change in clinical parameters: kidney function **Certainty of evidence: very low**	This is an important outcome because if renal damage (raised serum creatinine and urea are markers of this) is suspected, treatment with gender-affirming hormones may need to be stopped. One retrospective chart review (Stoffers et al. 2019) provided non-comparative evidence on the change in serum creatinine and serum urea levels in transmales between starting gender-affirming hormones and up to 24-months follow-up. In Stoffers et al. 2019 (n=62):

	• There was a statistically significant increase in creatinine levels in transmales at all timepoints up to 24 months (mean [SD]: start of hormones 62 umol/L [7], 6 months 70 umol/L [9] , 12 months 74 umol/L [10], 24 months 81 umol/L [10], p<0.001). • There was no statistically significant change in urea in transmales (follow-up duration not reported) **(VERY LOW)**. **This study provides very low certainty evidence on the effects of gender-affirming hormones on kidney function in transmales from baseline to 24 months follow-up. A statistically significant increase in creatinine levels was seen, but these were within the UK reference range. Urea levels were unchanged.**

Treatment discontinuation
 	
Certainty of evidence: very low
	This is an important outcome because there is uncertainty about the short- and long-term impact of stopping treatment with gender-affirming hormones in children and adolescents with gender dysphoria.
	
	One uncontrolled, retrospective chart review (Khatchadourian et al. 2014) provided evidence relating to permanent or temporary treatment discontinuation in children and adolescents with gender dysphoria.
	
	Khatchadourian et al. 2014 narratively reported treatment discontinuation in a cohort of 63 adolescents (24 transfemales and 39 transmales) who received gender-affirming hormones:
	• No participants permanently discontinued gender-affirming hormones.
	• No transfemales temporarily discontinued gender-affirming hormones.
	• Three transmales temporarily discontinued gender-affirming hormones due to:
	  ○ mental health comorbidities (n=2)
	  ○ androgenic alopecia (n=1).
	All 3 participants eventually resumed treatment, although timescales were not reported **(VERY LOW)**.
	
	This study provides very low certainty evidence that the rates of discontinuation during treatment with gender-affirming hormones are low (duration of treatment not reported).

Adverse effects
 	
Certainty of evidence: very low
	This is an important outcome because if there are adverse effects, gender-affirming hormones may need to be stopped.
	
	One uncontrolled, retrospective chart review (Khatchadourian et al. 2014) provided evidence relating to adverse effects from gender-affirming hormones in children and adolescents with gender dysphoria.
	
	Khatchadourian et al. 2014 narratively reported adverse effects in a cohort of 63 adolescents (24 transfemales and 39 transmales) receiving treatment with gender-affirming hormones:
	• No severe complications were reported.
	• No transfemales reported minor complications.
	• Twelve transmales developed minor complications, which were:
	  ○ severe acne, requiring isotretinoin treatment (n=7)
	  ○ androgenic alopecia (n=1)
	  ○ mild dyslipidaemia (further details not provided; n=3)
	  ○ significant mood swings (n=1) **(VERY LOW)**.

	This study provides very low certainty evidence about the potential adverse effects of gender-affirming hormones (duration of treatment not reported). No conclusions could be drawn.

Abbreviations: ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMAD: bone mineral apparent density; BMD: bone mineral density; BMI: body mass index; DBP: diastolic blood pressure; GGT: gamma-glutamyl transferase; HbA1c: glycated haemoglobin; HDL: high-density lipoproteins; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; IQR: interquartile range; LDL: low-density lipoproteins; p: p-value; SBP: systolic blood pressure; SD: standard deviation.

In children and adolescents with gender dysphoria, what is the cost-effectiveness of gender-affirming hormones compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Outcome	Evidence statement
Cost-effectiveness	No studies were identified to assess the cost-effectiveness of gender-affirming hormones for children and adolescents with gender dysphoria.

From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may benefit from gender-affirming hormones more than the wider population of interest?

Subgroup	Evidence statement
Sex assigned at birth males (transfemales) **Certainty of evidence: Very low**	Some studies reported data separately for sex assigned at birth males (transfemales). This included some direct comparisons with sex assigned at birth females (transmales). **Impact on mental health: depression and anxiety** One uncontrolled, prospective, longitudinal study (Kuper et al. 2020) reported the change in depression (measured using QIDS clinician-reported and self-reported), anxiety and anxiety-related symptoms (measured using SCARED) in transfemales. See the clinical effectiveness results above for full details. In Kuper et al. 2020 (n=33 to 45, varies by outcome), changes were seen in depression, anxiety and anxiety-related symptoms from baseline to follow-up but the authors did not report any statistical analyses, so it is unclear if was any changes were statistically significant **(VERY LOW)**. **This study provides very low certainty evidence on the effects of gender-affirming hormones on depression, anxiety and anxiety-related symptoms over time in sex assigned at birth males (transfemales; mean duration of treatment 10.9 months). No conclusions could be drawn.** **Impact on mental health: suicidality**

	One uncontrolled, retrospective, longitudinal study (Allen et al. 2019) reported the change in Ask Suicide-Screening Questions (ASQ) in transfemales compared with transmales. See the clinical effectiveness results above for full details. Between baseline and the final assessment, there was no statistically significant difference in change in ASQ score for transfemales compared with transmales (p=0.79; n=47) **(VERY LOW)**. One uncontrolled, prospective, longitudinal study (Achille et al. 2020) reported the change in suicidal ideation in transfemales measured using additional questions from the PHQ 9_Modified for Teens. See the clinical effectiveness results above for full details. At baseline, 11.8% (2/17) of transfemales had suicidal ideation, compared with 5.9% (1/17) at about 12-months follow-up (no statistical analysis reported) **(VERY LOW)**. **These studies provide very low certainty evidence that any change in suicidal ideation is not different between sex assigned at birth males (transfemales) and sex assigned at birth females (transmales) from baseline to follow-up of about 12 months.** **Impact on quality of life** One uncontrolled, retrospective, longitudinal study (Allen et al. 2019) reported the change in the GWBS of the Paediatric Quality of Life Inventory in transfemales compared with transmales. See the clinical effectiveness results above for full details. Between baseline and final assessment, there was no statistically significant difference in change in GWBS of the Paediatric Quality of Life Inventory for transfemales compared with transmales (p=0.32; n=47) **(VERY LOW)**. **This study provides very low certainty evidence that any change in general wellbeing is not different between sex assigned at birth males (transfemales) and sex assigned at birth females (transmales) from baseline to follow-up of about 12 months.** **Impact on body image** One uncontrolled, prospective, longitudinal study (Kuper et al. 2020) reported change in Body Image Scale (BIS) in transfemales. See the clinical effectiveness results above for full details. In Kuper et al. 2020 (n=30), the mean (±SD) BIS score was 67.5 points (±19.5) at baseline and 49.0 points (±21.6) at follow-up (no statistical analysis reported) **(VERY LOW).** **This study provides very low certainty evidence on the effects of gender-affirming hormones on body image over time in transfemales (mean duration of treatment 10.9 months). No conclusions could be drawn.** **Change in bone density: lumbar spine**

	Two uncontrolled, observational, retrospective studies provided evidence relating to the effect of gender-affirming hormones on lumber spine bone density in transfemales (Klink et al. 2015 and Vlot et al. 2017). See the safety results table above for a full description of the results. **These studies provide very low certainty evidence that lumbar spine bone density (measured by BMAD) increases during treatment with gender-affirming hormones in sex assigned at birth males (transfemales). Z-scores at the end of follow-up suggest average lumbar spine bone density was generally lower than in the equivalent cisgender population. The results for lumbar spine bone density (measured by BMD) were inconsistent.** **Change in bone density: femoral neck** Two uncontrolled, observational, retrospective studies provided evidence relating to the effect of gender-affirming hormones on femoral neck bone density in transfemales (Klink et al. 2015 and Vlot et al. 2017). See the safety results table above for a full description of the results. **These studies provide very low certainty evidence that femoral neck bone density (measured by BMAD) was unchanged in sex assigned at birth males (transfemales) during treatment with gender-affirming hormones (follow-up between 2 and 5 years). Z-scores at the end of follow-up suggest and the average femoral neck bone density was lower than in the equivalent cisgender population. The results for femoral neck bone density (measured by BMD) were inconsistent.** **Change in clinical parameters: glucose, insulin and HbA1c** One uncontrolled, retrospective chart review (Klaver et al. 2020) provided evidence on glucose, insulin and HbA1c in transfemales. See the safety results table above for a full description of the results. **This study provided very low certainty evidence that gender-affirming hormones do not affect HbA1c, glucose levels, insulin levels and insulin resistance in sex assigned at birth males (transfemales) from the start of treatment to age 22 years.** **Change in clinical parameters: lipids** One retrospective chart review (Klaver et al. 2020) provided evidence on the change in lipids (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides) in transfemales. See the safety results table above for a full description of the results. **This study provides very low certainty evidence that gender-affirming hormones do not affect lipid profiles in sex assigned at birth males (transfemales) from the start of treatment to age 22 years.** **Change in clinical parameters: blood pressure**

	One retrospective chart review (Klaver et al. 2020) provided evidence on the change in blood pressure in transfemales. See the safety results table above for a full description of the results. **This study provides very low certainty evidence that gender-affirming hormones statistically significantly increase blood pressure in sex assigned at birth males (transfemales), although the absolute increase was small from the start of treatment to age 22 years.** **Change in clinical parameters: body mass index (BMI)** One retrospective chart review (Klaver et al. 2020) provided evidence on the change in BMI in transfemales. See the safety results table above for a full description of the results. **This study provides very low certainty evidence that gender-affirming hormones statistically significantly increase BMI in sex assigned at birth males (transfemales), although most participants were within the healthy weight range from the start of treatment to age 22 years.** **Treatment discontinuation** One uncontrolled, retrospective chart review provided evidence relating to permanent or temporary discontinuation of gender-affirming hormones in transfemales (Khatchadourian et al. 2014). **This study provides very low certainty evidence that the rates of discontinuation during treatment with gender-affirming hormones in sex assigned at birth males (transfemales) are low. Duration of treatment with gender-affirming hormones was not reported.** **Adverse effects** One uncontrolled, retrospective chart review provided evidence relating to adverse effects from gender-affirming hormones in transfemales (Khatchadourian et al. 2014). **This study provides very low certainty evidence about the potential adverse effects of gender-affirming hormones in sex assigned at birth males (transfemales). No conclusions could be drawn. Duration of treatment with gender-affirming hormones was not reported.**
Sex assigned at birth females (transmales) **Certainty of evidence: Very low**	Some studies reported data separately for sex assigned at birth females (transmales). This included some direct comparisons with sex assigned at birth males (transfemales). **Impact on mental health: depression and anxiety** One uncontrolled, prospective, longitudinal study (Kuper et al. 2020) reported the change in depression (measured using QIDS clinician-reported and self-reported), anxiety and anxiety-related symptoms (measured using SCARED) in transmales. See the clinical effectiveness results above for full details. In Kuper et al. 2020 (n=65 to 78, varies by outcome), changes were seen in depression, anxiety and anxiety-related symptoms from

	baseline to follow-up but the authors did not report any statistical analysis, so it is unclear if any changes are statistically significant **(VERY LOW)**. **This study provides very low certainty evidence on the effects of gender-affirming hormones on depression, anxiety and anxiety-related symptoms over 10.9 months in transmales. No conclusions could be drawn.** **Impact on mental health: suicidality** One uncontrolled, retrospective, longitudinal study (Allen et al. 2019) reported the change in Ask Suicide-Screening Questions (ASQ) in transmales compared with transfemales. See the sex assigned at birth males (transfemales) row above for full details of the results. One uncontrolled, prospective, longitudinal study (Achille et al. 2020) reported the change in suicidal ideation in transmales measured using additional questions from the PHQ 9_Modified for Teens. See the clinical effectiveness results above for full details. At baseline, 9.1% (3/33) of transmales had suicidal ideation, compared with 6.1% (2/33) at about 12-months follow-up (no statistical analysis reported) **(VERY LOW)**. **These studies provide very low certainty evidence that any change in suicidal ideation is not different between sex assigned at birth females (transmales) and sex assigned at birth males (transfemales). Mean duration of treatment about 12 months.** **Impact on quality of life** One uncontrolled, retrospective, longitudinal study (Allen et al. 2019) reported the change in the GWBS of the Paediatric Quality of Life Inventory in transmales compared with transfemales. See the sex assigned at birth males (transfemales) row above for full details of the results. **This study provides very low certainty evidence that any change in general wellbeing is not different between sex assigned at birth females (transmales) and sex assigned at birth males (transfemales). Mean duration of treatment about 12 months.** **Impact on body image** One uncontrolled, prospective, longitudinal study (Kuper et al. 2020) reported change in Body Image Scale (BIS) in transmales. See the clinical effectiveness results above for full details. In Kuper et al. 2020 (n=66), the mean (±SD) BIS score was 71.1 points (±13.4) at baseline and 52.9 points (±16.8) at follow-up (no statistical analysis reported) **(VERY LOW)**. **This study provides very low certainty evidence on the effects of gender-affirming hormones on body image over 10.9 months in transmales. No conclusions could be drawn.** **Change in bone density: lumbar spine**

	Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of gender-affirming hormones on lumber spine bone density in transmales (Klink et al. 2015, Stoffers et al. 2019 and Vlot et al. 2017). See the safety results table above for a full details of the results. **These studies provide very low certainty evidence that lumbar spine bone density (measured by BMAD) increases during 2 to 5 years treatment with gender-affirming hormones in sex assigned at birth females (transmales). Z-scores at the end of follow-up suggest the average lumbar spine bone density was generally lower than in the equivalent cisgender population. The results for lumbar spine bone density (measured by BMD) were inconsistent.** **Change in bone density: femoral neck** Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of gender-affirming hormones on femoral neck bone density in transmales (Klink et al. 2015, Stoffers et al. 2019 and Vlot et al. 2017). See the safety results table above for a full details of the results. **These studies provide very low certainty evidence that femoral neck bone density (measured by BMAD) statistically significantly increased in sex assigned at birth females (transmales) during 2 to 5 years treatment with gender-affirming hormones. Z-scores at the end of follow-up suggest the average femoral neck bone density was generally lower than in the equivalent cisgender population. The results for femoral neck bone density (measured by BMD) were inconsistent.** **Change in clinical parameters: glucose, insulin and HbA1c** Two uncontrolled, retrospective chart reviews (Klaver et al. 2020; Stoffers et al. 2019) provided evidence on glucose, insulin and HbA1c in transmales. See the safety results table above for full details of the results. **This study provided very low certainty evidence that gender-affirming hormones do not affect HbA1c, glucose levels, insulin levels and insulin resistance in sex assigned at birth females (transmales). Reported from start of treatment to age 22 years.** **Change in clinical parameters: lipids** One retrospective chart review (Klaver et al. 2020) provided evidence on the change in lipids (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides) in transmales. See the safety results table above for full details of the results. **This study provides very low certainty evidence that treatment with gender-affirming hormones is associated with a small but statistically significant worsening of cholesterol levels in sex assigned at birth females (transmales), but mean cholesterol and triglyceride levels were within the UK reference range at end of treatment, from start of treatment to age 22 years.**

	Change in clinical parameters: blood pressure One retrospective chart review (Klaver et al. 2020) provided evidence on the change in blood pressure in transmales. See the safety results table above for full details of the results. **This study provides very low certainty evidence that gender-affirming hormones statistically significantly increase blood pressure in sex assigned at birth females (transmales), although the absolute increase was small, from start of treatment to age 22 years.** **Change in clinical parameters: body mass index (BMI)** One retrospective chart review (Klaver et al. 2020) provided evidence on the change in body mass index (BMI) in transmales. See the safety results table above for full details of the results. **This study provides very low certainty evidence that gender-affirming hormones statistically significantly increase BMI in sex assigned at birth females (transmales), although most participants were within the healthy weight range, from start of treatment to age 22 years.** **Change in clinical parameters: liver function** One retrospective chart review (Stoffers et al. 2019) provided non-comparative evidence on the change in liver enzymes in transmales between starting gender-affirming hormones and up to 24-months follow-up. See the safety results table above for full details of the results. **This study provides very low certainty evidence that gender-affirming hormones for about 12 months do not affect liver function in sex assigned at birth females (transmales).** **Change in clinical parameters: kidney function** One retrospective chart review (Stoffers et al. 2019) provided non-comparative evidence on the change in serum creatinine and serum urea levels in transmales between starting gender-affirming hormones and up to 24-months follow-up. See the safety results table above for full details of the results. **This study provides very low certainty evidence on the effects of gender-affirming hormones on kidney function in sex assigned at birth females (transmales). A statistically significant increase in creatinine levels was seen at about 12 months follow-up, but these were within the UK reference range. Urea levels were unchanged.** **Treatment discontinuation** One uncontrolled, retrospective chart review provided evidence relating to permanent or temporary discontinuation of gender-affirming hormones in transmales (Khatchadourian et al. 2014). See the safety results table above for full details of the results. **This study provides very low certainty evidence that the rates of treatment discontinuation with gender-affirming hormones in sex**

	assigned at birth females (transmales) is low. Duration of gender-affirming hormones not reported. **Adverse effects** One uncontrolled, retrospective chart review provided evidence for adverse effects from gender-affirming hormones in transmales (Khatchadourian et al. 2014). See the safety results table above for full details of the results. **This study provides very low certainty evidence about the potential adverse effects of gender-affirming hormones in sex assigned at birth females (transmales). No conclusions could be drawn. Duration of gender-affirming hormones not reported.**
Duration of gender dysphoria	No evidence was identified.
Age at onset of gender dysphoria	No evidence was identified.
Age at onset of puberty	No evidence was identified.
Tanner stage at which GnRH analogue or gender-affirming hormones started	One uncontrolled, prospective, longitudinal study (Kuper et al. 2020) reported the impact of Tanner stage on outcomes, although it is not clear whether this is referring to Tanner stage at initial assessment, at the start of GnRH analogues or at another timepoint.
Diagnosis of autistic spectrum disorder	No evidence was identified.
Diagnosis of a mental health condition	One uncontrolled, prospective, longitudinal study (Achille et al. 2020) reported outcomes that were adjusted for engagement in counselling and medicines for mental health problems. Information about diagnoses and treatment were not provided. Rates of mental health issues appear to be high in the cohort. **Impact on mental health** Achille et al. 2020 reported the change in depression scores, controlled for engagement in counselling and medicines for mental health problems (measured using the Center for Epidemiologic Studies Depression [CESD-R] scale and Patient Health Questionnaire Modified for Teens [PHQ 9_Modified for Teens] score: • There was no statistically significant change in CESD-R from baseline to about 12-months follow-up. • There was no statistically significant change in PHQ 9_Modified for Teens score from baseline to about 12-months follow-up **(VERY LOW)**. **Impact on quality of life** Achille et al. 2020 reported the change in quality of life scores, controlled for engagement in counselling and medicines for mental health problems (measured using the Quality of Life Enjoyment and Satisfaction Questionnaire [QLES-Q-SF] score: • There was no statistically significant change in QLES-Q-SF score from baseline to about 12-months follow-up **(VERY LOW)**.

	This study provides very low certainty evidence about outcomes that were adjusted for engagement in counselling and medicines for mental health problems. No conclusions could be drawn.

Abbreviations: ASQ: Ask Suicide-Screening Questions; CESD-R: Center for Epidemiologic Studies Depression; GnRH: Gonadotrophin releasing hormone; GWBS: General Well-Being Scale; HDL: high-density lipoproteins; LDL: low-density lipoproteins; p: p-value; PHQ 9_Modified for Teens: Patient Health Questionnaire Modified for Teens; QLES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire.

From the evidence selected,

(a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?

(b) what were the ages at which participants commenced treatment with gender-affirming hormones?

(c) what was the duration of treatment with GnRH analogues?

<table>
<tr><th>Outcome</th><th>Evidence statement</th></tr>
<tr><td>Diagnostic criteria</td><td>The DSM-IV-TR criteria was used in 3 studies (Klaver et al. 2020, Klink et al. 2015 and Vlot et al. 2017).

The DSM-V criteria was used in 2 studies (Kuper et al. 2020 and Stoffers et al. 2019). The DSM-V has one overarching definition of gender dysphoria with separate specific criteria for children and for adolescents and adults. The general definition describes a conflict associated with significant distress and/or problems functioning associated with this conflict between the way they feel and think of themselves which must have lasted at least 6 months.

The ICD-10 diagnosis of ‘transsexualism’ was used in 1 study (Kaltiala et al. 2020). The authors state that this is the corresponding diagnosis to ‘gender dysphoria’ in the DSM-V, and that diagnostic assessments in the study location (Finland) take place according to ICD-10.

It was not reported how gender dysphoria was defined in the remaining 4 studies (VERY LOW).

From the evidence selected, the most commonly reported diagnostic criteria for gender dysphoria (5/10 studies) was the DSM criteria in use at the time the study was conducted.</td></tr>
<tr><td>Age when gender-affirming hormones started</td><td>8/10 studies reported the age at which participants started treatment with gender-affirming hormones, either as the mean age (with SD) or median age (with the range):

<table>
<tr><th>Study</th><th>Mean age (± SD)</th></tr>
<tr><td>Allen et al. 2019</td><td>16.7 years (not reported)</td></tr>
<tr><td>Khatchadourian et al. 2014</td><td>17.4 years (1.9)</td></tr>
<tr><td>Klaver et al. 2020</td><td>16.4 years (1.1) in transfemales
16.9 years (0.9) in transmales</td></tr>
<tr><td>Kuper et al. 2020</td><td>16.2 (1.2)</td></tr>
<tr><td>Klink et al. 2015</td><td>16.6 years (1.4) in transfemales
16.4 years (2.3) in transmales</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><th>Study</th><th>Median age (range)</th></tr>
<tr><td>Stoffers et al. 2019</td><td>17.2 years (15 to 19.5)</td></tr>
<tr><td>Vlot et al. 2017</td><td>16.3 years (15.9 to 19.5) in transfemales
16.0 years (14.0 to 18.9) in transmales</td></tr>
</table>

Age at the start of treatment was not reported in 3 studies:
• In Achille et al. 2020 the mean age at initial assessment (baseline) was 16.2 years (SD ±2.2)
• In Kaltiala et al. 2020 the mean age at diagnosis was 18.1 years (range 15.2 to 19.9)
• In Lopez de Lara et al. 2020 the mean age of participants was 16 years (range 14 to 18), although it is not clear if this is at the initial assessment or at the start of gender-affirming hormones.

The evidence included showed that most children and adolescents started treatment with gender-affirming hormones at about 16 to 17 years, with a range of about 14 to 19 years.
</td></tr>
<tr><td>Duration of treatment with GnRH analogues</td><td>
The duration of treatment with GnRH analogues was reported in 3/10 studies:

<table>
<tr><th>Study</th><th>Median duration</th></tr>
<tr><td>Klaver et al. 2020</td><td>2.1 years (IQR 1.0 to 2.7) in transfemales
1.0 years (IQR 0.5 to 2.9) in transmales</td></tr>
<tr><td>Klink et al. 2015</td><td>1.3 years (range 0.5 to 3.8) in transfemales
1.5 years (range 0.25 to 5.2) in transmales
(GnRH analogue monotherapy)</td></tr>
<tr><td>Stoffers et al. 2019</td><td>8 months (range 3 to 39)</td></tr>
</table>

The evidence included showed wide variation in the duration of treatment with gender-affirming hormones, but most studies did not report this information. Treatment duration ranged from a few months up to about 5 years.
</td></tr>
</table>

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders criteria; GnRH, Gonadotrophin-releasing hormone; ICD, International Statistical Classification of Diseases and Related Health Problems; IQR, interquartile range; SD, standard deviation.

6. Discussion

A key limitation to identifying the effectiveness and safety of gender-affirming hormones for children and adolescents with gender dysphoria is the lack of reliable comparative studies. All the studies included in this evidence review are uncontrolled observational studies, which are subject to bias and confounding and were of very low certainty using modified GRADE. The size of the population with gender dysphoria means conducting a prospective trial may be unrealistic, at least on a single centre basis. There may also be ethical issues with a 'no treatment arm' in comparative trials of gender-affirming hormones, where there may be poor mental health outcomes if treatment is withheld. However, the use of an active comparator such as close psychological support may reduce ethical concerns in future trials. A fundamental limitation of all the uncontrolled studies included in this review is that any changes in scores from baseline to follow-up could be attributed to a regression-to-the-mean.

The included studies have relatively short follow-up, with an average duration of treatment with gender-affirming hormones between around 1 year and 5.8 years. Further studies with a longer follow-up are needed to determine the long-term effect of gender-affirming hormones for children and adolescents with gender dysphoria.

Most studies included in this review did not report comorbidities (physical or mental health) and no study reported concomitant treatments in detail. Because of this it is not clear whether any changes observed were due to gender-affirming hormones or other treatments the participants may have received. For example, we do not know if any improvement in depression symptom score over time was the result of gender-affirming hormones or the mental health support the person may be receiving (including medicines or counselling). This may be of particular importance for the mental health outcomes discussed in this review, since depression, anxiety and other related symptoms are common in children and adolescents with gender dysphoria. In Achille et al. 2020, at baseline around one-third of participants were taking medicines for mental health problems and around two-thirds reported being depressed in the past year. In Kaltiala et al. 2020, half the participants needed mental health treatment during and before gender identity assessment, with the most common reasons for treatment being depression, anxiety and suicidality. Only 1 study reported outcomes adjusted for engagement in counselling and medicines for mental health problems (Achille et al. 2020). This study found that gender-affirming hormones had no significant impact on depression and quality of life when adjusted for mental health care, despite significant approvements reported for the unadjusted results. However, it is not possible to draw conclusions on the impact of concurrent mental health treatment on the effect of gender-affirming hormones based on this study alone. Details of the mental health care provided are not reported in the study and results are presented for transfemales and transmales separately, resulting in small patient numbers and possible underpowering.

In most of the included studies, details of the gender-affirming hormone treatment regimens are poorly reported, with limited information provided about the medicines, doses and routes of administration used. It is not clear whether the interventions used in the studies are reflective of current UK practice for children and adolescents with gender dysphoria. There is also the suggestion that the hormone dose used in 1 study may have been too low; the authors of Klink et al. 2015 suggest that the relatively low initial dose of oestrogen for transfemales may be the reason for the observed lack of effect on lumber spine bone density. Duration of treatment with a GnRH analogue is also poorly reported and is only stated in 3/10 studies.

There is a degree of indirectness in some studies, with some participants included that fall outside of the population of this evidence review. For example, in Kuper et al. 2020 17% of participants received puberty suppression alone, and in Achille et al. 2020, 30% of participants received no treatment or puberty suppression alone. Some results and statistical analyses are only reported for the whole cohort in these studies and not the subgroup of participants who received gender-affirming hormones.

Participant numbers are poorly reported in some of the included studies. In Achille et al. 2020, 47% (45/95) of the people who entered the study did not have follow-up data and were excluded from the analyses, with no explanation or description of those people lost to follow-up. In Kuper et al. 2020, the number of participants varied by outcome, with less than

two-thirds of participants providing data for some outcomes. The authors provide no explanation for this incomplete reporting.

It is not clear whether some outcome measures, specifically those related to psychosocial functioning, are relevant to the UK population. In Kaltiala et al. 2020, an observational study conducted in Finland, the proportion of participants living with parents or guardians is reported as marker of appropriate functioning. The authors state that in Finnish culture young people tend to leave the parental home early, with only around one-quarter of 20 to 24 year olds still living at home. This is lower than in the UK, where around half of 20 to 24 year olds live with their parents or guardians (ONS: Why are more young people living with their parents?).

It is difficult to draw firm conclusions for many of the effectiveness and safety outcomes reported in the included studies because many different scoring tools and methods were used to assess the same outcome, often with conflicting results. For example, bone density is reported as bone mineral density (BMD) and bone mineral apparent density (BMAD) in the same study, the latter being a size-adjusted measure often useful for people whose bones are still growing. For some populations (transfemale versus transmale) and bone regions (lumber spine versus femoral neck), statistically significant differences in BMD are reported but not for BMAD, and vice versa.

In addition to this, most outcomes reported across the included studies do not have an accepted minimal clinically important difference (MCID), making it difficult the determine whether any observed statistically significant changes are clinically meaningful. However, the authors of some studies report thresholds to interpret the results of the scoring tools, so some conclusions can be made. For example, the mean Utrecht Gender Dysphoria Scale (UGDS) score (a measure of gender dysphoria symptoms) reduced to about 15 points after treatment with gender-affirming hormones (Lopez de Lara et al. 2020). The authors state that scores of 40 points or above signify gender dysphoria, suggesting that after about 12 months of treatment with gender-affirming hormones, the majority of participants did not have symptoms of gender dysphoria.

The impact of gender-affirming hormones on bone density was reported in 3 studies (Klink et al. 2015, Stoffers et al. 2019 and Vlot et al. 2017). Although these studies did not include a control group, comparisons to a reference population are reported using z-scores. Comparisons were made to a cisgender population, meaning for example that bone density in transfemales was compared with bone density in cisgender males. The authors of Klink et al. 2015 note that this may not be the ideal comparison, because androgens and oestrogens affect bone differently, and that bone properties in a trans population differ from their age- and sex assigned at birth-matched controls. Beyond this, a major limitation when trying to determine the impact of gender-affirming hormones on the short- and long-term bone health of children and adolescents is the lack of data on fracture rates and other patient-orientated outcomes, including rates of osteoporosis. Studies of GnRH analogues in children and adolescents with gender dysphoria suggest that GnRH analogue treatment may reduce the expected increase in bone density (which is expected during puberty). Although improvements in bone density were reported following treatment with gender-affirming hormones, Z-scores suggest that bone density remained lower in transfemales and transmales compared with an equivalent cisgender population.

One study reported on cardiovascular risk factors at age 22 years in people who started gender-affirming hormones for gender dysphoria as adolescents. While glucose levels, insulin levels and insulin resistance were broadly unchanged at 22 years, statistically significant increases in blood pressure and body mass index were seen. A small but statistically significant worsening of the lipid profile in transmales who received testosterone was also seen at age 22 years. However, further studies with a considerably longer follow-up and a focus on patient-oriented outcomes, including cardiovascular events and mortality are needed to determine the long-term impact on cardiovascular health of starting gender-affirming hormones during childhood and adolescence.

Only 1 study reported adverse events and discontinuation rates with gender-affirming hormones in children and adolescents. Conclusions on these outcomes cannot be made based on this study alone.

This review did not identify sub-groups of people who may benefit more from gender-affirming hormones. Limited evidence from 2 studies suggests there was no difference in response to treatment between transfemales and transmales for mental health and quality of life (Achille et al. 2020 and Allen et al. 2019).

7. Conclusion

This evidence review found limited evidence for the effectiveness and safety of gender-affirming hormones in children and adolescents with gender dysphoria, with all studies being uncontrolled, observational studies, and all outcomes of very low certainty. Any potential benefits of treatment must be weighed against the largely unknown long-term safety profile of these treatments.

The results from 5 uncontrolled, observational studies (Achille et al. 2020, Allen et al. 2019, Kaltiala et al. 2020. Kuper et al. 2020, Lopez de Lara et al. 2020) suggest that, in children and adolescents with gender dysphoria, gender-affirming hormones are likely to improve symptoms of gender dysphoria, and may also improve depression, anxiety, quality of life, suicidality, and psychosocial functioning. The impact of treatment on body image is unclear. All results were of very low certainty. The clinical relevance of any improvements to the person is difficult to determine because most outcomes do not have a recognised minimal clinically important difference, and the authors do not present statistical analysis for some outcomes.

A further 5 uncontrolled, observational studies (Khatchadourian et al. 2014, Klaver et al. 2020, Klink et al. 2015, Stoffers et al. 2019 and Vlot et al. 2017) reported on safety outcomes, all of which provided very low certainty evidence. Statistically significant increases in some measures of bone density were seen following treatment with gender-affirming hormones, although results varied by bone region (lumber spine versus femoral neck) and by population (transfemales versus transmales). However, z-scores suggest that bone density remained lower in transfemales and transmales compared with an equivalent cisgender population. Results from 1 study of gender-affirming hormones started during adolescence reported statistically significant increases in blood pressure and body mass index, and worsening of the lipid profile (in transmales) at age 22 years, although longer term studies that report on cardiovascular event rates are needed. Adverse events and discontinuation rates associated with gender-affirming hormones were only reported in 1 study, and no conclusions can be made on these outcomes.

This review did not identify sub-groups of people who may benefit more from gender-affirming hormones. Limited evidence from 2 studies suggests there was no difference in response to treatment between transfemales and transmales for mental health and quality of life (Achille et al. 2020 and Allen et al. 2019).

No cost-effectiveness evidence was found to determine whether gender-affirming hormones are a cost-effective treatment for children and adolescents with gender dysphoria.

Appendix A PICO

The review questions for this evidence review are:

1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
2. For children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
3. For children and adolescents with gender dysphoria, what is the cost-effectiveness of gender-affirming hormones compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?
4. From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria?
5. From the evidence selected,
   (a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?
   (b) what were the ages at which participants commenced treatment with gender-affirming hormones?
   (c) what was the duration of GnRH analogues treatment?

PICO table

P –Population and Indication	Children and adolescents aged 18 years or less who have gender dysphoria, gender identity disorder or gender incongruence of childhood as defined by the study. The following subgroups of children and adolescents with gender dysphoria, gender identity disorder or gender incongruence of childhood need to be considered:

	• Sex assigned at birth males • Sex assigned at birth females • The duration of gender dysphoria: less than 6 months, 6-24 months, and more than 24 months) • The age at which treatment was initiated with GnRH analogues and with gender-affirming hormones. • The age of onset of gender dysphoria • The age of onset of puberty • Adolescents with gender dysphoria who have a pre-existing diagnosis of autistic spectrum disorder. • Adolescents with gender dysphoria who had a significant mental health symptom load at diagnosis including anxiety, depression (with or without a history of self-harm and suicidality), psychosis, personality disorder, Attention Deficit Hyperactivity Disorder and eating disorders.
I – Intervention	Gender-affirming hormone treatments: • A testosterone preparation for sex assigned at birth female patients which may include testosterone in the form of Sustanon injections*; testosterone enantate injections; Tostran gel*; Testogel; Testim gel; oral testosterone capsules in the form of testosterone undecanoate (Restandol); Andriol testocaps; Nebido • An oestradiol preparation** for sex assigned at birth male patients which may include: oral estradiol valerate*; oestrogen patches (7β-oestradiol patches e.g. Evorel or Estradem); Estradot patches; ethinyloestradiol *** *These are the used by Leeds Hospital, England. ** Be aware that the American spelling is oestrogen without the ‘o’. ***Ethinyloestradiol is rarely used.
C – Comparator(s)	One or a combination of: • Psychological support • Social transitioning to the gender with which the individual identifies. No intervention
O – Outcomes	There are no known minimal clinically important differences and there are no preferred timepoints for the outcome measures selected. **All outcomes should be stratified by:** • The age at which treatment with gender-affirming hormones was initiated • The length of treatment with GnRH analogues where possible. **A: Clinical Effectiveness** *Critical to decision making* • **Impact on gender dysphoria** This outcome is critical because gender dysphoria in adolescents and children is associated with significant distress and problems functioning. Impact on gender

	dysphoria may be measured by the Utrecht Gender Dysphoria Scale. Other measures as reported in studies may be used as an alternative to the stated measure. • **Impact on mental health** Examples of mental health problems include self-harm, thoughts of suicide, suicide attempts, suicide, eating disorders, depression/low mood and anxiety. These outcomes are critical because self-harm and thoughts of suicide have the potential to result in significant physical harm and for completed suicides the death of the young person. Disordered eating habits may cause significant morbidity in young people. Depression and anxiety are also critical outcomes because they may impact on social, occupational, or other areas of functioning of children and adolescents. The Child and Adolescent Psychiatric Assessment (CAPA) may be used to measure depression and anxiety. The impact on self-harm and suicidality (ideation and behaviour) may be measured using the Suicide Ideation Questionnaire Junior. Other measures may be used as an alternative to the stated measure. • **Impact on Quality of Life** This outcome is critical because gender dysphoria in children and adolescents may be associated with a significant reduction in health-related quality of life. Quality of Life may be measured by the KINDL questionnaire, Kidscreen 52. Other measures as reported in studies may be used as an alternative to the stated measures. *Important to decision making* • **Impact on body image** This outcome is important because some young people with gender dysphoria may desire to take steps to suppress features of their physical appearance associated with their sex assigned at birth or accentuate physical features of their experienced gender. The Body Image Scale could be used as a measure. Other measures as reported in studies may also be used as an alternative to the stated measure. • **Psychosocial Impact** Examples of psychosocial impact are: coping mechanisms which may impact on substance misuse; family relationships; peer relationships. This outcome is important because gender dysphoria in adolescents and children is associated with internalising and externalising behaviours and emotional and behavioural problems which may impact on social and occupational functioning. The child behavioural check list (CBCL) may be used to measure the impact on psychosocial functioning. Other measures as reported in studies may be used as an alternative to the stated measure. • **Engagement with health care services** This outcome is important because patient engagement with healthcare services will impact on their clinical outcomes. Engagement with health care services may be measured using the Youth Health Care measure-satisfaction, utilization, and needs (YHC-SUN) questionnaire. Loss to follow up and

	should also be ascertained as part of this outcome. Alternative measures to the YHC-SUN questionnaire may be used as reported in studies. • **Transitioning surgery - Impact on extent of and satisfaction with surgery** This outcome is important because some children and adolescents with gender dysphoria may in adulthood proceed to transitioning surgery. Stated measures of the extent of surgery and satisfaction with surgery in studies may be reported. • **De-transition** The proportion of patients who de-transition following the commencement of gender-affirming hormone treatment and the reasons why. This outcome is important to patients because there is uncertainty about the short and long term safety and adverse effects of gender-affirming hormones in children and adolescents with gender dysphoria. **B: Safety** • Short and long -term safety and adverse effects of taking gender-affirming hormones is important to assess whether treatment causes acute side effects that may lead to withdrawing the treatment or long term effects that may impact on decisions for transitioning or de-transitioning. Aspects to be reported on should include Impact of the drug use such as clinically relevant derangement in renal and liver function tests, lipids, glucose, insulin and glycosylated haemoglobin, cognitive development and functioning. The clinical and physical impact of temporary and permanent withdrawal the drug such as when patients decide to de-transition – e.g. delay in the attainment of peak bone mass, attenuation of peak bone mass, permanent physical effects. **C: Cost effectiveness** Cost effectiveness studies should be reported.
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	18 years or less
Date limits	2000-2020

Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines and pre-publication prints
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, the Cochrane Library, HTA and APA PsycInfo were searched on 21 July 2020, limiting the search to papers published in English language in the last 20 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines, pre-publication prints, case reports and resource utilisation studies were excluded.

Database: Medline
Platform: Ovid
Version: Ovid MEDLINE(R) <1946 to July 17, 2020>
Search date: 21 Jul 2020
Number of results retrieved: 650
Search strategy:
Database: Ovid MEDLINE(R) <1946 to July 17, 2020>
Search Strategy:
---
1 Gender Dysphoria/ (485)
2 Gender Identity/ (18431)
3 "Sexual and Gender Disorders"/ (75)
4 Transsexualism/ (3758)
5 Transgender Persons/ (3134)
6 Health Services for Transgender Persons/ (136)
7 exp Sex Reassignment Procedures/ (835)
8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (7223)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (12665)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (102312)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (6969)
12 (male-to-female or m2f or female-to-male or f2m).tw. (114785)
13 or/1-12 (252562)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (1137237)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (852126)
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1912796)
17 Minors/ (2572)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (2360626)
19 exp pediatrics/ (58102)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (835833)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (2023650)
22 Puberty/ (13277)

23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (424041)
24 Schools/ (38087)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (7199)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (468784)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (89314)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (887443)
29 or/14-28 (5532185)
30 13 and 29 (79220)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (7)
32 30 or 31 (79220)
33 Hormones/ad, tu, th (4514)
34 exp Progesterone/ad, tu, th (10899)
35 exp Estrogens/ad, tu, th (28936)
36 exp Gonadal Steroid Hormones/ad, tu, th (34137)
37 (progesteron* or oestrogen* or estrogen*).tw. (196074)
38 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (544)
39 exp Estradiol/ad, tu, th (10823)
40 exp Testosterone/ad, tu, th (8318)
41 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (74936)
42 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (90464)
43 or/33-42 (304239)
44 32 and 43 (3183)
45 limit 44 to yr="2000 -Current" (2019)
46 animals/ not humans/ (4685420)
47 45 not 46 (1194)
48 limit 47 to english language (1155)
49 (MEDLINE or pubmed).tw. (163678)
50 systematic review.tw. (121198)
51 systematic review.pt. (130231)
52 meta-analysis.pt. (117148)
53 intervention$.ti. (123904)
54 or/49-53 (380217)
55 randomized controlled trial.pt. (509468)
56 randomi?ed.mp. (796957)
57 placebo.mp. (194937)
58 or/55-57 (848627)
59 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ (5562241)
60 ((control and (group* or study)) or (time and factors)).mp. (3274107)
61 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (4624419)
62 or/59-61 (9030680)
63 Observational Studies as Topic/ (5177)
64 Observational Study/ (81866)
65 Epidemiologic Studies/ (8358)

66 exp Case-Control Studies/ (1090891)
67 exp Cohort Studies/ (2011414)
68 Cross-Sectional Studies/ (332273)
69 Controlled Before-After Studies/ (526)
70 Historically Controlled Study/ (185)
71 Interrupted Time Series Analysis/ (913)
72 Comparative Study.pt. (1866044)
73 case control$.tw. (112152)
74 case series.tw. (59119)
75 (cohort adj (study or studies)).tw. (170281)
76 cohort analy$.tw. (6758)
77 (follow up adj (study or studies)).tw. (45131)
78 (observational adj (study or studies)).tw. (86247)
79 longitudinal.tw. (204239)
80 prospective.tw. (495367)
81 retrospective.tw. (442876)
82 cross sectional.tw. (284856)
83 or/63-82 (4368140)
84 54 or 58 or 62 or 83 (9402123)
85 48 and 84 (683)
86 limit 85 to (letter or historical article or comment or editorial or news or case reports) (33)
87 85 not 86 (650)

Database: Medline in-process
Platform: Ovid
Version: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to July 17, 2020>
Search date: 21 July 2020
Number of results retrieved: 122
Search strategy:
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to July 17, 2020>
Search Strategy:
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1 Gender Dysphoria/ (0)
2 Gender Identity/ (0)
3 "Sexual and Gender Disorders"/ (0)
4 Transsexualism/ (0)
5 Transgender Persons/ (0)
6 Health Services for Transgender Persons/ (0)
7 exp Sex Reassignment Procedures/ (0)
8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (1473)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (2315)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (20821)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (963)
12 (male-to-female or m2f or female-to-male or f2m).tw. (15453)
13 or/1-12 (39735)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (0)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (80295)

16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)
17 Minors/ (0)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (320315)
19 exp pediatrics/ (0)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (119124)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)
22 Puberty/ (0)
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (59969)
24 Schools/ (0)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (68979)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (10287)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (112220)
29 or/14-28 (523053)
30 13 and 29 (9143)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (3)
32 30 or 31 (9144)
33 Hormones/ad, tu, th (0)
34 exp Progesterone/ad, tu, th (0)
35 exp Estrogens/ad, tu, th (0)
36 exp Gonadal Steroid Hormones/ad, tu, th (0)
37 (progesteron* or oestrogen* or estrogen*).tw. (13291)
38 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (241)
39 exp Estradiol/ad, tu, th (0)
40 exp Testosterone/ad, tu, th (0)
41 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (5458)
42 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (4772)
43 or/33-42 (19706)
44 32 and 43 (316)
45 limit 44 to yr="2000 -Current" (303)
46 animals/ not humans/ (1)
47 45 not 46 (303)
48 limit 47 to english language (303)
49 (MEDLINE or pubmed).tw. (36030)
50 systematic review.tw. (29830)
51 systematic review.pt. (1007)
52 meta-analysis.pt. (49)
53 intervention$.ti. (21354)
54 or/49-53 (68976)
55 randomized controlled trial.pt. (277)
56 randomi?ed.mp. (74978)
57 placebo.mp. (18290)
58 or/55-57 (81427)
59 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ (455)

60 ((control and (group* or study)) or (time and factors)).mp. (214372)
61 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (339764)
62 or/59-61 (507046)
63 Observational Studies as Topic/ (0)
64 Observational Study/ (91)
65 Epidemiologic Studies/ (0)
66 exp Case-Control Studies/ (1)
67 exp Cohort Studies/ (1)
68 Cross-Sectional Studies/ (0)
69 Controlled Before-After Studies/ (0)
70 Historically Controlled Study/ (0)
71 Interrupted Time Series Analysis/ (0)
72 Comparative Study.pt. (46)
73 case control$.tw. (14451)
74 case series.tw. (13070)
75 (cohort adj (study or studies)).tw. (29119)
76 cohort analy$.tw. (1039)
77 (follow up adj (study or studies)).tw. (3540)
78 (observational adj (study or studies)).tw. (17421)
79 longitudinal.tw. (34485)
80 prospective.tw. (63689)
81 retrospective.tw. (73761)
82 cross sectional.tw. (60195)
83 or/63-82 (250805)
84 54 or 58 or 62 or 83 (687622)
85 48 and 84 (126)
86 limit 85 to (letter or historical article or comment or editorial or news or case reports) (4)
87 85 not 86 (122)

Database: Medline epubs ahead of print
Platform: Ovid
Version: Ovid MEDLINE(R) Epub Ahead of Print <July 17, 2020>
Search date: 21 July 2020
Number of results retrieved: 32
Search strategy:
Database: Ovid MEDLINE(R) Epub Ahead of Print <July 17, 2020>
Search Strategy:
---

1 Gender Dysphoria/ (0)
2 Gender Identity/ (0)
3 "Sexual and Gender Disorders"/ (0)
4 Transsexualism/ (0)
5 Transgender Persons/ (0)
6 Health Services for Transgender Persons/ (0)
7 exp Sex Reassignment Procedures/ (0)
8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (430)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (637)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (1499)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (179)
12 (male-to-female or m2f or female-to-male or f2m).tw. (2460)

13 or/1-12 (4883)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (0)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (15416)
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)
17 Minors/ (0)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (53285)
19 exp pediatrics/ (0)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (22649)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)
22 Puberty/ (0)
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (13005)
24 Schools/ (0)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (12420)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (1407)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (20083)
29 or/14-28 (87968)
30 13 and 29 (1618)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (1)
32 30 or 31 (1618)
33 Hormones/ad, tu, th (0)
34 exp Progesterone/ad, tu, th (0)
35 exp Estrogens/ad, tu, th (0)
36 exp Gonadal Steroid Hormones/ad, tu, th (0)
37 (progesteron* or oestrogen* or estrogen*).tw. (1876)
38 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (63)
39 exp Estradiol/ad, tu, th (0)
40 exp Testosterone/ad, tu, th (0)
41 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (846)
42 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (665)
43 or/33-42 (2850)
44 32 and 43 (64)
45 limit 44 to yr="2000 -Current" (61)
46 animals/ not humans/ (0)
47 45 not 46 (61)
48 limit 47 to english language (61)
49 (MEDLINE or pubmed).tw. (7948)
50 systematic review.tw. (7508)
51 systematic review.pt. (28)
52 meta-analysis.pt. (37)
53 intervention$.ti. (4267)
54 or/49-53 (15048)
55 randomized controlled trial.pt. (1)

56 randomi?ed.mp. (14113)
57 placebo.mp. (3097)
58 or/55-57 (15128)
59 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ (34)
60 ((control and (group* or study)) or (time and factors)).mp. (31615)
61 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (65735)
62 or/59-61 (88222)
63 Observational Studies as Topic/ (0)
64 Observational Study/ (4)
65 Epidemiologic Studies/ (0)
66 exp Case-Control Studies/ (0)
67 exp Cohort Studies/ (0)
68 Cross-Sectional Studies/ (0)
69 Controlled Before-After Studies/ (0)
70 Historically Controlled Study/ (0)
71 Interrupted Time Series Analysis/ (0)
72 Comparative Study.pt. (0)
73 case control$.tw. (2577)
74 case series.tw. (2480)
75 (cohort adj (study or studies)).tw. (7959)
76 cohort analy$.tw. (287)
77 (follow up adj (study or studies)).tw. (632)
78 (observational adj (study or studies)).tw. (3763)
79 longitudinal.tw. (7079)
80 prospective.tw. (12148)
81 retrospective.tw. (16600)
82 cross sectional.tw. (9459)
83 or/63-82 (48534)
84 54 or 58 or 62 or 83 (119752)
85 48 and 84 (32)
86 limit 85 to (letter or historical article or comment or editorial or news or case reports) (0)
87 85 not 86 (32)

Database: Medline daily update
Platform: Ovid
Version: Ovid MEDLINE(R) Daily Update <July 21, 2020>
Search date: 22 July 2020
Number of results retrieved: 3
Search strategy

Database: Ovid MEDLINE(R) Daily Update <July 21, 2020>
Search Strategy:
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1 Gender Dysphoria/ (4)
2 Gender Identity/ (38)
3 "Sexual and Gender Disorders"/ (0)
4 Transsexualism/ (2)
5 Transgender Persons/ (26)
6 Health Services for Transgender Persons/ (1)
7 exp Sex Reassignment Procedures/ (3)
8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (22)

9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (39)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (87)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (15)
12 (male-to-female or m2f or female-to-male or f2m).tw. (181)
13 or/1-12 (358)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (932)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (981)
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1756)
17 Minors/ (3)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (3672)
19 exp pediatrics/ (75)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (1658)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (2006)
22 Puberty/ (8)
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (732)
24 Schools/ (56)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (5)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (622)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (98)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (1301)
29 or/14-28 (6705)
30 13 and 29 (130)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (0)
32 30 or 31 (130)
33 Hormones/ad, tu, th (3)
34 exp Progesterone/ad, tu, th (3)
35 exp Estrogens/ad, tu, th (8)
36 exp Gonadal Steroid Hormones/ad, tu, th (22)
37 (progesteron* or oestrogen* or estrogen*).tw. (161)
38 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (3)
39 exp Estradiol/ad, tu, th (8)
40 exp Testosterone/ad, tu, th (8)
41 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (79)
42 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (61)
43 or/33-42 (261)
44 32 and 43 (7)
45 limit 44 to yr="2000 -Current" (7)
46 animals/ not humans/ (3647)
47 45 not 46 (6)
48 limit 47 to english language (6)
49 (MEDLINE or pubmed).tw. (529)
50 systematic review.tw. (512)

51 systematic review.pt. (522)
52 meta-analysis.pt. (370)
53 intervention$.ti. (247)
54 or/49-53 (1065)
55 randomized controlled trial.pt. (595)
56 randomi?ed.mp. (1203)
57 placebo.mp. (219)
58 or/55-57 (1234)
59 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ (7958)
60 ((control and (group* or study)) or (time and factors)).mp. (4307)
61 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (5828)
62 or/59-61 (11814)
63 Observational Studies as Topic/ (27)
64 Observational Study/ (449)
65 Epidemiologic Studies/ (7)
66 exp Case-Control Studies/ (2173)
67 exp Cohort Studies/ (3287)
68 Cross-Sectional Studies/ (837)
69 Controlled Before-After Studies/ (1)
70 Historically Controlled Study/ (0)
71 Interrupted Time Series Analysis/ (6)
72 Comparative Study.pt. (768)
73 case control$.tw. (182)
74 case series.tw. (139)
75 (cohort adj (study or studies)).tw. (561)
76 cohort analy$.tw. (22)
77 (follow up adj (study or studies)).tw. (40)
78 (observational adj (study or studies)).tw. (253)
79 longitudinal.tw. (429)
80 prospective.tw. (778)
81 retrospective.tw. (1032)
82 cross sectional.tw. (739)
83 or/63-82 (5471)
84 54 or 58 or 62 or 83 (12581)
85 48 and 84 (3)
86 limit 85 to (letter or historical article or comment or editorial or news or case reports) (0)
87 85 not 86 (3)

Database: Embase
Platform: Ovid
Version: Embase <1974 to 2020 July 22>
Search date: 23 July 2020
Number of results retrieved: 1207
Search strategy:

Database: Embase <1974 to 2020 July 22>
Search Strategy:
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1 exp Gender Dysphoria/ (5399)
2 Gender Identity/ (16820)
3 "Sexual and Gender Disorders"/ (24689)
4 Transsexualism/ (3869)
5 exp Transgender/ (6597)

6 Health Services for Transgender Persons/ (158848)
7 exp Sex Reassignment Procedures/ (1108)
8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (12470)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (22509)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (154446)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (10327)
12 (male-to-female or m2f or female-to-male or f2m).tw. (200166)
13 or/1-12 (581748)
14 exp juvenile/ or Child Behavior/ or Child Welfare/ or Child Health/ or infant welfare/ or "minor (person)"/ or elementary student/ or adolescent health/ or middle school student/ or high school student/ (3440943)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (1186161)
16 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (3586795)
17 exp pediatrics/ (106214)
18 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (1491597)
19 exp adolescence/ or exp adolescent behavior/ or adolescent health/ or high school student/ or middle school student/ (105108)
20 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (641660)
21 school/ or high school/ or kindergarten/ or middle school/ or primary school/ or nursery school/ or day care/ (103791)
22 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (687437)
23 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (138908)
24 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (1562903)
25 or/14-24 (7130881)
26 13 and 25 (181778)
27 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (17)
28 26 or 27 (181778)
29 hormone/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (5160)
30 exp progesterone derivative/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (23479)
31 exp estrogen/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (57641)
32 steroid hormone/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (372)
33 sex hormone/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (1984)
34 hormonal therapy/ (42222)
35 (progesteron* or oestrogen* or estrogen*).tw. (254142)
36 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (1224)
37 exp estradiol derivative/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (30740)

38 exp testosterone derivative/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (15868)
39 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (99596)
40 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (114290)
41 or/29-40 (438737)
42 28 and 41 (6053)
43 limit 42 to yr="2000 -Current" (4741)
44 nonhuman/ not human/ (4649157)
45 43 not 44 (3636)
46 limit 45 to english language (3513)
47 (MEDLINE or pubmed).tw. (261145)
48 exp systematic review/ or systematic review.tw. (302985)
49 meta-analysis/ (191173)
50 intervention$.ti. (200041)
51 or/47-50 (660206)
52 random:.tw. (1552336)
53 placebo:.mp. (455979)
54 double-blind:.tw. (210671)
55 or/52-54 (1807280)
56 cohort analysis/ (596360)
57 exp epidemiology/ (3434332)
58 exp clinical trial/ (1504711)
59 evaluation study/ (45870)
60 statistics/ (301181)
61 ((control and (group* or study)) or (time and factors)).mp. (3324555)
62 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (6067112)
63 or/56-62 (11048972)
64 Clinical study/ (155444)
65 Case control study/ (157943)
66 Family study/ (26047)
67 Longitudinal study/ (141660)
68 Retrospective study/ (937696)
69 comparative study/ (859061)
70 Prospective study/ (613138)
71 Randomized controlled trials/ (182542)
72 70 not 71 (606604)
73 Cohort analysis/ (596360)
74 cohort analy$.tw. (13020)
75 (Cohort adj (study or studies)).tw. (302159)
76 (Case control$ adj (study or studies)).tw. (137432)
77 (follow up adj (study or studies)).tw. (63423)
78 (observational adj (study or studies)).tw. (168428)
79 (epidemiologic$ adj (study or studies)).tw. (106448)
80 (cross sectional adj (study or studies)).tw. (220073)
81 case series.tw. (104089)
82 prospective.tw. (861922)
83 retrospective.tw. (886445)
84 or/64-69,72-83 (4047788)
85 51 or 55 or 63 or 84 (12494560)
86 46 and 85 (2151)
87 86 not (letter or editorial).pt. (2137)

88 87 not (conference abstract or conference paper or conference proceeding or "conference review").pt. (1207)

Database: APA PsycInfo

Platform: Ovid
Version: APA PsycInfo <1806 to July Week 2 2020>
Search date: 22 July 2020
Number of results retrieved: 581
Search strategy:

Database: APA PsycInfo <1806 to July Week 2 2020>
Search Strategy:
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1 Gender Dysphoria/ (936)
2 Gender Identity/ (8648)
3 Transsexualism/ (2825)
4 Transgender/ (5257)
5 exp Gender Reassignment/ (568)
6 (gender* adj3 (dysphori* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)).tw. (15276)
7 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (13028)
8 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (7679)
9 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (5796)
10 (male-to-female or m2f or female-to-male or f2m).tw. (63688)
11 or/1-10 (99498)
12 exp Infant Development/ (21841)
13 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (150219)
14 Child Characteristics/ or exp Child Behavior/ or Child Psychology/ or exp Child Welfare/ or Child Psychiatry/ (23423)
15 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (984230)
16 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (78962)
17 Adolescent Psychiatry/ or Adolescent Behavior/ or Adolescent Development/ or Adolescent Psychology/ or Adolescent Characteristics/ or Adolescent Health/ (62142)
18 Puberty/ (2753)
19 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (347604)
20 Schools/ (29181)
21 Child Day Care/ or Nursery Schools/ (2836)
22 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (772814)
23 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (21475)
24 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (285697)
25 or/12-24 (1765408)
26 11 and 25 (49560)
27 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (14)

28 26 or 27 (49561)
29 hormones/ (8408)
30 sex hormones/ (1777)
31 exp progestational hormones/ (2409)
32 estrogens/ (3889)
33 steroids/ (3797)
34 (progesteron* or oestrogen* or estrogen*).tw. (11188)
35 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (457)
36 estradiol/ (3120)
37 testosterone/ (5606)
38 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (9625)
39 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (6741)
40 or/29-39 (30344)
41 28 and 40 (1005)
42 limit 41 to yr="2000 -Current" (749)
43 limit 42 to english language (692)
44 limit 43 to ("0200 book" or "0240 authored book" or "0280 edited book" or "0300 encyclopedia" or "0400 dissertation abstract") (111)
45 43 not 44 (581)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL

Platform: Wiley
Version:
CDSR –Issue 7 of 12, July 2020
CENTRAL – Issue 7 of 12, July 2020
Search date: 22 July 2020
Number of results retrieved: CDSR 0 ; CENTRAL 67.

ID Search Hits
#1 MeSH descriptor: [Gender Dysphoria] this term only 3
#2 MeSH descriptor: [Gender Identity] this term only 227
#3 MeSH descriptor: [Sexual and Gender Disorders] this term only 2
#4 MeSH descriptor: [Transsexualism] this term only 27
#5 MeSH descriptor: [Transgender Persons] this term only 36
#6 MeSH descriptor: [Health Services for Transgender Persons] this term only 0
#7 MeSH descriptor: [Sex Reassignment Procedures] explode all trees 4
#8 (gender* near/3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)):ti,ab,kw 702
#9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*):ti,ab,kw 959
#10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*):ti,ab,kw 3969
#11 ((sex or gender*) near/3 (reassign* or chang* or transform* or transition*)):ti,ab,kw 524
#12 (male-to-female or m2f or female-to-male or f2m):ti,ab,kw 516
#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 6413
#14 MeSH descriptor: [Infant] explode all trees 28440
#15 MeSH descriptor: [Infant Health] this term only 49
#16 MeSH descriptor: [Infant Welfare] this term only 82

#17 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*):ti,ab,kw,so 89530
#18 MeSH descriptor: [Child] explode all trees 44089
#19 MeSH descriptor: [Child Behavior] explode all trees 2061
#20 MeSH descriptor: [Child Health] this term only 98
#21 MeSH descriptor: [Child Welfare] this term only 325
#22 MeSH descriptor: [Minors] this term only 8
#23 (child* or minor or minors or boy* or girl* or kid or kids or young*):ti,ab,kw,so 265417
#24 MeSH descriptor: [Pediatrics] explode all trees 661
#25 (pediatric* or paediatric* or peadiatric*):ti,ab,kw,so 57725
#26 MeSH descriptor: [Adolescent] this term only 102154
#27 MeSH descriptor: [Adolescent Behavior] this term only 1358
#28 MeSH descriptor: [Adolescent Health] this term only 29
#29 MeSH descriptor: [Puberty] this term only 295
#30 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*):ti,ab,kw,so 140927
#31 MeSH descriptor: [Schools] this term only 1914
#32 MeSH descriptor: [Child Day Care Centers] this term only 231
#33 MeSH descriptor: [Nurseries, Infant] explode all trees 17
#34 MeSH descriptor: [Schools, Nursery] this term only 37
#35 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*):ti,ab,kw,so 97810
#36 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") near/2 (year or years or age or ages or aged)):ti,ab 6710
#37 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") near/2 (year or years or age or ages or aged)):ti,ab 196881
#38 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 516067
#39 #13 and #38 2488
#40 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*):ti,ab,kw 0
#41 #39 or #40 2488
#42 MeSH descriptor: [Hormones] this term only 2241
#43 MeSH descriptor: [Progesterone] explode all trees 3135
#44 MeSH descriptor: [Estrogens] explode all trees 1841
#45 MeSH descriptor: [Gonadal Steroid Hormones] explode all trees 10747
#46 (progesteron* or oestrogen* or estrogen*):ti,ab,kw 18387
#47 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)):ti,ab,kw 24
#48 MeSH descriptor: [Estradiol] explode all trees 4434
#49 MeSH descriptor: [Testosterone] explode all trees 2945
#50 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan):ti,ab,kw 7386
#51 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle):ti,ab,kw 11410
#52 #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 31870
#53 #41 and #52 121
#54 "conference":pt or (clinicaltrials or trialsearch):so 492465
#55 #53 not #54 72

Database: HTA

Platform: Wiley
Version: up to 2018
Search date: 22nd July 2020
Number of results retrieved: 4
Search strategy:

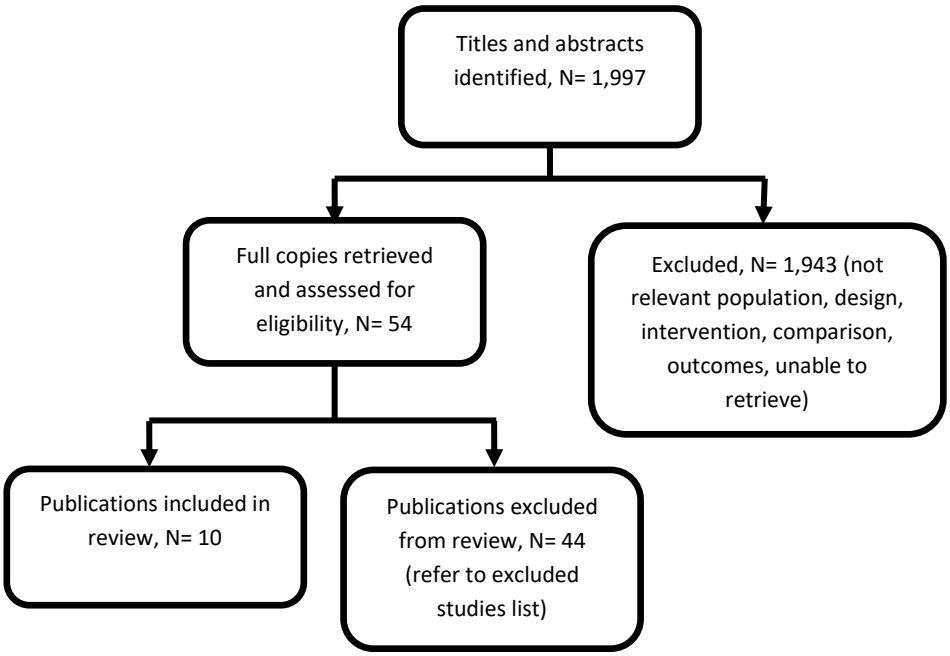
#1 MeSH DESCRIPTOR Gender Dysphoria 0
#2 MeSH DESCRIPTOR Gender Identity 12
#3 MeSH DESCRIPTOR Sexual and Gender Disorders 2
#4 MeSH DESCRIPTOR Transsexualism 12
#5 MeSH DESCRIPTOR Transgender Persons 3
#6 MeSH DESCRIPTOR Health Services for Transgender Persons 0
#7 MeSH DESCRIPTOR Sex Reassignment Procedures EXPLODE ALL TREES 1
#8 ((gender* near3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*))) 28
#9 ((transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*)) 76
#10 ((trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*)) 83
#11 (((sex or gender*) near3 (reassign* or chang* or transform* or transition*))) 24
#12 ((male-to-female or m2f or female-to-male or f2m)) 86
#13 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 261
#14 MeSH DESCRIPTOR Infant EXPLODE ALL TREES 2964
#15 MeSH DESCRIPTOR Infant Health 0
#16 MeSH DESCRIPTOR Infant Welfare 22
#17 ((prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*)) 5510
#18 MeSH DESCRIPTOR Child EXPLODE ALL TREES 4935
#19 MeSH DESCRIPTOR Child Behavior EXPLODE ALL TREES 64
#20 MeSH DESCRIPTOR Child Health 2
#21 MeSH DESCRIPTOR Child Welfare 80
#22 MeSH DESCRIPTOR Minors 2
#23 ((child* or minor or minors or boy* or girl* or kid or kids or young*)) 13575
#24 MeSH DESCRIPTOR Pediatrics EXPLODE ALL TREES 119
#25 ((pediatric* or paediatric* or peadiatric*)) 2842
#26 MeSH DESCRIPTOR Adolescent 4594
#27 MeSH DESCRIPTOR Adolescent Behavior 94
#28 MeSH DESCRIPTOR Adolescent Health 0
#29 MeSH DESCRIPTOR Puberty 3
#30 ((adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*)) 5621
#31 MeSH DESCRIPTOR Schools 168
#32 MeSH DESCRIPTOR Child Day Care Centers 12
#33 MeSH DESCRIPTOR Schools, Nursery 3
#34 ((pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*)) 4454
#35 ((("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") near2 (year or years or age or ages or aged))) 380
#36 ((("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") near2 (year or years or age or ages or aged))) 7996

#37 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 22640
#38 #13 AND #37 116
#39 (#13 AND #37) IN HTA 4

Appendix C Evidence selection

The literature searches identified 1,997 references. These were screened using their titles and abstracts and 54 references were obtained and assessed for relevance. Of these, 10 references are included in the evidence review. The remaining 44 references were excluded and are listed in appendix D.

Figure 1 – Study selection flow diagram



References submitted with Preliminary Policy Proposal

There is no preliminary policy proposal for this policy.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Aranda G, Mora M, Hanzu FA et al. (2019) Effects of sex steroids on cardiovascular risk profile in transgender men under gender affirming hormone therapy. Endocrinologia, diabetes y nutricion 66(6): 385–392	Excluded on population – adult study, participants not 18 years or less (mean age 27.1 years).
Arnold, Justin D, Sarkodie, Eleanor P, Coleman, Megan E et al. (2016) Incidence of Venous Thromboembolism in Transgender Women	Excluded on population – adult study, participants not 18 years or less (mean age 33.2 years).

Study reference	Reason for exclusion
Receiving Oral Estradiol. The journal of sexual medicine 13(11): 1773–1777	
Asscheman, Henk, Giltay, Erik J, Megens, Jos A J et al. (2011) A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. European journal of endocrinology 164(4): 635–42	Excluded on population – although some participants started gender-affirming hormones when young, the study does not report the proportion who started treatment when 18 years or less. Mean ages at start of treatment were 31.4 years (transfemales) and 26.1 years (transmales), suggesting the majority of participants were older than 18 years at the start of treatment. Outcomes not reported separately for people aged 18 years or less.
Author not, found (2014) Hormone therapy for the treatment of gender dysphoria. Lansdale, PA: HAYES, Inc	Full text paper not available.
Baba, T., Endo, T., Honnma, H. et al. (2007) Association between polycystic ovary syndrome and female-to-male transsexuality. Human Reproduction 22(4): 1011–1016	Excluded on population – although study included some younger people (age range 17 to 47), most participants were adults (mean age around 25 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.
Becerra-Fernandez A, Perez-Lopez G, Roman MM et al. (2014) Prevalence of hyperandrogenism and polycystic ovary syndrome in female to male transsexuals. Endocrinologia y Nutricion: Organo de la Sociedad Espanola de Endocrinologia y Nutricion 61(7): 351–8	Excluded on population – although study included some younger people (age range 18 to 45), most participants were adults (mean age around 25 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.
Becker I, Auer M, Barkmann C et al. (2018) A Cross-Sectional Multicenter Study of Multidimensional Body Image in Adolescents and Adults with Gender Dysphoria Before and After Transition-Related Medical Interventions. Archives of Sexual Behavior 47(8): 2335–2347	Excluded on population – study included people aged 14 to 21 years. Outcomes not reported separately for people aged 18 years or less. Better evidence available – only 11 participants received gender-affirming hormones. The majority of the study cohort were either pre-treatment, received puberty suppression alone, or received hormones and underwent surgery.
Chew D, Anderson J, Williams K et al. (2018) Hormonal Treatment in Young People With Gender Dysphoria: A Systematic Review. Pediatrics 141(4): e20173742	Excluded on better available evidence - systematic review did not meta-analyse results from. Individual studies from this systematic review are either

Study reference	Reason for exclusion
	included, or excluded because they did not meet the PICO criteria.
Connolly MD, Zervos MJ, Barone CJ 2nd et al. (2016) The Mental Health of Transgender Youth: Advances in Understanding. The Journal of Adolescent Health: Official Publication of the Society for Adolescent Medicine 59(5): 489–495	Excluded on intervention - review did not investigate gender-affirming hormones
de Vries ALC, McGuire JK, Steensma TD et al. (2014) Young adult psychological outcome after puberty suppression and gender reassignment. Pediatrics 134(4): 696–704	Exclude on intervention – all participants had surgery after gender-affirming hormones. Unable to determine whether changes were due to hormones or surgery. Complete data only available for 40 patients. Details of gender-affirming hormones are poorly reported. Outcomes reported in other study (with a population that more closely matches PICO)
Elamin MB, Garcia MZ, Murad MH et al. (2010) Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. Clinical Endocrinology 72(1): 1–10	Exclude on population – all included studies conducted in adult population. Unclear whether hormones were started when participants were aged 18 years or less. Outcomes not reported by age at treatment initiation.
Fernandez JD and Tannock LR (2016) Metabolic effects of hormone therapy in transgender patients. Endocrine Practice: Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 22(4): 383–8	Excluded on population – adult study, participants not 18 years or less (mean ages 31 and 27 years).
Fighera TM, Ziegelmann PK, Da Silva TR et al. (2019) Bone mass effects of cross-sex hormone therapy in transgender people: Updated systematic review and meta-analysis. Journal of the Endocrine Society 3(5): 943–964	Excluded on population – all included studies conducted in adult population. Unclear whether hormones were started when participants were aged 18 years or less. Outcomes not reported by age at treatment initiation.
Getahun D, Nash R, Flanders WD et al. (2018) Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons: A Cohort Study. Annals of Internal Medicine 169(4): 205–213	Excluded on population – adult study, participants not 18 years or less.
Gomez-Gil E, Zubiaurre-Elorza L, de Antonio IE et al. (2014) Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. Quality of Life Research: an International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation 23(2): 669–76	Excluded on population – although study included some younger people (age range 16 to 67), most participants were adults (mean age 31.2 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.
Gomez-Gil E, Zubiaurre-Elorza L, Esteva I et al. (2012) Hormone-treated transsexuals report less	Excluded on population – adult study, participants not 18 years or less (mean age 24.6 years).

Study reference	Reason for exclusion
social distress, anxiety and depression. Psychoneuroendocrinology 37(5): 662–70	
Gooren LJ, van Trotsenburg MAA, Giltay EJ et al. (2013) Breast cancer development in transsexual subjects receiving cross-sex hormone treatment. The Journal of Sexual Medicine 10(12): 3129–34	Excluded on population – study reports on cancer rates in people aged 18-80 years. The 3 cases of cancer all started gender-affirming hormone treatment >18 years.
Grimstad FW, Boskey E, Grey M (2020) New-Onset Abdominopelvic Pain After Initiation of Testosterone Therapy Among TransMasculine Persons: A Community-Based Exploratory Survey. LGBT health 7(5): Published Online:13 Jul 2020https://doi.org/10.1089/lgbt.2019.0258	Excluded on population – adult study, participants not 18 years or less.
Hannema SE, Schagen SEE, Cohen-Kettenis PT et al. (2017) Efficacy and Safety of Pubertal Induction Using 17beta-Estradiol in Transgirls. The Journal of Clinical Endocrinology and Metabolism 102(7): 2356–2363	Excluded on better evidence available – small study (n=28) with high drop-out rate (n=16 at final follow-up). Same outcomes reported in larger studies.
Jarin J, Pine-Twaddell E, Trotman G et al. (2017) Cross-Sex Hormones and Metabolic Parameters in Adolescents With Gender Dysphoria. Pediatrics 139(5)	Excluded on population and better evidence available. Although the study included some younger people (age range 13 to 25; mean age 16 and 18), the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less. Outcomes were limited to physiological results (including haemoglobin, lipids and BMI). Follow-up only 6 months, other included studies report same outcomes with longer follow-up (12 to 31 months).
Keo-Meier CL, Herman LI, Reisner SL et al. (2015) Testosterone treatment and MMPI-2 improvement in transgender men: a prospective controlled study. Journal of consulting and clinical psychology 83(1): 143–56	Excluded on population – although study included some younger people (age range 18 to 54), most participants were adults (mean age 26.6 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.
Klaver M, de Mutsert R, Wiepjes CM et al. (2018) Early Hormonal Treatment Affects Body Composition and Body Shape in Young Transgender Adolescents. The Journal of Sexual Medicine 15(2): 251–260	Excluded on outcomes – reported outcomes not included in PICO document. The risk of obesity with gender-affirmed hormones was reported in an included study.
McFarlane T, Zajac JD, Cheung AS (2018) Gender-affirming hormone therapy and the risk of sex hormone-dependent tumours in transgender individuals-A systematic review. Clinical Endocrinology 89(6): 700-711	Exclude on population – all included studies conducted in adult population.

Study reference	Reason for exclusion
Meriggiola MC, Armillotta F, Costantino A et al. (2008) Effects of testosterone undecanoate administered alone or in combination with letrozole or dutasteride in female to male transsexuals. The Journal of Sexual Medicine 5(10): 2442–53	Excluded on population – adult study, participants not 18 years or less.
Nota NM, Wiepjes CM, de Blok, CJM et al. (2018) The occurrence of benign brain tumours in transgender individuals during cross-sex hormone treatment. Brain: A Journal of Neurology 141(7): 2047–2054	Excluded on population – adult study, participants not 18 years or less.
Oda H and Kinoshita T (2017) Efficacy of hormonal and mental treatments with MMPI in FtM individuals: Cross-sectional and longitudinal studies. BMC Psychiatry 17(1): 256	Excluded on population – although study included some younger people (age range 15 to 43), most participants were adults (mean age around 25.6 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.
Olson-Kennedy J, Okonta V, Clark LF et al. (2018) Physiologic Response to Gender-Affirming Hormones Among Transgender Youth. The Journal of Adolescent Health: Official Publication of the Society for Adolescent Medicine 62(4): 397–401	Excluded on population – although study included some younger people (age range 12 to 23; mean age 18 years). Outcomes not reported separately for people aged 18 years or less. Outcomes limited to physiological results (including haemoglobin, lipids, liver enzymes and BMI). Same outcomes reported in included studies that had a less indirect population and a longer follow-up.
Ott J, Kaufmann U, Bentz K et al. (2010) Incidence of thrombophilia and venous thrombosis in transsexuals under cross-sex hormone therapy. Fertility and sterility 93(4): 1267–72	Excluded on population – adult study, participants not 18 years or less.
Pakpoor J, Wotton CJ, Schmierer K et al. (2016) Gender identity disorders and multiple sclerosis risk: A national record-linkage study. Multiple sclerosis. Multiple Sclerosis Journal. 22(13): 1759–1762	Excluded on population – although study included some younger people, outcomes not reported separately for people aged 18 years or less. Also exclude for intervention – unclear if people received gender-affirming hormones.
Pyra M, Casimiro I, Rusie L et al. (2020) An Observational Study of Hypertension and Thromboembolism among Transgender Patients Using Gender-Affirming Hormone Therapy. Transgender Health 5(1): 1–9	Excluded on population – adult study (age range 20-70). Age at which gender-affirming hormones started not reported.
Quiros C, Patrascioiu I, Mora M et al. (2015) Effect of cross-sex hormone treatment on cardiovascular risk factors in transsexual individuals. Experience in a specialized unit in Catalonia. Endocrinologia y nutricion : organo de la Sociedad Espanola de Endocrinologia y Nutricion 62(5): 210–6	Excluded on population – adult study, participants not 18 years or less.

Study reference	Reason for exclusion
Rowniak S, Bolt L, Sharifi C (2019) Effect of cross-sex hormones on the quality of life, depression and anxiety of transgender individuals: A quantitative systematic review. JBI Database of Systematic Reviews and Implementation Reports 17(9): 1826–1854	Exclude on population – all included studies conducted in adult population.
Sequeira GM, Kidd K, El Nokali NE et al. (2019) Early Effects of Testosterone Initiation on Body Mass Index in Transmasculine Adolescents. Journal of Adolescent Health 65(6): 818–820	Exclude on outcome - study only reports BMI z-score over 12 month testosterone treatment. BMI not listed as an outcome of interest in the PICO document. Other included studies have investigated the impact of gender-affirming hormone treatment on CV risk profile, including longer term obesity rates, with a longer follow-up and more participants.
Shim JY, Laufer MR, Grimstad FW (2020) Dysmenorrhea and Endometriosis in Transgender Adolescents. Journal of Pediatric and Adolescent Gynecology. Available online 11 June 2020. https://doi.org/10.1016/j.jpag.2020.06.001	Exclude on population – only 2 participants taking testosterone before diagnosis of dysmenorrhea.
Slabbekoorn D, Van Goozen SHM, Gooren, LJG et al. (2001) Effects of cross-sex hormone treatment on emotionality in transsexuals. International Journal of Transgenderism 5(3): http://www.symposion.com/ijt/ijtvo05no03_02.htm	Excluded on population – adult study (age range 21 to 28 years)
Smith YLS., Van Goozen SHM, Kuiper AJ et al. (2005) Sex reassignment: Outcomes and predictors of treatment for adolescent and adult transsexuals. Psychological Medicine 35(1): 89–99	Excluded on population – results on adults only used to assess hormone treatment.
Sutherland N, Espinel W, Grotzke M et al. (2020) Unanswered Questions: Hereditary breast and gynecological cancer risk assessment in transgender adolescents and young adults. Journal of Genetic Counseling 29(4): 625–633	Excluded on study type – narrative review of 3 case reports.
van Velzen DM, Paldino A, Klaver M et al. (2019) Cardiometabolic Effects of Testosterone in Transmen and Estrogen Plus Cyproterone Acetate in Transwomen. The Journal of Clinical Endocrinology and Metabolism 104(6): 1937–1947	Excluded on population – adult study, participants not 18 years or less.
White Hughto JM and Reisner SL (2016) A Systematic Review of the Effects of Hormone Therapy on Psychological Functioning and Quality of Life in Transgender Individuals. Transgender Health 1(1): 21–31	Exclude on population – all included studies conducted in adult population.
Wiepjes CM, de Blok CJM, Staphorsius AS et al. (2020) Fracture Risk in Trans Women and Trans Men Using Long-Term Gender-Affirming Hormonal Treatment: A Nationwide Cohort Study. Journal of Bone and Mineral Research 35(1): 64–70	Excluded on population – adult study, all participants started gender-affirming hormones after 18 years.
Wierckx K, Mueller S, Weyers S et al. (2012) Long-term evaluation of cross-sex hormone treatment in	Excluded on population – adult study, participants not 18 years or less.

Study reference	Reason for exclusion
transsexual persons. The Journal of Sexual Medicine 9(10): 2641–51	
Wierckx K, Van Caenegem E, Schreiner T et al. (2014) Cross-sex hormone therapy in trans persons is safe and effective at short-time follow-up: results from the European network for the investigation of gender incongruence. The journal of sexual medicine 11(8): 1999–2011	Excluded on population – adult study, participants not 18 years or less.
Wilson R, Jenkins C, Miller H et al. (2006) The effect of oestrogen on cytokine and antioxidant levels in male to female transsexual patients. Maturitas 55(1): 14–8	Excluded on population – adult study, participants not 18 years or less.
Witcomb GL, Bouman WP, Claes L et al. (2018) Levels of depression in transgender people and its predictors: Results of a large matched control study with transgender people accessing clinical services. Journal of Affective Disorders 235: 308–315	Excluded on population – although study included some younger people (age range 15 to 79), most participants were adults (mean age around 30.4 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.

Appendix E Evidence tables

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Achille, C., Taggart, T., Eaton, N.R. et al. (2020) Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: Preliminary results. International Journal of Pediatric Endocrinology 2020(1): 8 **Study location** Single centre, New York, United States **Study type** Prospective longitudinal study **Study aim** To assess the psychological wellbeing and quality of life in children and adolescents who have sought endocrine	Inclusion and exclusion not reported- it appears from the description in the publication that all people referred for gender dysphoria were invited to participate, and the vast majority agreed. Of the 95 treatment naïve people who entered the study, 50 people completed all follow-up questionnaires and were included in the analysis. No description of the 45 people without follow-up data reported. The study included 50 children, adolescents and young adults with gender dysphoria.	**Intervention** Endocrine interventions (the collective term used by authors for puberty suppression and gender-affirming hormones) were introduced as per Endocrine Society and the World Professional Association for	**Critical Outcomes** ***Impact on mental health*** Depression symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CESD-R). Statistically significant improvements in CESD-R score were observed from baseline (initial assessment; 21.4 points) to about 12 months follow-up (13.9 points; p<0.001). Regression analysis, controlling for reported medicines for mental health problems and engagement in counselling, found no statistically significant change from baseline in transfemales (p=0.27) and transmales (p=0.43). The Patient Health Questionnaire Modified for Teens (PHQ 9_Modified for Teens) was also used to assess depression symptoms. Depression scores improved from baseline (p< 0.001; absolute scores not reported numerically). Regression analysis, controlling for reported medicines for mental health problems and engagement in counselling, found no statistically significant change from baseline in transfemales (p=0.07) and transmales (p=0.67). Suicidal ideation measured using the additional questions from the PHQ 9_Modified for Teens, was presented in 10% (5/50) of	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain** 1. b) somewhat representative 2. c) no-non exposed cohort 3. a) secure record 4. b) no **Domain 2: Comparability** 1. c) no comparator **Domain 3: Outcome** 1. c) self-report 2. a) yes – 6 monthly assessment up to 12 months (preliminary results from an ongoing study) 3. c) Follow up rate less than 80% and no description of those lost **Overall quality is assessed as poor** Other comments: Although regression analysis results for some outcomes were controlled for use of medicines for mental health problems,

intervention to help with gender dysphoria. **Study dates** Study recruitment ran from December 2013 to December 2018; study is ongoing	17 transfemales and 33 transmales. Diagnostic criteria for gender dysphoria not reported. Mean age at baseline was 16.2 years (SD 2.2). Mean age at the start of gender-affirming hormone treatment not reported.	Transgender Health (WPATH) guidelines. Puberty suppression was: • GnRH agonist and/or anti-androgens (transfemales) • GnRH agonist or medroxyprogesterone (transmales) Average duration of GnRH analogue treatment not reported. Once eligible, gender-affirming hormones were offered, these were: • Oestradiol (transfemales) • Testosterone (transmales) Doses and route of administration not reported. After about 12-months treatment ('wave 3' in the study): • 24 people (48%) were on gender-affirming hormones alone • 12 people (24%) were on puberty suppression alone	participants at baseline and 6% (3/50) at about 12-month follow-up, no statistical analysis reported. The study also reported results by gender: In transfemales, 11.8% (2/17) had suicidal ideation at baseline compared with 5.9% (1/17) at 12-month follow-up (no statistically analysis reported) In transmales, 9.1% (3/33) had suicidal ideation at baseline compared with 6.1% (2/33) at 12-month follow-up (no statistically analysis reported) ***Impact on quality of life*** Quality of Life Enjoyment and Satisfaction Questionnaire (QLES-Q-SF) scores: there was no statistically significant change in score from baseline to about 12-months (p=0.085; absolute scores not reported numerically). Regression analysis, controlling for reported medicines for mental health problems and engagement in counselling, found not statistically significant change from baseline in transfemales (p=0.06) and transmales (p=0.08). *No other critical or important outcomes reported*	details of these is not reported. Other co-morbidities not reported. Source of funding: None

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
		• 11 people (22%) were on both gender-affirming hormones and puberty suppression • 3 people (6%) were on no endocrine intervention Results not represented separately for the sub-group of people who received gender-affirming hormones. Average duration of treatment with gender-affirming hormones not reported. **Comparison** No comparison group. Change overtime reported.		

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Allen, LR, Watson, LB, Egan, AM et al. (2019) Well-being and suicidality among transgender youth after gender-affirming hormones. Clinical Practice in Pediatric	The study included adolescents and young adults (age range 13-20 years) who received services for gender dysphoria in a clinic in the United States. Participants were required to have received gender-	39 participants received gender-affirming hormones only 8 participants received a GnRH analogue followed by gender-affirming hormones.	**Critical Outcomes** ***Impact on mental health*** The Ask Suicide-Screening Questions (ASQ) instrument was used to assess suicidality. Following an average of about 12 months treatment with gender-affirming hormones, adjusted mean ASQ score was statistically significantly lower (from 1.11 [standard error	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain** 1. b) somewhat representative 2. c) no-non exposed cohort

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Psychology 7(3): 302-311 **Study location** Single centre, Kansas City, United States **Study type** Retrospective longitudinal study **Study aim** To examine suicidality and general well-being following administration of gender-affirming hormones. **Study dates** Participants first presented to the clinic between 2015 and 2018.	affirming hormones for at least 3 months, and have pre-test and final assessment data points. No exclusion criteria reported. In total 47 adolescents and young adults with gender dysphoria were included: 14 transfemales (sex assigned at birth male) and 33 transmales (sex assigned at birth female). Diagnostic criteria for gender dysphoria not reported. Mean age at pre-test (before administration of gender-affirming hormones) was 16.59 years (range 13.73 to 19.04). Mean age at the start of treatment in the sub-group who received gender-affirming hormones-only was 16.72 years. Mean age at the start of treatment with gender-affirming hormones in people who previously	Mean duration of treatment in the gender-affirming hormones only subgroup was 366 days. Mean duration of gender-affirming hormone treatment in people who had previously received a GnRH analogue was not reported. Mean duration of treatment with a GnRH analogue was not reported. Participants were assessed at the start of treatment and at least 3 months after treatment.	(SE) 0.22] at baseline to 0.27 [SE 0.12] at final assessment; p<0.001). The authors also reported change in ASQ separately for transfemales (from 1.21 [SE 0.36] at baseline to 0.24 [SE 0.19] at final assessment) and transmales (from 1.01 [SE 0.36] at baseline to 0.29 [0.13] at final assessment). There was no statistically significant difference in change from baseline between transfemales and transmales (p=0.79) ***Impact on quality of life*** Assessed using the General Well-Being Scale (GWBS) of the Pediatric Quality of Life Inventory. Following an average of about 12 months treatment with gender-affirming hormones, adjusted mean GWBS score was statistically significantly higher (from 61.7 [SE 2.43] at baseline to 70.23 [2.15] at final assessment; p<0.002). The authors also reported change in GWBS of the Pediatric Quality of Life Inventory for transfemales (from 58.44 [SE 4.09] at baseline to 69.52 [SE 3.62] at final assessment) and transmales (from 64.95 [SE 2.66] at baseline to 70.94 [2.35] at final assessment). There was no statistically significant difference in change from baseline between transfemales and transmales (p=0.32) *No other critical or important outcomes reported*	3. a) secure record 4. b) no **Domain 2: Comparability** 2. c) no comparator **Domain 3: Outcome** 1. b) record linkage 2. a) yes – mean duration of treatment was 366 days 3. a) complete follow up - all subjects accounted for **Overall quality is assessed as poor** Other comments: None Source of funding: Not reported

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
	received a GnRH analogue was not reported.			

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Kaltiala, R., Heino, E., Tyolajarvi, M. et al. (2020) Adolescent development and psychosocial functioning after starting cross-sex hormones for gender dysphoria. Nordic Journal of Psychiatry 74(3): 213-219 **Study location** Single centre, Tampere, Finland **Study type** Retrospective chart review **Study aim** To evaluate the psychosocial functioning and need for mental health treatment during the gender identity diagnostic phase and after about	The study included adolescents who were referred to the gender identity service before they 18 years old, were diagnosed with gender dysphoria, received gender-affirming hormones and completed a follow-up of approximately 12 months after starting hormones. In total 52 adolescents were included, comprising of 11 transfemales and 41 transmales. Gender dysphoria was diagnosed according to International Classification of Disease 10 (ICD-10). The authors state that the corresponding diagnosis to 'gender dysphoria' in	Intervention referred to as 'hormonal sex reassignment treatment' – details of intervention not reported, although gender-affirming hormones were prescribed to all participants. It is not clear from the study whether additional interventions were prescribed. Medical records reviewed for the 'real-life phase' – the approximately 12 months follow-up period for this population in Finland.	**Critical Outcomes** ***Impact on mental health*** Of the 52 people who received gender-affirming hormones, 50% (26/52) needed mental health treatment before or during the assessment and 46% (24/51) needed mental health treatment during the 12-month 'real life' phase (no statistically significant difference). For specific symptoms / conditions: • depression: 54% (28/52) needed treatment before or during the assessment and 15% (8/52) needed treatment during the 12-month 'real life' phase (statistically significant reduction, p<0.001) • anxiety: 48% (25/52) needed treatment before or during the assessment and 15% (8/52) needed treatment during the 12-month 'real life' phase (statistically significant reduction, p<0.001) • suicidality/self-harm: 35% (18/52) needed treatment before or during the assessment and 4% (2/52) needed treatment during the 12-month 'real life' phase (statistically significant reduction, p<0.001) • conduct problems/antisocial: 14% (7/52) needed treatment before or during the	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain** 1. b) somewhat representative 2. c) no-non exposed cohort 3. a) secure record 4. b) no **Domain 2: Comparability** 1. c) cohorts are not comparable on the basis of the design or analysis controlled for confounders **Domain 3: Outcome** 1. b) record linkage 2. a) yes – 12 month follow-up 3. a) complete follow up - all subjects accounted for **Overall quality is assessed as poor**

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
a year on gender-affirming hormones. **Study dates** 2011 to 2017	the ICD-10 is 'transsexualism'. Mean age at diagnosis 18.1 years (range 15.2 to 19.9)		assessment and 6% (3/52) needed treatment during the 12-month 'real life' phase (no statistically significant difference, p= 0.18) • psychotic symptoms/psychosis: 2% (1/52) needed treatment before or during the assessment and 4% (2/52) needed treatment during the 12-month 'real life' phase (no statistically significant difference, p= 0.56) • substance abuse: 4% (2/52) needed treatment before or during the assessment and 2% (1/52) needed treatment during the 12-month 'real life' phase (no statistically significant difference, p= 0.56) • autism: 12% (6/52) needed treatment before or during the assessment and 6% (3/52) needed treatment during the 12-month 'real life' phase (no statistically significant difference, p= 0.30) • ADHD: 10% (5/52) needed treatment before or during the assessment and 2% (1/52) needed treatment during the 12-month 'real life' phase (no statistically significant difference, p= 0.09) • eating disorder: 2% (1/52) needed treatment before or during the assessment and 2% (1/52) needed treatment during the 12-month 'real life' phase (no statistically significant difference, p= 1.0). No details of actual treatment reported. **Important Outcomes** ***Psychosocial Impact*** Study reported on measures of functioning in different domains of adolescent development,	Other comments: None Source of funding: No source of funding reported

			reported over the approximately 12-month period after starting gender-affirming hormones (referred to as the 'real-life phase' in Finland) Significantly fewer participants were living with parent(s)/ guardians during the real-life phase (40%; 21/50) compared with during gender identity assessment (73%; 38/52; p=0.001)) There was a statistically significant reduction in the number of participants with normative peer contacts, from gender identity assessment (89%; 46/52) to the real-life phase (81%; 42/52; p<0.001). There was no significant difference in the number of participants who were progressing normally in school or work during gender identity assessment (64%; 33/52) compared with the real-life phase (60%; 31/52). There was no significant difference in the number of participants who have been dating or were in steady relationships during gender identity assessment (62%; 32/50) compared with the real-life phase (58%; 30/52). There was no significant difference in the number of participants who were able to deal with matters outside of the home in an age-appropriate manner during gender identity assessment (81% (42/52) compared with the real-life phase (81%; 42/52)	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			No other critical or important outcomes reported	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding

Full citation
Khatchadourian K, Amed S, Metzger DL (2014) Clinical management of youth with gender dysphoria in Vancouver. The Journal of pediatrics 164(4): 906-11
 	
Study location
Single centre study, Vancouver, Canada
 	
Study type
Retrospective chart review
 	
Study aim
To describe the patient characteristics, clinical management, and response to treatment in a cohort of people seen in a single clinic.
 	
Study dates
1998 to 2011
	Inclusion criteria were at least Tanner stage 2 pubertal development, previous assessment by a mental health professional and a confirmed diagnosis of gender dysphoria (diagnostic criteria not specified). No exclusion criteria are specified.
	
	63 children, adolescents and young people with gender dysphoria who started gender-affirming hormones, out of 84 young people seen in the unit between 1998 and 2011.
	39 transfemales and 24 transmales.
	
	Diagnostic criteria for gender dysphoria not reported.
	
	Mean age at the start of gender-affirming hormone treatment was 17.4 years (SD 1.9).
		Intervention
		Transfemales: Oestrogen (oral micronized 17β-oestradiol)
		Transmales: Testosterone (injectable testosterone enanthate and/or cypionate)
		
		19 participants (30%) had previously received a GnRH analogue. The median time from start of GnRH analogue to start of gender-affirming hormones was 11.3 months (range 2.2 to 42.0). 11 participants continued GnRH analogues after starting gender-affirming hormones.
		
		Average duration of treatment with a GnRH analogue not reported
		
		Comparison
		No comparator
			Critical Outcomes
			
			No critical outcomes assessed.
			
			Important outcomes
			
			Safety
			Of the 63 participants who received gender-affirming hormones:
			• No participants permanently discontinued gender-affirming hormones
			• 3 participants (5%) temporarily discontinued treatment:
			  ○ 2 transmales due to concomitant mental health comorbidities
			  ○ 1 transmale due to androgenic alopecia.
			  ○ No transfemale stopped treatment.
			The authors report that all patients eventually restarted gender-affirming hormones, although they do not report how long treatment was
				This study was appraised using the Newcastle-Ottawa tool for cohort studies.
				
				Domain 1: Selection domain
				1. b) somewhat representative
				2. c) no-non exposed cohort
				3. a) secure record*
				4. b) no
				Domain 2: Comparability
				1. c) cohorts are not comparable on the basis of the design or analysis controlled for confounders
				Domain 3: Outcome
				1. b) record linkage
				2. b) no – although follow-up time is reported for patients with more than 1 clinic visit, duration of treatment with gender-affirming hormones is not reported
				3. c) incomplete - missing data
				
				Overall quality is assessed as poor

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			stopped for, or what the effect of stopped treatment was. • No participants reported major complications • 12 participants (19%) had minor complications: ○ 7 transmales had severe acne (requiring isotretinoin) ○ 1 transmale had andogenic alopecia ○ 3 transmales had mild dyslipidaemia (levels not reported) ○ 1 transmale had significant mood swings ○ No transfemales had minor complications	Other comments: Mental health comorbidity was reported for all participants but not for the gender-affirming hormone cohort separately. Concomitant use of other medicines was not reported. Source of funding: No source of funding identified.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Klaver, Maartje, de Mutsert, Renee, van der Loos, Maria A T C et al. (2020) Hormonal Treatment and Cardiovascular Risk Profile in Transgender Adolescents. Pediatrics 145(3) **Study location** Single centre, Amsterdam, Netherlands	Participants were included if i) they had started GnRH analogue treatment before 18 years, ii) if whole body dual-energy radiograph absorptiometry was performed at least once during treatment (4 months before or after the start of GnRH analogues or gender-affirming hormones, or	Transfemales: Oestrogen (17-β oestradiol [E2]) orally, starting with 5 mcg/kg body weight per day, which was increased every 6 months until the maintenance dose of 2 mg per day was reached. Transmales: mixed testosterone esters (Sustanon), 25 mg/m^2 body surface area every 2 weeks intramuscularly,	**Critical Outcomes** No critical outcomes assessed. **Important outcomes** ***Safety*** Safety outcomes reported separately for transfemales and transmales. **For transfemales**, from the start of gender-affirming hormone treatment to age 22 years: • Mean BMI statistically significantly increased (mean change +1.9, 95% CI 0.6 to 3.2, p<0.005; mean BMI at	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain** 1. b) somewhat representative 2. c) no-non exposed cohort 3. a) secure record* 4. b) no **Domain 2: Comparability** 1. c) cohorts are not comparable on the basis

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Study type Retrospective chart review **Study aim** To examine the effects of treatment on changes in cardiovascular risk factors, including BMI, blood pressure, insulin sensitivity, and lipid levels. **Study dates** 1998-2015	within 1.5 years before or after the 22nd birthday), iii) if they were likely to have had at least 1 medical consultation in young adulthood. The study included 192 young people with dysphoria who met the above inclusion criteria: 71 transfemales and 121 transmales. Gender dysphoria was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria. Mean age at the start of gender-affirming hormones was 16.4 years (SD 1.1) for transfemales and 16.9 years (SD 0.9) for transmales.	increased every 6 months to maintenance dose of 250 mg every 3 to 4 weeks. When GnRH analogues were started after the age of 16 years a different hormone starter dose was used (1 mg oestrogen daily and 75 mg testosterone weekly). Median (IQR) duration of GnRH analogue (monotherapy) was 2.1 years (1.0 to 2.7) in transfemales and 1.0 (0.5 to 2.9) for transmales.	22 years= 23.2, 95% CI 21.6 to 24.8). At age 22 years, 9.9% of the cohort were obese, compared with 3.0% in reference cisgender population[1]. • Mean systolic blood pressure (SBP) did not significantly change (mean change -3 mmHg, 95% CI -8 to 2; mean SBP at 22 years= 117 mmHg, 95% CI 113 to 122) • Mean diastolic blood pressure (DBP) statistically significantly increased (mean change +6 mmHg, 95% CI 3 to 10, p<0.001; mean DBP at 22 years= 75 mmHg, 95% CI 72 to 78) • Mean glucose level did not significantly change (mean change +0.1 mmol/L, 95% CI -0.1 to 0.2; mean glucose level at 22 years= 5.0 mmol/L, 95% CI 4.8 to 5.1) • Mean insulin level did not significantly change (mean change +2.7 mU/L, 95% CI -1.7 to 7.1; mean insulin level at 22 years= 5.0 mU/L (4.8 to 5.1) • Insulin resistance (mean Homeostatic Model Assessment of Insulin Resistance [HOMA-IR]) did not significantly change (mean change +0.7, 95% CI -0.2 to 1.5; mean HOMA-IR at 22 years 2.9, 95% CI 1.9 to 3.9) • Mean total cholesterol did not significantly change (mean change +0.1 mmol/L, 95% CI -0.2 to 0.4; mean total cholesterol at 22 years 4.1 mmol/L, 95% CI 3.8 to 4.4) • Mean HDL cholesterol did not significantly change (mean change +0.0 mmol/L, 95% CI -0.1 to 0.2; mean HDL cholesterol at 22 years 1.6 mmol/L, 95% CI 1.4 to 1.7) • Mean LDL cholesterol did not significantly change (mean change +0.0 mmol/L, 95%	of the design or analysis controlled for confounders **Domain 3: Outcome** 1. b) record linkage 2. a) yes- follow-up from start of gender-affirming hormones to age 22 years, around 5 years 3. a) complete follow up - all subjects accounted for **Overall quality is assessed as poor** Other comments: None Source of funding: No external funding

			CI -0.3 to 0.2; mean LDL cholesterol at 22 years 2.0 mmol/L, 95% CI 1.8 to 2.3) • Mean triglycerides statistically significantly increased (mean change +0.2 mmol/L, 95% CI 0.0 to 0.5, p<0.05; triglyceride level at 22 years 1.1 mmol/L, 95% CI 0.9 to 1.4) **For transmales**, from the start of gender-affirming hormone treatment to age 22 years: • Mean BMI statistically significantly increased (mean change +1.4, 95% CI 0.8 to 2.0, p<0.005; mean BMI at 22 years= 23.9, 95% CI 23.0 to 24.7). At age 22 years, 6.6% of the cohort were obese, compared with 2.2% in reference cisgender population[1]. • Mean systolic blood pressure (SBP) statistically significantly increased (mean change +5 mmHg, 95% CI 1 to 9; mean SBP at 22 years= 126 mmHg, 95% CI 122 to 130) • Mean diastolic blood pressure (DBP) statistically significantly increased (mean change +6 mmHg, 95% CI 4 to 9, p<0.001; mean DBP at 22 years= 74 mmHg, 95% CI 72 to 77) • Mean glucose level did not significantly change (mean change 0.0 mmol/L, 95% CI -0.2 to 0.2; mean glucose level at 22 years= 4.8 mmol/L, 95% CI 4.7 to 5.0) • Mean insulin level statistically significantly decreased (mean change -2.1 mU/L, 95% CI -3.9 to -0.3, p<0.05; mean insulin level at 22 years= 8.6 mU/L (6.9 to 10.2) • Insulin resistance (mean Homeostatic Model Assessment of Insulin Resistance [HOMA-IR]) statistically significantly	

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			decreased (mean change -0.5, 95% CI -1.0 to -0.1, p<0.05; mean HOMA-IR at 22 years 1.8, 95% CI 1.4 to 2.2) • Mean total cholesterol statistically significantly increased (mean change +0.4 mmol/L, 95% CI 0.2 to 0.6, p<0.001; mean total cholesterol at 22 years 4.6 mmol/L, 95% CI 4.3 to 4.8) • Mean HDL cholesterol statistically significantly decreased (mean change -0.3 mmol/L, 95% CI -0.4 to -0.2, p<0.001; mean HDL cholesterol at 22 years 1.3 mmol/L, 95% CI 1.2 to 1.3) • Mean LDL cholesterol statistically significantly increased (mean change +0.4 mmol/L, 95% CI 0.2 to 0.6, p<0.001; mean LDL cholesterol at 22 years 2.6 mmol/L, 95% CI 2.4 to 2.8) • Mean triglycerides statistically significantly increased (mean change +0.5 mmol/L, 95% CI 0.3 to 0.7, p<0.001; triglyceride level at 22 years 1.3 mmol/L, 95% CI 1.1 to 1.5)	

[1] Reference population taken from Fredriks et al. (2000)

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Klink D, Caris M, Heijboer A et al. (2015) Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. The Journal of Clinical Endocrinology and Metabolism 100(2): e270-5 **Study location** Single centre, Amsterdam, Netherlands **Study type** Retrospective longitudinal study **Study aim** To assess peak bone mass in young adults with gender dysphoria who had received GnRH analogues and gender-affirming hormones during their pubertal years. **Study dates**	34 young people with gender dysphoria who received GnRH analogues, gender-affirming hormones and gonadectomy. The study included 15 transfemales and 19 transmales; mean age at start of gender-affirming hormones was 16.6 years (SD 1.4) and 16.4 years (SD 2.3) respectively. Participants were required to meet the DSM-IV-TR criteria for gender identity disorder of adolescence. Participants were included if they had undergone gonadectomy between June 1998 and August 2012, and they were at least 21 years old when they had the surgery. Bone mineral density data were also required at the start of GnRH analogue, gender-affirming hormones and at the age of 22 years. No concomitant treatments were reported.	**Intervention** Transfemales - oral 17-β oestradiol (incremental dosing) Transmales – IM testosterone (Sustanon 250 mg/ml; incremental dosing) Median duration of treatment with gender-affirming hormones for transfemales was 5.8 years (range 3.0 to 8.0) and for transmales was 5.4 years (range 2.8 to 7.8). The GnRH analogue was SC triptorelin 3.75 mg every 4 weeks. No details of gonadectomy reported. **Comparison** No comparison group. Comparison over time reported.	**Critical outcomes** No critical outcomes reported **Important outcomes** **Safety** ***Bone density: lumbar spine*** **Lumbar spine bone mineral apparent density (BMAD)** Change from starting gender-affirming hormones to age 22 years in transfemales-Mean (SD); g/m^3 • Start of gender-affirming hormones: 0.22 (0.02) • Age 22 years: 0.23 (0.03) • p=0.003 z-score (range) • Start of gender-affirming hormones: -0.90 (0.80) • Age 22 years: -0.78 (1.03) • No statistically significant difference Change from starting gender-affirming hormones to age 22 years in transmales-Mean (SD); g/m^3 • Start of gender-affirming hormones: 0.24 (0.02) • Age 22 years: 0.25 (0.28 • p=0.001 z-score (SD) • Start of gender-affirming hormones: -0.50 (0.81) • Age 22 years: -0.033 (0.95) • p=0.002	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain** 1. b) somewhat representative 2. c) no-non exposed cohort 3. a) secure record* 4. b) no **Domain 2: Comparability** 1. c) cohorts are not comparable on the basis of the design or analysis controlled for confounders **Domain 3: Outcome** 1. b) record linkage 2. a) yes – mean duration of gender-affirming hormone treatment was 5.8 and 5.4 years. 3. c) follow-up rate variable across timepoints and no description of those lost **Overall quality is assessed as poor** Other comments: Within person comparison. Small numbers of participants in each subgroup. No

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Gonadectomy took place between June 1998 and August 2012	At the start of gender-affirming hormone treatment, in the transfemale subgroup the median Tanner P was 4 (IQR 2) and the median Tanner G was 12 (IQR 11). In the transmale subgroup the median Tanner B was 5 (IQR 2) and the median Tanner P was 5 (IQR 0).		**Lumbar spine bone mineral density (BMD)** Change from starting gender-affirming hormones to age 22 years in transfemales-Mean (SD); g/m^2 • Start of gender-affirming hormones: 0.84 (0.11) • Age 22 years: 0.93 (0.10) • p<0.001 z-score (range) • Start of gender-affirming hormones: -1.01 (0.98) • Age 22 years: -1.36 (0.83) • No statistically significant difference Change from starting gender-affirming hormones to age 22 years in transmales-Mean (SD); g/m^2 • Start of gender-affirming hormones: 0.91 (0.10) • Age 22 years: 0.99 (0.13) • P<0.001 z-score (range) • Start of gender-affirming hormones: -0.72 (0.99) • Age 22 years: -0.33 (1.12) • No statistically significant difference ***Bone density: femoral region, nondominant side*** **Femoral region, nondominant side BMAD** Change from starting gender-affirming hormones to age 22 years in transfemales-Mean (SD); g/m^3 • Start of gender-affirming hormones: 0.26 (0.04) • Age 22 years: 0.28 (0.05)	concomitant treatments or comorbidities were reported. Source of funding: None disclosed

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			• No statistically significant difference z-score (SD) • Start of gender-affirming hormones: -1.57 (1.74) • Age 22 years: Not reported • No statistical analysis reported Change from starting gender-affirming hormones to age 22 years in transmales-Mean (SD); g/m^3 • Start of gender-affirming hormones: 0.31 (0.04) • Age 22 years: 0.33 (0.05) • p=0.010 z-score (SD) • Start of gender-affirming hormones: -0.28 (0.74) • Age 22 years: Not reported • No statistical analysis reported **Femoral region, nondominant side BMD** Change from starting gender-affirming hormones to age 22 years in transfemales-Mean (SD); g/m^2 • Start of gender-affirming hormones: 0.87 (0.08) • Age 22 years: 0.94 (0.11) • P=0.009 z-score (SD) • Start of gender-affirming hormones: -0.95 (0.63) • Age 22 years: -0.69 (0.74) • No statistically significant difference Change from starting gender-affirming hormones to age 22 years in transmales-Mean (SD); g/m^2 • Start of gender-affirming hormones: 0.88 (0.09) • Age 22 years: 0.95 (0.10)	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			• P<0.001 z-score (SD) • Start of gender-affirming hormones: -0.35 (0.79) • Age 22 years: -0.35 (0.74) • p=0.006	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Kuper, Laura E, Stewart, Sunita, Preston, Stephanie et al. (2020) Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy. Pediatrics 145(4) **Study location** Single centre, Texas, USA **Study type** Prospective longitudinal study **Study aim** To: • explore how baseline body dissatisfaction, depression, and anxiety symptoms vary by gender,	148 children and adolescents with gender dysphoria, n=148, of whom: • 25 received puberty suppression only • 93 received gender-affirming hormone therapy only • 30 received both Results for treatments reported separately. Mean age at initial assessment was 15.4 years (range 9 to 18). Mean age at start of gender-affirming hormone therapy was 16.2 years (range 13.2 to 18.6). All participants met the Diagnostic and Statistical	Hormone therapy, guided by Endocrine Society Clinical Practice Guidelines Follow-up at least 18 months from initial assessment at the clinic. Mean duration of gender-affirming hormone therapy before follow-up was 10.9 months (range 1 to 18; SD 3.3)	**Critical Outcomes** ***Impact on mental health*** Mean depression score, assessed using the Quick Inventory of Depressive Symptoms (QIDS), self-reported was 9.6 (SD 5.0) at baseline and 7.4 (SD 4.5) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant. Mean depression score, assessed using the QIDS, clinician-reported was 5.9 (SD 4.1) at baseline and 6.0 (SD 3.8) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant. Mean anxiety score, assessed using the Screen for Child Anxiety Related Emotional Disorders (SCARED) questionnaire was 32.6 (SD 16.3) at baseline and 28.4 (SD 15.9) at	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain** 1. b) somewhat representative 2. c) no-non exposed cohort 3. a) secure record 4. b) no **Domain 2: Comparability** 1. c) cohorts are not comparable on the basis of the design or analysis controlled for confounders **Domain 3: Outcome** 1. d) assessors not blinded to treatment 2. a) yes – follow-up at least 18 months from initial assessment. Mean duration of gender-affirming hormone

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
age at initial assessment, and Tanner stage at first medical visit • examine how body dissatisfaction, depression, and anxiety symptoms change over the first year of gender-affirming hormone treatment • explore how any changes vary by affirmed gender, Tanner stage, age, type of treatment, months on gender-affirming hormone therapy, mental health treatment received, and whether chest surgery was also obtained (among transmales). **Study dates** Initial participant assessments took place between August 2014 and March 2018.	Manual of Mental Disorders, Fifth Edition criteria for gender dysphoria. Specific inclusion and exclusion criteria for the study are not reported. It would appear that all children and adolescents eligible for gender-affirming hormones were considered eligible for the study. The authors state that before initial assessment with a psychologist, psychiatrist, and/or clinical therapist, parents completed a phone intake survey. Around one-third of families did not follow-up after the phone intake.		follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant. Mean panic score, assessed using specific questions from the SCARED questionnaire was 8.1 (SD 6.3) at baseline and 7.1 (SD 6.5) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant. Mean generalised anxiety score, assessed using specific questions from the SCARED questionnaire was 10.0 (SD 5.1) at baseline and 8.8 (SD 6.5) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant. Mean social anxiety score, assessed using specific questions from the SCARED questionnaire was 8.5 (SD 4.1) at baseline and 7.7 (SD 4.2) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant. Mean separation anxiety score, assessed using specific questions from the SCARED	treatment was 10.9 months. 3. c) patient numbers vary by outcome with no explanation **Overall quality is assessed as poor** Other comments: None Source of funding: Supported by Children's Health. The Research Electronic Data Capture database was funded by the Clinical and Translational Science Awards program

			questionnaire was 3.5 (SD 3.0) at baseline and 3.1 (SD 2.5) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant. Mean school avoidance score, assessed using specific questions from the SCARED questionnaire was 2.6 (SD 2.1) at baseline and 2.0 (SD 2.0) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant. The authors also reported results separately for transfemales and transmales: **Transfemales** No statistical analyses were reported for this sub-group and it is unclear whether any changes in score were statistically significant. • Mean depression symptoms, assessed using the QIDS, self-reported was 7.5 (SD 4.9) at baseline and 6.6 (SD 4.4) at follow-up. • Mean depression symptoms, assessed using the QIDS, clinician-reported was 4.2 (SD 3.2) at baseline and 5.4 (SD 3.4) at follow-up. • Mean anxiety symptoms, assessed using the SCARED questionnaire was 26.4 (SD 14.2) at baseline and 24.3 (SD 15.4) at follow-up.	

			• Mean panic symptoms, assessed using specific questions from the SCARED questionnaire was 5.7 (SD 4.9) at baseline and 5.1 (SD 4.9) at follow-up. • Mean generalised anxiety symptoms, assessed using specific questions from the SCARED questionnaire was 8.6 (SD 5.1) at baseline and 8.0 (SD 5.1) at follow-up. • Mean social anxiety symptoms, assessed using specific questions from the SCARED questionnaire was 7.1 (SD 3.9) at baseline and 6.8 (SD 4.4) at follow-up. • Mean separation anxiety symptoms, assessed using specific questions from the SCARED questionnaire was 3.4 (SD 3.3) at baseline and 2.7 (SD 2.3) at follow-up. • Mean school avoidance symptoms, assessed using specific questions from the SCARED questionnaire was 1.8 (SD 1.7) at baseline and 1.9 (SD 2.1) at follow-up. **Transmales** No statistical analyses were reported for this sub-group and it is unclear whether any changes in score were statistically significant. • Mean depression symptoms, assessed using the QIDS, self-reported was 10.4 (SD 5.0) at baseline and 7.5 (SD 4.5) at follow-up. • Mean depression symptoms, assessed using the QIDS, clinician-reported was 6.7 (SD 4.4) at baseline and 6.2 (SD 4.1) at follow-up. • Mean anxiety symptoms, assessed using the SCARED questionnaire was 35.4 (SD	

			16.5) at baseline and 29.8 (SD 15.5) at follow-up. • Mean panic symptoms, assessed using specific questions from the SCARED questionnaire was 9.3 (SD 6.5) at baseline and 7.9 (SD 6.5) at follow-up. • Mean generalised anxiety symptoms, assessed using specific questions from the SCARED questionnaire was 10.4 (SD 5.0) at baseline and 9.0 (SD 5.1) at follow-up. • Mean social anxiety symptoms, assessed using specific questions from the SCARED questionnaire was 8.5 (SD 4.0) at baseline and 7.8 (SD 4.1) at follow-up. • Mean separation anxiety symptoms, assessed using specific questions from the SCARED questionnaire was 4.2 (SD 3.4) at baseline and 3.4 (SD 2.6) at follow-up. • Mean school avoidance symptoms, assessed using specific questions from the SCARED questionnaire was 2.6 (SD 2.1) at baseline and 2.0 (SD 2.0) at follow-up. No difference in impact on mental health found by Tanner age. Numerical results, statistical analysis and information on specific outcomes not reported. It is unclear from the paper whether Tanner age is at initial assessment, start of GnRH analogues, start of gender-affirming hormones, or another timepoint. **Important Outcomes** ***Impact on body image***	

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			Mean Body Image Scale (BIS) score was 70.7 (SD 15.2) at baseline and 51.4 (SD 18.3) at follow-up. The authors do not present statistical analysis for this population and it is unclear whether the change in score was statistically significant. The authors also reported body image results separately for transfemales and transmales. No statistical analyses were reported for this sub-groups and it is unclear whether changes in score were statistically significant. • In transfemales, BIS score was 67.5 (SD 19.5) at baseline and 49.0 (SD 21.6) at follow-up. • In transmales, BIS score was 71.1 (SD 13.4) at baseline and 52.9 (SD 16.8) at follow-up. No difference in body image score found by Tanner age. Numerical results, statistical analysis and information on specific outcomes not reported. It is unclear from the paper whether Tanner age is at initial assessment, start of GnRH analogues, start of gender-affirming hormones, or another timepoint. *No other critical or important outcomes reported*	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Study dates Lopez de Lara, D., Perez Rodriguez, O., Cuellar Flores, I. et al. (2020) Psychosocial assessment in transgender adolescents. Anales de Pediatria **Study location** Single centre in Madrid, Spain **Study type** Prospective analytical study **Study aim** To assess the psychosocial status of patients seeking care in the paediatric endocrinology clinic for gender dysphoria, and the impact on psychosocial status of gender-affirming hormone therapy at 12 months of treatment **Study dates** Not reported	23 adolescents with gender dysphoria; 16 transmale and 7 transfemale. Participants were required to be at a stage of pubertal development of Tanner 2 or higher. People with mental health comorbidity that could affect the experience of gender dysphoria were excluded. Mean age at baseline was 16 years (range 14 to 18). 30 cisgender controls, matched for age, ethnicity, and socioeconomic status	Gender-affirming hormones- • Oral oestradiol • Intramuscular testosterone Participants had previously received gonadotropin-releasing hormone (GnRH) analogues in the intermediate pubertal stages (Tanner 2---3).	**Critical Outcomes** ***Impact on gender dysphoria*** Following gender-affirming hormones for 12 months, mean (±SD) Utrecht Gender Dysphoria Scale (UGDS) score statistically significantly improved, from 57.1 (±4.1) at baseline to 14.7 (±3.2; p<0.001) ***Impact on mental health*** Mean depression score statistically significantly improved following treatment with gender-affirming hormones. Mean Beck Depression Inventory II (BDI-II) score (±SD) reduced from 19.3 points (±5.5) at baseline to 9.7 points (±3.9) at 12 months (p<0.001). Mean anxiety scores statistically significantly improved following treatment with gender-affirming hormones. Mean (±SD) State-Trait Anxiety Inventory (STAI) State subscale score improved from 33.3 points (±9.1) at baseline to 16.8 points (±8.1) at 12 months (p<0.001). Mean (±SD) State-Trait Anxiety Inventory (STAI) Trait subscale score improved from 33.0 points (±7.2) at baseline to 18.5 points (±8.4) at 12 months (p<0.001). **Important Outcomes** ***Psychosocial Impact*** There was not change in family functioning, measured using the Family APGAR test, from baseline (17.9 points) to 1 year after starting	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain** 1. b) somewhat representative 2. Not applicable – although a control group is reported on, people in this group did not have gender dysphoria. 3. a) secure record* 4. b) no **Domain 2: Comparability** 1. Not applicable – although a control group is reported on, people in this group did not have gender dysphoria. **Domain 3: Outcome** 1. d) assessors not blinded to treatment 2. a) yes – 12 months treatment with gender-affirming hormones 3. a) complete follow up - all subjects accounted for **Overall quality is assessed as poor**

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			gender-affirming hormones (18.0 points; no statistical analysis reported). Results from the Strengths and Difficulties Questionnaire, Spanish Version (SDQ-Cas) showed statistically significant improvements from baseline (14.7 points; SD±3.3) to 12 months after gender-affirming hormones (10.3 points; SD±2.9; p<0.001) *No other critical or important outcomes reported*	Other comments: None Source of funding: Not reported

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Stoffers, Iris E; de Vries, Martine C; Hannema, Sabine E (2019) Physical changes, laboratory parameters, and bone mineral density during testosterone treatment in adolescents with gender dysphoria. The journal of sexual medicine 16(9): 1459-1468 **Study location** Single centre, Leiden, Netherlands **Study type** Retrospective chart review **Study aim** To report changes in height, BMI, blood pressure, laboratory parameters and bone density. **Study dates** November 2010 to August 2018	62 transmales with gender dysphoria. participants were required to have been receiving testosterone therapy for at least 6 months. Further inclusion or exclusion criteria not reported. Gender dysphoria was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria. .	Testosterone intramuscular injection (Sustanon 250 mg). Dose escalated every 6 months up to the standard adult dose of 125 mg every 2 weeks or 250 mg every 3-4 weeks. A more rapid dose escalation was using in patients who started GnRH analogue treatment at 16 years or older. Median age at start of testosterone treatment was 17.2 years (range 14.9 to 18.4) Median duration of testosterone treatment was 12 months (range 5 to 33) Median duration of GnRH analogue treatment was 8 months (range 3 to 39)	**Critical Outcomes** No critical outcomes assessed. **Important outcomes** ***Safety*** ***Bone mineral density (BMD): lumbar spine*** There was no statistically significant difference in lumber spine bone mineral density (BMD) from start of testosterone treatment to any timepoint, up to 24 months follow-up. Mean (±SD), g/cm^2: • Start of testosterone: 0.90 (±0.11) • 6 months: 0.94 (±0.10) • 12 months: 0.95 (±0.09) • 24 months: 0.95 (±0.11) z-score (±SD): • Start of testosterone: -0.81 (±1.02) • 6 months: -0.67 (±0.95) • 12 months: -0.66 (±0.81) • 24 months: -0.74 (±1.17) ***Bone mineral density (BMD): femoral neck (hip)*** There was no statistically significant difference in right or left femoral neck (hip) bone mineral density (BMD) from start of	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain** 1. b) somewhat representative 2. c) no-non exposed cohort 3. a) secure record* 4. b) no **Domain 2: Comparability** 1. c) cohorts are not comparable on the basis of the design or analysis controlled for confounders **Domain 3: Outcome** 1. b) record linkage 2. a) yes – mean duration of gender-affirming hormone treatment was 5.8 and 5.4 years. 3. a) complete follow up - all subjects accounted for **Overall quality is assessed as poor** Other comments: None Source of funding: None

			testosterone treatment to any timepoint, up to 24 months follow-up.
			Right
			Mean (±SD), g/cm^2:
			• Start of testosterone: 0.77 (±0.08)
			• 6 months: 0.84 (±0.11)
			• 12 months: 0.82 (±0.08)
			• 24 months: 0.85 (±0.11)
			z-score (±SD):
			• Start of testosterone: -0.97 (0.79)
			• 6 months: -0.54 (±0.96)
			• 12 months: -0.80 (±0.69)
			• 24 months: -0.31 (±0.84)
			Left
			Mean (±SD), g/cm^2:
			• Start of testosterone: 0.76 (±0.09)
			• 6 months: 0.83 (±0.12)
			• 12 months: 0.81 (±0.08)
			• 24 months: 0.86 (±0.09)
			z-score (±SD):
			• Start of testosterone: -1.07 (0.85)
			• 6 months: -0.62 (±1.12)
			• 12 months: -0.93 (±0.63)
			• 24 months: -0.20 (±0.70)
			
			Other safety-related outcomes
			• Alkaline phosphatase: statistically significant increases observed from start of testosterone treatment to 6 months and 12 months ($p<0.001$), although difference at 24 months was not statistically significant. Median (IQR), U/L
			  ○ Start of testosterone: 102 (78 to 136)
			  ○ 6 months: 115 (102 to 147)
			  ○ 12 months: 112 (88 to 143)
			  ○ 24 months: 81 (range 69 to 98)
			• Creatinine: statistically significant increases observed from start of	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			testosterone treatment to 6, 12 and 24 months (p<0.001). Mean (±SD), umol/L ○ Start of testosterone: 62 (±7) ○ 6 months: 70 (±9) ○ 12 months: 74 (±10) ○ 24 months: 81 (±10) There was no statistically significant change from start of testosterone treatment in: • HbA1c • Aspartate aminotransferase (AST) • Alanine aminotransferase (ALT) • Gamma-glutamyl transferase • Urea Numerical results, follow-up duration and further details of statistical analysis not reported.	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Vlot MC, Klink DT, den Heijer M et al. (2017) Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. Bone 95: 11-19 **Study location** Single centre, Amsterdam, Netherlands **Study type** Retrospective chart review **Study aim** To investigate the impact of GnRH analogues and gender-affirming hormones on bone mineral apparent density (BMAD) in transgender adolescents. The study also report on levels of bone turnover markers, although the authors concluded that the	70 adolescents with gender dysphoria (42 transmales and 28 transfemales). Median age (range) at the start of gender-affirming hormones was 16.3 years (15.9 to 19.5) for transmales and 16.0 years (14.0 to 18.9) for transfemales. Participants were included if they had a diagnosis of gender dysphoria according to DSM-IV-TR criteria who received GnRH analogues and then gender-affirming hormones. No concomitant treatments were reported. The study categorised participants into a young and old pubertal group, based on their bone age. The young transmales had a bone age of <14 years and the old transmales had a bone age of ≥14 years. The young transfemales	Transfemales: Oestradiol oral Dose escalated every 6 months until standard adult dose of 2 mg daily was reached Transmales: Testosterone intramuscular injection (Sustanon 250 mg). Dose escalated every 6 months up to the standard adult dose of 250 mg every 4 weeks or 250 mg every 3-4 weeks. All participants previously received a GnRH analogue (triptorelin 3.75 mg subcutaneously every 4 weeks) Median duration of GnRH analogue therapy not reported.	**Critical outcomes** No critical outcomes reported **Important outcomes** ***Bone density: lumbar spine*** **Lumbar spine bone mineral apparent density (BMAD)** Transfemales (bone age <15 years), change from starting gender-affirming hormones to 24 months follow-up. Median (range), g/m^3 • Start of gender-affirming hormones (C0): 0.20 (0.18 to 0.24) • 24-month follow-up (C24): 0.22 (0.19 to 0.27) • Statistically significant increase (p≤0.01) z-score (range) • Start of gender-affirming hormones (C0): -1.52 (-2.36 to 0.42) • 24-month follow-up (C24): • Statistically significant increase (p≤0.05) Transfemales (bone age ≥15 years), change from starting gender-affirming hormones to 24 months follow-up. Median (range), g/m^3 • Start of gender-affirming hormones: 0.22 (0.19 to 0.24) • 24-months: 0.23 (0.21 to 0.26) • Statistically significant increase (p≤0.05) z-score (range) • Start of gender-affirming hormones: -1.15 (-2.21 to 0.08) • 24-months: -0.66 (-1.66 to 0.54)	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain** 1. b) somewhat representative 2. c) no-non exposed cohort 3. a) secure record* 4. b) no **Domain 2: Comparability** 1. c) cohorts are not comparable on the basis of the design or analysis controlled for confounders **Domain 3: Outcome** 1. b) record linkage 2. a) yes- 24 month follow-up 3. a) complete follow up - all subjects accounted for **Overall quality is assessed as poor.** Other comments: None Source of funding: grant from Abbott diagnostics

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
added value of these seems to be limited. **Study dates** Participants started gender-affirming therapy between 2001 and 2011	group had a bone age of <15 years and the old transfemales group ≥15 years.		Statistically significant increase (p≤0.05) Transmales (bone age <14 years), change from starting gender-affirming hormones to 24 months follow-up. Median (range), g/m^3 • Start of gender-affirming hormones: 0.23 (0.19 to 0.28) • 24-months: 0.25 (0.22 to 0.28) • Statistically significant increase (p≤0.01) z-score (range) • Start of gender-affirming hormones: -0.84 (-2.2 to 0.87) • 24-months: -0.15 (-1.38 to 0.94) Statistically significant increase (p≤0.01) Transmales (bone age ≥14 years), change from starting gender-affirming hormones to 24 months follow-up. Median (range), g/m^3 • Start of gender-affirming hormones: 0.24 (0.20 to 0.28) • 24-months: 0.25 (0.21 to 0.30) • Statistically significant increase (p≤0.01) z-score (range) • Start of gender-affirming hormones: -0.29 (-2.28 to 0.90) • 24-months: -0.06 (-1.75 to 1.61) Statistically significant increase (p≤0.01) ***Bone density: femoral neck*** **Femoral neck BMAD** Transfemales (bone age <15 years), change from starting gender-affirming hormones to 24 months follow-up.	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			Median (range), g/m^3 • Start of gender-affirming hormones: 0.27 (0.20 to 0.33) • 24-months: 0.27 (0.20 to 0.36) • No statistically significant change z-score (range) • Start of gender-affirming hormones: -1.32 (-3.39 to 0.21) • 24-months: -1.30 (-3.51 to 0.92) • No statistically significant change Transfemales (bone age ≥15 years), change from starting gender-affirming hormones to 24 months follow-up. Median (range), g/m^3 • Start of gender-affirming hormones: 0.30 (0.26 to 0.34) • 24-months: 0.29 (0.24 to 0.38) • No statistically significant change z-score (range) • Start of gender-affirming hormones: -0.36 (-1.50 to 0.46) • 24-months: -0.56 (-2.17 to 1.29) • No statistically significant change Transmales (bone age <14 years), change from starting gender-affirming hormones to 24 months follow-up. Median (range), g/m^3 • Start of gender-affirming hormones: 0.30 (0.22 to 0.35) • 24-months: 0.33 (0.23 to 0.37) • Statistically significant increase (p≤0.01) z-score (range) • Start of gender-affirming hormones: -0.37 (-2.28 to 0.47) • 24-months: -0.37 (-2.03 to 0.85)	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			• Statistically significant increase (p≤0.01) Transmales (bone age ≥14 years), change from starting gender-affirming hormones to 24 months follow-up. • Start of gender-affirming hormones: 0.30 (0.23 to 0.41) • 24-months: 0.32 (0.23 to 0.41) • Statistically significant increase (p≤0.01) z-score (range) • Start of gender-affirming hormones: -0.27 ((-1.91 to 1.29) • 24-months: 0.02 (-2.1 to 1.35) • Statistically significant increase (p≤0.05)	

Appendix F Quality appraisal checklists

Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort
    a) Truly representative (one star)
    b) Somewhat representative (one star)
    c) Selected group
    d) No description of the derivation of the cohort
2) Selection of the non-exposed cohort
    a) Drawn from the same community as the exposed cohort (one star)
    b) Drawn from a different source
    c) No description of the derivation of the non exposed cohort
3) Ascertainment of exposure
    a) Secure record (e.g., surgical record) (one star)
    b) Structured interview (one star)
    c) Written self report
    d) No description
    e) Other
4) Demonstration that outcome of interest was not present at start of study
    a) Yes (one star)
    b) No

Comparability

1) Comparability of cohorts on the basis of the design or analysis controlled for confounders
    a) The study controls for age, sex and marital status (one star)
    b) Study controls for other factors (list) _____ (one star)
    c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcome

1) Assessment of outcome
    a) Independent blind assessment (one star)
    b) Record linkage (one star)
    c) Self report
    d) No description
    e) Other
2) Was follow-up long enough for outcomes to occur
    a) Yes (one star)
    b) No
    Indicate the median duration of follow-up and a brief rationale for the assessment above:_____
3) Adequacy of follow-up of cohorts
    a) Complete follow up- all subject accounted for (one star)

b) Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. (one star)
c) Follow up rate less than 80% and no description of those lost
d) No statement

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Appendix G Grade profiles

Table 2: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? - Gender dysphoria

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on gender dysphoria (1 uncontrolled, prospective observational study)									
Change from baseline in mean gender dysphoria score, measured using the UGDS (duration of treatment 12 months). Higher scores indicate greater gender dysphoria.									
1 cohort study Lopez de Lara et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=23	None	T0 (baseline) = 57.1 (SD 4.1) T1 (12 months) = 14.7 (SD 3.2) Statistically significant improvement, p<0.001	Critical	VERY LOW

Abbreviations: p: p-value; SD: standard deviation; UGDS: Utrecht Gender Dysphoria Scale

1 Downgraded 1 level - the cohort study by Lopez de Lara et al. 2020 was assessed at high risk of bias (poor quality overall; lack of blinding and no control group)

Table 3: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Mental health

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on mental health (3 uncontrolled, prospective observational studies and 2 uncontrolled, retrospective observational studies)									
Change from baseline in mean depression score, measured using the BDI-II (duration of treatment 12 months). Higher scores indicate more severe depression.									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 cohort study Lopez de Lara et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=23	None	T0 (baseline) = 19.3 (SD 5.5) T1 (12 months) = 9.7 (SD 3.9) Statistically significant improvement, p<0.001	Critical	VERY LOW
Change from baseline in mean depression score, measured using the CESD-R (approximately 12-month follow-up). Higher scores indicate more severe depression.									
1 cohort study Achille et al. 2020	Serious limitations[2]	Serious indirectness[3]	No serious inconsistency	Not calculable	N=50	None	Wave 1 (baseline) = 21.4 Wave 3 (approx. 12 months) = 13.9 Statistically significant improvement (p<0.001)	Critical	VERY LOW
Change from baseline in depression score, measured using the Patient Health Questionnaire Modified for Teens (PHQ 9_Modified for Teens) (approximately 12-month follow-up). Higher scores indicate more severe depression.									
1 cohort study Achille et al. 2020	Serious limitations[2]	Serious indirectness[3]	No serious inconsistency	Not calculable	N=50	None	Statistically significant reductions in mean score, p<0.001 Results presented diagrammatically, numerical results for mean score not reported	Critical	VERY LOW
Change from baseline in depression symptoms, measured using the Quick Inventory of Depressive Symptoms (QIDS), self-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.									
1 cohort study Kuper et al. 2020	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=105	None	Baseline = 9.6 (SD 5.0) Follow-up = 7.4 (SD 4.5) No statistical analysis reported for the sub-group of participants receiving gender-affirming hormones	Critical	VERY LOW
Change from baseline in depression symptoms, measured using the Quick Inventory of Depressive Symptoms (QIDS), clinician-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.									
1 cohort study	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=106	None	Baseline = 5.9 (SD 4.1) Follow-up = 6.0 (SD 3.8)	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Kuper et al. 2020							No statistical analysis reported for the sub-group of participants who received gender-affirming hormones		
Need for treatment due to depression, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 54% (28/52) During real life phase 15% (8/52) Statistically significant reduction (p<0.001)	Critical	VERY LOW
Change from baseline in anxiety score, measured using the STAI-State subscale (duration of treatment 12 months). Higher scores indicate more severe anxiety.									
1 cohort study Lopez de Lara et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=23	None	T0 (baseline) = 33.3 (SD 9.1) T1 (12 months) = 16.8 (SD 8.1) Statistically significant improvement, p<0.001	Critical	VERY LOW
Change from baseline in anxiety score, measured using the STAI-Trait subscale (duration of treatment 12 months). Higher scores indicate more severe anxiety.									
1 cohort study Lopez de Lara et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=23	None	T0 (baseline) = 33.0 (SD 7.2) T1 (12 months) = 18.5 (SD 8.4) Statistically significant improvement, p<0.001	Critical	VERY LOW
Change from baseline in anxiety symptoms, measured using the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe anxiety.									
1 cohort study Kuper et al. 2020	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=80	None	Baseline = 32.6 (SD 16.3) Follow-up = 28.4 (SD 15.9) No statistical analysis reported for the sub-group of participants	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							who received gender-affirming hormones		
Change from baseline in panic symptoms, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=82	None	Baseline = 8.1 (SD 6.3) Follow-up = 7.1 (SD 6.5) No statistical analysis reported for the sub-group of participants who received gender-affirming hormones	Critical	VERY LOW
Change from baseline in generalised anxiety symptoms, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=82	None	Baseline = 10.0 (SD 5.1) Follow-up = 8.8 (SD 5.0) No statistical analysis reported for the sub-group of participants who received gender-affirming hormones	Critical	VERY LOW
Change from baseline in social anxiety symptoms, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=82	None	Baseline = 8.5 (SD 4.1) Follow-up = 7.7 (SD 4.2) No statistical analysis reported for the sub-group of participants who received gender-affirming hormones	Critical	VERY LOW
Change from baseline in separation anxiety symptoms, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=81	None	Baseline = 3.5 (SD 3.0) Follow-up = 3.1 (SD 2.5) No statistical analysis reported for the sub-group of participants	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							who received gender-affirming hormones		
Change from baseline in school avoidance, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=80	None	Baseline = 2.6 (SD 2.1) Follow-up = 2.0 (SD 2.0) No statistical analysis reported for the sub-group of participants who received gender-affirming hormones	Critical	VERY LOW
Need for treatment due to anxiety, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 48% (25/52) During real life phase 15% (8/52) Statistically significant reduction (p<0.001)	Critical	VERY LOW
Change from baseline in adjusted mean suicidality score, measured using the ASQ instrument (mean treatment duration 349 days). Higher scores indicate a greater degree of suicidality.									
1 cohort study Allen et al. 2019	Serious limitations[5]	No serious indirectness	No serious inconsistency	Not calculable	N=39	None	T0 (baseline) = 1.11 (SE 0.22) T1 (final assessment) = 0.27 (SE 0.12) Statistically significant improvement in score from T0 to T1, p<0.001	Critical	VERY LOW
Change from baseline in percentage of participants with suicidal ideation, measured using the additional questions from the PHQ 9_Modified for Teens (approximately 12-month follow-up)									
1 cohort study Achille et al. 2020	Serious limitations[2]	Serious indirectness[3]	No serious inconsistency	Not calculable	N=50	None	Wave 1 (baseline) = 10% (5/50) Wave 3 (approx. 12 months) = 6% (3/50)	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							No statistical analysis reported		
Change from baseline in suicidal ideation (passive), information on which was collected by clinician, exact methods / tools not reported (mean duration of gender-affirming hormone treatment was 10.9 months)									
1 cohort study Kuper et al. 2020	Serious limitations[4]	Serious indirectness [6]	No serious inconsistency	Not calculable	N=130	None	Lifetime = 81% (105 people) 1 month before initial assessment = 25% (33 people) Follow-up period = 38% (51 people) No statistical analysis reported	Critical	VERY LOW
Change from baseline in suicide attempts, information on which was collected by clinician, exact methods / tools not reported (mean duration of gender-affirming hormone treatment was 10.9 months)									
1 cohort study Kuper et al. 2020	Serious limitations[4]	Serious indirectness[6]	No serious inconsistency	Not calculable	N=130	None	Lifetime = 15% (20 people) 3 months before initial assessment = 2% (3 people) Follow-up period = 5% (6 people) No statistical analysis reported	Critical	VERY LOW
Change from baseline in non-suicidal self-injury, information on which was collected by clinician, exact methods / tools not reported (mean duration of gender-affirming hormone treatment was 10.9 months)									
1 cohort study Kuper et al. 2020	Serious limitations[4]	Serious indirectness[6]	No serious inconsistency	Not calculable	N=130	None	Lifetime = 52% (68 people) 3 months before initial assessment = 10% (13 people) Follow-up period = 17% (23 people) No statistical analysis reported	Critical	VERY LOW
Need for treatment due to suicidality / self-harm, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 35% (18/52) During real life phase	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							4% (2/52) Statistically significant reduction (p<0.001)		
Need for mental health treatment, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 50% (26/52) During real life phase 46% (24/51) No statistically significant difference (p= 0.77)	Critical	VERY LOW
Need for treatment due to conduct problems / antisocial, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 14% (7/52) During real life phase 6% (3/52) No statistically significant difference (p= 0.18)	Critical	VERY LOW
Need for treatment due to psychotic symptoms or psychosis, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 2% (1/52) During real life phase 4% (2/52) No statistically significant difference (p= 0.56)	Critical	VERY LOW
Need for treatment due to substance abuse, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 4% (2/52) During real life phase 2% (1/52) No statistically significant difference (p= 0.56)	Critical	VERY LOW
Need for treatment due to autism, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 12% (6/52) During real life phase 6% (3/52) No statistically significant difference (p= 0.30)	Critical	VERY LOW
Need for treatment due to ADHD, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 10% (5/52) During real life phase 2% (1/52) No statistically significant difference (p= 0.09)	Critical	VERY LOW
Need for treatment due to eating disorder, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 2% (1/52)	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							During real life phase 2% (1/52) No statistically significant difference (p=1.0)		

Abbreviations: ADHD: attention deficit hyperactivity disorder; ASQ: Ask Suicide-Screening Questions; CESD-R: Center for Epidemiologic Studies Depression Scale; BDI-II: Beck Depression Inventory II (BDI-II); p: p-value; PHQ 9_Modified for Teens: Patient Health Questionnaire Modified for Teens; SCARED: Screen for Child Anxiety Related Emotional Disorders; SD: standard deviation; STAI: State-Trait Anxiety Inventory

1 Downgraded 1 level - the cohort study by Lopez de Lara et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding and no control group).
2 Downgraded 1 level - the cohort study by Achille et al (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).
3 Serious indirectness in Achille 2020- Outcome reported for full study cohort, of whom 30% were taking no treatment or puberty suppression alone at follow-up. Results for people taking gender-affirming hormones not reported separately.[4] Downgraded 1 level - the cohort study by Kuper et al. (2020) was assessed at high risk of bias (poor quality).
5 Downgraded 1 level - the cohort study by Allen et al. (2019) was assessed at high risk of bias (poor quality; lack of blinding and no control group).
6 Serious indirectness in Kuper et al. 2020- Outcome reported for full study cohort, of whom approximately 17% received puberty suppression alone and did not receive gender-affirming hormones
7 Downgraded 1 level - the cohort study by Kaltiala et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding and no control group).

Table 4: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Quality of life

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on quality of life (1 uncontrolled, prospective observational study and 1 uncontrolled, retrospective observational study)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Change from baseline in mean quality of life score, measured using the QLES-Q-SF) (approximately 12-month follow-up). Higher scores indicated better quality of life.									
1 cohort study Achille et al. 2020	Serious limitations[1]	Serious indirectness[2]	No serious inconsistency	Not calculable	N=50	None	Numerical improvements in mean score reported from wave 1 (baseline) to wave 3 (approx. 12 months), but difference not statistically significant (p = 0.085) Results presented diagrammatically, numerical results for mean score not reported	Critical	VERY LOW
Change from baseline in adjusted mean well-being score, measured using the GWBS of the Pediatric Quality of Life Inventory (mean treatment duration 349 days). Higher scores indicated better well-being.									
1 cohort study Allen et al. 2019	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=39	None	T0 (baseline) = 61.70 (SE 2.43) T1 (final assessment) = 70.23 (SE 2.15) Statistically significant improvement in well-being score, p<0.002	Critical	VERY LOW

Abbreviations: GWBS: General Well-Being Scale; p: p-value; QLES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire; SE: standard error

1 Downgraded 1 level - the cohort study by Achille et al (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).
2 Serious indirectness in Achille et al. 2020 - Outcome reported for full study cohort, of whom 30% were taking no treatment or puberty suppression alone at follow-up. Results for people taking gender-affirming hormones not reported separately.
3 Downgraded 1 level - the cohort study by Allen et al. (2019) was assessed at high risk of bias (poor quality; lack of blinding and no control group).

Table 5: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Body image

QUALITY	Summary of findings	IMPORTANCE	CERTAINTY

					No of patients		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Intervention**	**Comparator**	**Result**		
Impact on body image *(1 uncontrolled, prospective observational study)*									
Change from baseline in mean body image, measured using the BIS (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores represent a higher degree of body dissatisfaction.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=86	None	Baseline = 70.7 (SD 15.2) Follow-up = 51.4 (SD 18.3) No statistical analysis reported for the sub-group of participants who received gender-affirming hormones	Important	VERY LOW

Abbreviations: BIS: Body Image Scale; p: p-value; SD: standard deviation

1 Downgraded 1 level - the cohort study by Kuper et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).

Table 6: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Psychological impact

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Intervention**	**Comparator**	**Result (95% CI)**		
Psychosocial Impact (1 uncontrolled, prospective observational study and 1 uncontrolled, retrospective observational study)									
Change from baseline in family functioning, measured using the Family APGAR test. Higher scores suggest more family dysfunction.									
1 cohort study Lopez de Lara et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=23	None	T0 (baseline) = 17.9 T1 (12 months) = 18.0 No statistical analysis reported	Important	VERY LOW
Change from baseline in mean patient strengths and difficulties score, measured using the SDQ, Spanish Version (total difficulties score) (duration of treatment 12 months). Higher scores suggest the presence of a behavioural disorder.									
1 cohort study	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=23	None	T0 (baseline) = 14.7 (SD 3.3) T1 (12 months) = 10.3 (SD 2.9)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Lopez de Lara et al. 2020							Statistically significant improvement p<0.001		
Functioning in adolescent development: Living with parent(s)/ guardians[2] (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the 'real-life phase' in Finland). Not living with parent(s) or guardian in your early 20s is a marker of age-appropriate functioning in Finnish culture.									
1 cohort study Kaltiala et al. 2020	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During gender identity assessment = 73% (38/52) During real life phase = 40% (21/50) Statistically significant reduction (p=0.001)	Important	VERY LOW
Functioning in adolescent development: Normative peer contacts[4] (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the 'real-life phase' in Finland)									
1 cohort study Kaltiala et al. 2020	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During gender identity assessment = 89% (46/52) During real life phase = 81% (42/52) Statistically significant reduction (p<0.001)	Important	VERY LOW
Functioning in adolescent development: Progresses normatively in school/ work[5] (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the 'real-life phase' in Finland)									
1 cohort study Kaltiala et al. 2020	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During gender identity assessment = 64% (33/52) During real life phase = 60% (31/52) No statistically significant difference (p=0.69)	Important	VERY LOW
Functioning in adolescent development: Has been dating or had steady relationships[6] (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the 'real-life phase' in Finland)									
1 cohort study	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During gender identity assessment = 62% (32/50)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Kaltiala et al. 2020							During real life phase = 58% (30/52) No statistically significant difference (p=0.51)		
Functioning in adolescent development: Is age-appropriately able to deal with matters outside of the home[7] (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the 'real-life phase' in Finland)									
1 cohort study Kaltiala et al. 2020	Serious limitations[2]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During gender identity assessment = 81% (42/52) During real life phase = 81% (42/52) No statistically significant difference (p=1.00)	Important	VERY LOW

Abbreviations: APGAR: Adaptability, Partnership, Growth, Affection and Resolve; p: p-value; SD: standard deviation; SDQ: Strengths and Difficulties Questionnaire

1 Downgraded 1 level - the cohort study by Lopez de Lara et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding and no control group).
2 Living arrangements were classified as (1) living with at least one parent/guardian, (2) living in a boarding school, with an adult relative, in some form of supported accommodation or the like, where supervision and guidance by a responsible adult is provided, (3) independently alone or in a shared household with a peer, (4) with a romantic partner. In the analyses dichotomised living arrangements as (a) parent(s)/guardian(s) vs. in other arrangements.
3 Downgraded 1 level - the cohort study by Kaltiala et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding and no control group).
4 Peer relationships were classified as: (1) socialises with friends in leisure time, outside of activities supervised by adults, (2) socialises with peers only at school or in the context of rehabilitative activity, (3) spends time close to peers, for example in school or rehabilitative activity, but does not connect with them, (4) does not meet peers at all. In the analyses, peer relationships during (a) gender identity assessment and (b) the real-life phase were dichotomized to age-appropriate (normative) (1) vs. restricted or lacking (2–4).
5 School/work participation was classified as (1) age appropriate participation in mainstream curriculum, progresses without difficulties, (2) participates in mainstream curriculum with difficulty, (3) participates in rehabilitative educational or work activity, (4) not involved in education and working life. Age-appropriate participation during (1) was recorded if the adolescent attended mainstream secondary education or upper secondary education at a regular rate (a class per year in comprehensive school; has not changed more than once between tracks in upper secondary education) or had proceeded to work life after completing vocational education. Participation with difficulty (2) was recorded if the adolescent was enrolled in mainstream education but had to repeat a class, studied with special arrangements (for example, in a special small group), or followed some form of adjusted curriculum. In the analyses, school/work life during (a) gender identity assessment and (b) real-life phase was dichotomised to normative (1) vs. any other (2, 3 or 4).
6 Romantic involvement was recorded (1) has or has had a dating or steady relationship, not only online, (2) has had a romantic relationship only online, (3) has not had dating or steady relationships. In the analyses we compared has or has had (1) vs. has not had (2,3) a dating or steady relationship during (a) gender identity assessment and (b) real-life phase. Sexual history was recorded in more detail in case histories during gender identity assessment, and for this period we also collected the experiences of (French) kissing (yes/no), intercourse (yes/no) and experience of any genitally intimate contact with a partner (petting under clothes or naked, intercourse, oral sex) (yes/no).

7 In recording age-appropriate competence in managing everyday matters it was expected that early adolescents (up to 14 years) would be able, for example, to do shopping and travel alone on local public transport, and to help with household duties assigned by their parents. Middle adolescents (15–17 years) were further assumed, for example, to be able make telephone calls in matters important to them (for example, when seeking a summer job), to deal with school-related issues with school personnel without parental participation, to select and start new hobbies independently and to fulfil their role in summer jobs and in similar responsibilities of young people. Late adolescents (18 years and over), legally adults, were expected to have, in addition to the above, competence to talk to authorities such as professionals in health and social services, employment or educational institutions, to deal with banks or health insurance, to manage their financial issues and to manage their housekeeping if they chose to move to live independently of parents/guardians. Competence in managing everyday matters was recorded as follows: (1) the adolescent is able to cope age appropriately outside home, (2) the adolescent needs support in age-appropriate matters outside home but functions age-appropriately in the home (manages her/his own hygiene, clothing and nutrition, participates in (younger subjects) or takes responsibility for (older subjects) housekeeping) and (3) the adolescent's functioning is inadequate both at home and outside home. For the analyses, participants were determined to be able to age-appropriately able cope with matters outside of the home (1) vs. not (2,3).

Table 7: Question 2: For children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Bone density

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Lumbar spine bone mineral apparent density (BMAD) (2 uncontrolled, retrospective observational studies)									
Change from start of gender-affirming hormones to age 22 years in lumber spine BMAD in transfemales									
1 cohort study Klink et al. 2015	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	N=13 (Mean) N=14 (z-score)	None	Mean (SD), g/m^3 Start of gender-affirming hormones: 0.22 (0.02) Age 22 years: 0.23 (0.03) P=0.003 z-score (SD) Start of gender-affirming hormones: -0.90 (0.80) Age 22 years: -0.78 (1.03) No statistically significant difference	Important	VERY LOW
Change from baseline in lumbar spine BMAD in transfemales with a bone age less than 15 years ('young'; 24 months follow-up)									
1 cohort study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=15	None	Median (range), g/m^3 Start of gender-affirming hormones (C0): 0.20 (0.18 to 0.24)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							24-month follow-up (C24): 0.22 (0.19 to 0.27) Statistically significant increase (p≤0.01) z-score (range) Start of gender-affirming hormones (C0): -1.52 (-2.36 to 0.42) 24-month follow-up (C24): -1.10 (-2.44 to 0.69) Statistically significant increase (p≤0.05)		
Change from baseline in lumbar spine BMAD in transfemales with a bone age of 15 years or more ('old'; 24 months follow-up)									
1 cohort study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=5	None	Median (range), g/m^3 Start of gender-affirming hormones (C0): 0.22 (0.19 to 0.24) 24-month follow-up (C24): 0.23 (0.21 to 0.26) Statistically significant increase (p≤0.05) z-score (range) Start of gender-affirming hormones (C0): -1.15 (-2.21 to 0.08) 24-month follow-up (C24): -0.66 (-1.66 to 0.54) Statistically significant increase (p≤0.05)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in lumber spine BMAD in transmales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
1 cohort study Klink et al. 2015	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	N=19 (Mean and z-score)	None	Mean (SD), g/m^3 Start of gender-affirming hormones: 0.24 (0.02) Age 22 years: 0.25 (0.28) P=0.001 z-score Start of gender-affirming hormones: -0.50 (0.81) Age 22 years: -0.033 (0.95) P=0.002	Important	VERY LOW
Change from baseline in lumbar spine BMAD in transmales with a bone age of less than 14 years ('young'; 24 months follow-up)									
1 cohort study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=11	None	Median (range), g/m^3 Start of gender-affirming hormones (C0): 0.23 (0.19 to 0.28) 24-month follow-up (C24): 0.25 (0.22 to 0.28) Statistically significant increase (p≤0.01) z-score (range) Start of gender-affirming hormones (C0): -0.84 (-2.2 to 0.87) 24-month follow-up (C24): -0.15 (-1.38 to 0.94) Statistically significant increase (p≤0.01)	Important	VERY LOW
Change from baseline in lumbar spine BMAD in transmales with a bone age of 14 years or more ('old'; 24 months follow-up)									
1 cohort study	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=23	None	Median (range), g/m^3	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Vlot et al. 2017							Start of gender-affirming hormones (C0): 0.24 (0.20 to 0.28) 24-month follow-up (C24): 0.25 (0.21 to 0.30) Statistically significant increase (p≤0.01) z-score (range) Start of gender-affirming hormones (C0): -0.29 (-2.28 to 0.90) 24-month follow-up (C24): -0.06 (-1.75 to 1.61) Statistically significant increase (p≤0.01)		
Change in femoral neck BMAD (2 uncontrolled, retrospective observational studies)									
Change from start of gender-affirming hormones to age 22 years in femoral neck BMAD in transfemales									
1 cohort study Klink et al. 2015	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	N=14 (Mean) N=10 (z-score)	None	Mean (SD), g/m^3 Start of gender-affirming hormones: 0.26 (0.04) Age 22 years: 0.28 (0.05) No statistically significant difference z-score (SD) Start of gender-affirming hormones: -1.57 (1.74) Age 22 years: Not reported	Important	VERY LOW
Change from baseline in femoral neck BMAD in transfemales with a bone age less than 15 years ('young'; 24 months follow-up)									
1 cohort study	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=16	None	Median (range), g/m^3 C0: 0.27 (0.20 to 0.33) C24: 0.27 (0.20 to 0.36)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Vlot et al. 2017							No statistically significant change z-score (range) C0: -1.32 (-3.39 to 0.21) C24: -1.30 (-3.51 to 0.92) No statistically significant change		
Change from baseline in femoral neck BMAD in transfemales with a bone age of 15 years or more ('old'; 24 months follow-up)									
1 cohort study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=6	None	Median (range), g/m^3 C0: 0.30 (0.26 to 0.34) C24: 0.29 (0.24 to 0.38) No statistically significant change z-score (range) C0: -0.36 (-1.50 to 0.46) C24: -0.56 (-2.17 to 1.29) No statistically significant change	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in femoral neck BMAD in transmales									
1 cohort study Klink et al. 2015	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	N=19 (Mean) N=18 (z-score)	None	Mean (SD), g/m^3 Start of gender-affirming hormones: 0.31 (0.04) Age 22 years: 0.33 (0.05) P=0.010 z-score (SD) Start of gender-affirming hormones: -0.28 (0.74) Age 22 years: Not reported	Important	VERY LOW
Change from baseline in femoral neck BMAD in transmales with a bone age of less than 14 years ('young'; 24 months follow-up)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
1 cohort study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=10	None	Median (range), g/m^3 C0: 0.30 (0.22 to 0.35) C24: 0.33 (0.23 to 0.37) Statistically significant increase (p≤0.01) z-score (range) C0: -0.37 (-2.28 to 0.47) C24: -0.37 (-2.03 to 0.85) Statistically significant increase (p≤0.01)	Important	VERY LOW
Change from baseline in femoral neck BMAD in transmales with a bone age of 14 years or more ('old'; 24 months follow-up)									
1 cohort study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=23	None	Median (range), g/m^3 C0: 0.30 (0.23 to 0.41) C24: 0.32 (0.23 to 0.41) Statistically significant increase (p≤0.01) z-score (range) C0: -0.27 ((-1.91 to 1.29) C24: 0.02 (-2.1 to 1.35) Statistically significant increase (p≤0.05)	Important	VERY LOW
Change in lumbar spine BMD (2 uncontrolled, retrospective observational studies)									
Change from start of gender-affirming hormones to age 22 years in lumbar spine BMD in transfemales									
1 cohort study Klink et al. 2015	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	N=15 (Mean) N=13 (z-score)	None	Mean (SD), g/m^2 Start of gender-affirming hormones: 0.84 (0.11) Age 22 years: 0.93 (0.10) P<0.001 z-score (SD)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							Start of gender-affirming hormones: -1.01 (0.98) Age 22 years: -1.36 (0.83) No statistically significant difference		
Change from start of gender-affirming hormones to age 22 years in lumbar spine BMD in transmales									
1 cohort study Klink et al. 2015	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	N=19 (Mean and z-score)	None	Mean (SD), g/m^2 Start of gender-affirming hormones: 0.91 (0.10) Age 22 years: 0.99 (0.13) P<0.001 z-score (SD) Start of gender-affirming hormones: -0.72 (0.99) Age 22 years: -0.33 (1.12) No statistically significant difference	Important	VERY LOW
Change from start of testosterone treatment in lumbar spine BMD in transmen (follow-up 6 to 24 months)									
1 cohort study Stoffers et al. 2019	Serious limitations[4]	No serious indirectness	Not applicable	Not calculable	N=62 (T0 and T6) N=37 (T12) N=15 (T24)	None	Mean (SD), g/cm^2 T0: 0.90 (0.11) T6: 0.94 (0.10) T12: 0.95 (0.09) T24: 0.95 (0.11) No statistically significant difference from T0 to any timepoint z-score (SD) T0: -0.81 (1.02) T6: -0.67 (0.95) T12: -0.66 (0.81) T24: -0.74 (1.17)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							No statistically significant difference from T0 to any timepoint		
Change in femoral neck BMD (2 uncontrolled, retrospective observational studies)									
Change from start of gender-affirming hormones to age 22 years in femoral neck BMD in transfemales									
1 cohort study Klink et al. 2015	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	N=15 (Mean) N=11 (z-score)	None	Mean (SD), g/m^2 Start of gender-affirming hormones: 0.87 (0.08) Age 22 years: 0.94 (0.11) P=0.009 z-score (SD) Start of gender-affirming hormones: -0.95 (0.63) Age 22 years: -0.69 (0.74) No statistically significant difference	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in femoral neck BMD in transmales									
1 cohort study Klink et al. 2015	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	N=19 (Mean) N=16 (z-score)	None	Mean (SD), g/m^2 Start of gender-affirming hormones: 0.88 (0.09) Age 22 years: 0.95 (0.10) P<0.001 z-score (SD) Start of gender-affirming hormones: -0.35 (0.79) Age 22 years: -0.35 (0.74) P=0.006	Important	VERY LOW
Change from start of testosterone treatment in right femoral neck (hip) BMD in transmales (follow-up 6 to 24 months)									
1 cohort study	Serious limitations[4]	No serious indirectness	Not applicable	Not calculable	N=62 (T0 and T6)	None	Mean (SD), g/cm^2 T0: 0.77 (0.08)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Stoffers et al. 2019					N=37 (T12) N=15 (T24)		T6: 0.84 (0.11) T12: 0.82 (0.08) T24: 0.85 (0.11) No statistically significant difference from T0 to any timepoint z-score (SD) T0: -0.97 (0.79) T6: -0.54 (0.96) T12: -0.80 (0.69) T24: -0.31 (0.84) No statistically significant difference from T0 to any timepoint		
Change from start of testosterone treatment in left femoral neck (hip) BMD in transmales (follow-up 6 to 24 months)									
1 cohort study Stoffers et al. 2019	Serious limitations[4]	No serious indirectness	Not applicable	Not calculable	N=62 (T0 and T6) N=37 (T12) N=15 (T24)	None	Mean (SD), g/cm^2 T0: 0.76 (0.09) T6: 0.83 (0.12) T12: 0.81 (0.08) T24: 0.86 (0.09) No statistically significant difference from T0 to any timepoint z-score (SD) T0: -1.07 (0.85) T6: -0.62 (1.12) T12: -0.93 (0.63) T24: -0.20 (0.70) No statistically significant difference from T0 to any timepoint	Important	VERY LOW

Abbreviations: BMAD: bone mineral apparent density; BMD: bone mineral density; g: grams; m: metre; SD: standard deviation

1 Downgraded 1 level - the cohort study by Klink et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding, no control group and high number of participants lost to follow-up)
2 Outcomes reported after gender reassignment surgery and not after gender-affirming hormones alone. Unclear whether observed changes are due to hormones or surgery
3 Downgraded 1 level - the cohort study by Vlot et al. (2017) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control)
4 Downgraded 1 level - the cohort study by Stoffers et al. (2019) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group)

Table 8: Question 2: For children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Cardiovascular risk factors

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Change in body mass index (1 uncontrolled, retrospective observational study)									
Change from start of gender-affirming hormones to age 22 years in BMI in transfemales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI) +1.9 (0.6 to 3.2) Statistically significant increase (p<0.005) Mean BMI at 22 years (95% CI): 23.2 (21.6 to 24.8)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in BMI in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI) +1.4 (0.8 to 2.0) Statistically significant increase (p<0.005) Mean BMI at 22 years (95% CI): 23.9 (23.0 to 24.7)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Obesity rates at age 22 years (1 uncontrolled, retrospective observational study)									
Obesity rates at age 22 years in transfemales who started gender-affirming hormones as adolescents (1 uncontrolled, retrospective observational study)									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	At 22 years, 9.9% of transfemales were obese, compared with 3.0% in reference cisgender population No statistically analysis reported	Important	VERY LOW
Obesity rates at age 22 years in transfemales who started gender-affirming hormones as adolescents (1 uncontrolled, retrospective observational study)									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	At 22 years, 6.6% of transmales were obese, compared with 2.2% in reference cisgender population No statistically analysis reported	Important	VERY LOW
Change in blood pressure (1 uncontrolled, retrospective observational study)									
Change from start of gender-affirming hormones to age 22 years in systolic blood pressure (SBP) in transfemales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI) -3 (-8 to 2) No statistically significant difference Mean SBP at 22 years (95% CI): 117 (113 to 122)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in diastolic blood pressure (DBP) in transfemales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI) +6 (3 to 10) Statistically significant increase (p<0.001) Mean DBP at 22 years (95% CI): 75 (72 to 78)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in systolic blood pressure (SBP) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI): +5 (1 to 9) Statistically significant increase (p<0.05) Mean SBP at 22 years (95% CI): 126 (122 to 130)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in diastolic blood pressure (DBP) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI): +6 (4 to 9) Statistically significant increase (p<0.001) Mean DBP at 22 years (95% CI): 74 (72 to 77)	Important	VERY LOW
Change in glucose levels, insulin levels, insulin resistance and HbA1c (2 uncontrolled, retrospective observational studies)									
Change from start of gender-affirming hormones to age 22 years in glucose level (mmol/L) in transfemales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI): +0.1 (-0.1 to 0.2)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							No statistically significant difference Mean glucose level at 22 years (95% CI): 5.0 (4.8 to 5.1)		
Change from start of gender-affirming hormones to age 22 years in insulin level (mU/L) in transfemales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI) +2.7 (-1.7 to 7.1) No statistically significant difference Mean insulin level at 22 years (95% CI): 13.0 (8.4 to 17.6)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in insulin resistance (HOMA-IR) in transfemales. Higher scores indicate more insulin resistance.									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI) +0.7 (-0.2 to 1.5) No statistically significant difference Mean HOMA-IR at 22 years (95% CI): 2.9 (1.9 to 3.9)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in glucose level (mmol/L) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI) 0.0 (-0.2 to 0.2) No statistically significant difference	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							Mean glucose level at 22 years (95% CI): 4.8 (4.7 to 5.0)		
Change from start of gender-affirming hormones to age 22 years in insulin level (mU/L) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI) -2.1 (-3.9 to -0.3) Statistically significant decrease (p<0.05) Mean insulin level at 22 years (95% CI): 8.6 (6.9 to 10.2)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in insulin resistance (HOMA-IR) in transmales. Higher scores indicate more insulin resistance.									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI): -0.5 (-1.0 to -0.1) Statistically significant decrease (p<0.05) Mean HOMA-IR at 22 years (95% CI): 1.8 (1.4 to 2.2)	Important	VERY LOW
Change from start of testosterone in HbA1c in transmales (up to 24 months follow-up)									
1 cohort study Stoffers et al. 2019	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N= Not reported	None	No statistically significant change from start of testosterone treatment Numerical results, follow-up duration and further details of	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							statistical analysis not reported.		
Change in lipid profile (1 uncontrolled, retrospective observational study)									
Change from start of gender-affirming hormones to age 22 years in total cholesterol (mmol/L) in transfemales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI): +0.1 (-0.2 to 0.4) No statistically significant difference Mean total cholesterol at 22 years (95% CI): 4.1 (3.8 to 4.4)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in HDL cholesterol (mmol/L) in transfemales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI): 0.0 (-0.1 to 0.2) No statistically significant difference Mean HDL cholesterol at 22 years (95% CI): 1.6 (1.4 to 1.7)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in LDL cholesterol (mmol/L) in transfemales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI): 0.0 (-0.3 to 0.2) No statistically significant difference Mean LDL cholesterol at 22 years (95% CI): 2.0 (1.8 to 2.3)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Change from start of gender-affirming hormones to age 22 years in triglycerides (mmol/L) in transfemales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI): +0.2 (0.0 to 0.5) Statistically significant increase (p<0.05) Mean triglycerides at 22 years (95% CI): 1.1 (0.9 to 1.4)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in total cholesterol (mmol/L) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI): +0.4 (0.2 to 0.6) Statistically significant increase (p<0.001) Mean total cholesterol at 22 years (95% CI): 4.6 (4.3 to 4.8)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in HDL cholesterol (mmol/L) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI) -0.3 (-0.4 to -0.2) Statistically significant decrease (p<0.001) Mean HDL cholesterol at 22 years (95% CI): 1.3 (1.2 to 1.3)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in LDL cholesterol (mmol/L) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI): +0.4 (0.2 to 0.6)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							Statistically significant increase (p<0.001) Mean LDL cholesterol at 22 years (95% CI): 2.6 (2.4 to 2.8)		
Change from start of gender-affirming hormones to age 22 years in triglycerides (mmol/L) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI) +0.5 (0.3 to 0.7) Statistically significant increase (p<0.001) Mean triglycerides at 22 years (95% CI): 1.3 (1.1 to 1.5)	Important	VERY LOW

Abbreviations: BMI: boss mass index; CI: confidence interval; DBP: diastolic blood pressure; HbA1c: glycated haemoglobin; HDL: high-density lipoproteins; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; LDL: low-density lipoproteins; mmol/L: millimoles per litre; mU/L: milliunits per litre; SBP: systolic blood pressure; SD: standard deviation

1 Downgraded 1 level - the cohort study by Klaver et al. (2020) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group)
2 Downgraded 1 level - the cohort study by Stoffers et al. (2019) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group)

Table 9: Question 2: For children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Other safety outcomes

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Liver enzymes (1 uncontrolled, retrospective observational study)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Change from start of testosterone in aspartate aminotransferase (AST) level in transmales (up to 24 months follow-up)									
1 cohort study Stoffers et al. 2019	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N= Not reported	None	No statistically significant change from start of testosterone treatment Numerical results, follow-up duration and further details of statistical analysis not reported.	Important	VERY LOW
Change from start of testosterone in alanine aminotransferase (ALT) level in transmales (up to 24 months follow-up)									
1 cohort study Stoffers et al. 2019	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N= Not reported	None	No statistically significant change from start of testosterone treatment Numerical results, follow-up duration and further details of statistical analysis not reported.	Important	VERY LOW
Change from start of testosterone in gamma-glutamyl transferase (GGT) level in transmales (up to 24 months follow-up)									
1 cohort study Stoffers et al. 2019	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N= Not reported	None	No statistically significant change from start of testosterone treatment Numerical results, follow-up duration and further details of statistical analysis not reported.	Important	VERY LOW
Change from start of testosterone in alkaline phosphatase (ALP) level in transmales (up to 24 months follow-up)									
1 cohort study Stoffers et al. 2019	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=62 (T0 and T1) N=37 (T12)	None	Median (IQR), U/L T0: 102 (78 to 136) T6: 115 (102 to 147) T12: 112 (88 to 143) T24: 81 (range 69 to 98)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
					N-15 (T24)		Statistically significant increase from T0 at T6 and T12 (p<0.001)		
Kidney markers (1 uncontrolled, retrospective observational study)									
Change from start of testosterone in serum creatinine level in transmales (up to 24 months follow-up)									
1 cohort study Stoffers et al. 2019	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=62 (T0 and T1) N=37 (T12) N=15 (T24)	None	Mean (SD), umol/L T0: 62 (7) T6: 70 (9) T12: 74 (10) T24: 81 (10) Statistically significant increase from T0 at all timepoints (p<0.001)	Important	VERY LOW
Change from start of testosterone in serum urea[2] level in transmales (up to 24 months follow-up)									
1 cohort study Stoffers et al. 2019	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N= Not reported	None	No statistically significant change from start of testosterone treatment Numerical results, follow-up duration and further details of statistical analysis not reported.	Important	VERY LOW
Adverse effects (1 uncontrolled, retrospective observational study)									
Permanent discontinuation of gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3)									
1 cohort study Khatchadourian et al. 2014	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=63	None	No participants permanently discontinued gender-affirming hormones.	Important	VERY LOW
Temporary discontinuation of gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3)									
1 cohort study	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=63	None	3/37 transmales receiving testosterone temporarily	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Khatchadourian et al. 2014							discontinued treatment, 2 due to concomitant mental health comorbidities and 1 due to androgenic alopecia. All eventually resumed treatment. No transfemales receiving oestrogen temporarily discontinued treatment		
Minor complications during treatment with gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3)									
1 cohort study Khatchadourian et al. 2014	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=63	None	12/63 participants had minor complications during treatment with gender-affirming hormones All 12 were transmales receiving testosterone. Complications were severe acne (n=7), androgenic alopecia (n=1) mild dyslipidaemia (n=3) and significant mood swings (n=1) No transfemales receiving oestrogen had minor complications	Important	VERY LOW
Severe complications during treatment with gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3)									
1 cohort study Khatchadourian et al. 2014	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=63	None	No severe complications reported during gender-affirming treatment	Important	VERY LOW

Abbreviations: ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; IQR: interquartile range; SD: standard deviation; U/L: units per litre; umol/L: micromole per litre

1 Downgraded 1 level - the cohort study by Stoffers et al. (2019) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group)
2 Referred to as 'ureum' in original publication
3 Downgraded 1 level - the cohort study by Khatchadourian et al. (2014) was assessed as at high risk of bias (poor quality overall; lack of blinding, no control group and high number of participants lost to follow-up)

Table 10: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Transfemales compared with transmales

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Transfemales**	**Transmales**	**Result (95% CI)**		
Impact on mental health (1 uncontrolled, retrospective observational study)									
Change from baseline in adjusted mean suicidality score, measured using the ASQ tool (mean treatment duration 349 days). Higher scores indicate a greater degree of suicidality.									
1 cohort study Allen et al. 2019	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=14	N=33	**Transfemales** T0 (baseline) = 1.21 (SE 0.36) T1 (final assessment) = 0.24 (SE 0.19) **Transmales** T0 (baseline) = 1.01 (SE 0.23) T1 (final assessment) = 0.29 (SE 0.13) No statistically significant difference in change from baseline between transfemales and transmales (p=0.79)	Critical	VERY LOW
Impact on quality of life (1 uncontrolled, retrospective observational study)									
Change from baseline in adjusted mean well-being score, measured using the GWBS of the Pediatric Quality of Life Inventory (mean treatment duration 349 days). Higher scores indicate better well-being.									
1 cohort study Allen et al. 2019	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=14	N=33	**Transfemales** T0 (baseline) = 58.44 (SE 4.09) T1 (final assessment) = 69.52 (SE 3.62)	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Transfemales	Transmales	Result (95% CI)		
							Transmales T0 (baseline) = 64.95 (SE 2.66) T1 (final assessment) = 70.94 (SE 2.35) No statistically significant difference in change from baseline between transfemales and transmales (p=0.32)		

Abbreviations: ASQ: Ask Suicide-Screening Questions; GWBS: General Well-Being Scale; SE: standard error

1 The cohort study by Allen et al. 2019 was assessed at high risk of bias (poor quality; lack of blinding and no control group).

Table 11: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Sex assigned at birth males (transfemales)

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study type and number of studies Author year	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Change from baseline in mean depression symptoms in transfemales, measured using the Quick Inventory of Depressive Symptoms (QIDS), self-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more depression.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=40	None	Baseline = 7.5 (SD 4.9) Follow-up = 6.6 (SD 4.4) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean depression symptoms in transfemales, measured using the Quick Inventory of Depressive Symptoms (QIDS), clinician-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.									
1 cohort study	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=45	None	Baseline = 4.2 (SD 3.2) Follow-up = 5.4 (SD 3.4)	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study type and number of studies Author year	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Kuper et al. 2020							No statistical analysis reported for this sub-group		
Change from baseline in mean anxiety symptoms in transfemales, measured using the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe anxiety.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=33	None	Baseline = 26.4 (SD 14.2) Follow-up = 24.3 (SD 15.4) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean panic symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=34	None	Baseline = 5.7 (SD 4.9) Follow-up = 5.1 (SD 4.9) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean generalised anxiety symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=34	None	Baseline = 8.6 (SD 5.1) Follow-up = 8.0 (SD 5.1) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean social anxiety symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=34	None	Baseline = 7.1 (SD 3.9) Follow-up = 6.8 (SD 4.4) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean separation anxiety symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=34	None	Baseline = 3.4 (SD 3.3) Follow-up = 2.7 (SD 2.3) No statistical analysis reported for this sub-group	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study type and number of studies Author year	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Change from baseline in mean school avoidance symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=33	None	Baseline = 1.8 (SD 1.7) Follow-up = 1.9 (SD 2.1) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in percentage of participants with suicidal ideation in transfemales, measured using the additional questions from the PHQ 9_Modified for Teens (approximately 12-month follow-up)									
1 cohort study Achille et al. 2020	Serious limitations[2]	Serious indirectness[2]	No serious inconsistency	Not calculable	N=17	None	Wave 1 (baseline) = 11.8% (2/17) Wave 2 (approx. 12 months) = 5.9% (1/17) No statistical analysis reported	Critical	VERY LOW
Impact on body image (1 uncontrolled, prospective observational study)									
Change from baseline in mean body image in transfemales, measured using the BIS (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores represent a higher degree of body dissatisfaction.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=30	None	Baseline = 67.5 (SD 19.5) Follow-up = 49.0 (SD 21.6) No statistical analysis reported for this sub-group	Important	VERY LOW

Abbreviations: BIS: Body Image Scale; PHQ 9: Patient Health Questionnaire 9; SCARED: Screen for Child Anxiety Related Emotional Disorders; SD: standard deviation

1 Downgraded 1 level - the cohort study by Kuper et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).
2 Downgraded 1 level - the cohort study by Achille et al. 2020 was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).
3 Serious indirectness in Achille 2020- Approximately 30% of the full sample received puberty suppression alone or were receiving no treatment at final follow-up.

Table 12: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Sex assigned at birth females (transmales)

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Change from baseline in mean depression symptoms in transmales, measured using the Quick Inventory of Depressive Symptoms (QIDS), self-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=76	None	Baseline = 10.4 (SD 5.0) Follow-up = 7.5 (SD 4.5) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean depression symptoms in transmales, measured using the Quick Inventory of Depressive Symptoms (QIDS), clinician-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=78	None	Baseline = 6.7 (SD 4.4) Follow-up = 6.2 (SD 4.1) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean anxiety symptoms in transmales, measured using the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe anxiety.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=65	None	Baseline = 35.4 (SD 16.5) Follow-up = 29.8 (SD 15.5) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean panic symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=66	None	Baseline = 9.3 (SD 6.5) Follow-up = 7.9 (SD 6.5) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean generalised anxiety symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=66	None	Baseline = 10.4 (SD 5.0) Follow-up = 9.0 (SD 5.1) No statistical analysis reported for this sub-group	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Change from baseline in mean social anxiety symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=66	None	Baseline = 8.5 (SD 4.0) Follow-up = 7.8 (SD 4.1) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean separation anxiety symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=65	None	Baseline = 4.2 (SD 3.4) Follow-up = 3.4 (SD 2.6) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean school avoidance symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=65	None	Baseline = 2.9 (SD 2.3) Follow-up = 2.0 (SD 2.3) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in percentage of participants with suicidal ideation in transmales, measured using the additional questions from the PHQ 9_Modified for Teens (approximately 12-month follow-up)									
1 cohort study Achille et al. 2020	Serious limitations[2]	Serious indirectness[3]	No serious inconsistency	Not calculable	N=33	None	Wave 1 (baseline) = 9.1% (3/33) Wave 2 (approx. 12 months) = 6.1% (2/33) No statistical analysis reported	Critical	VERY LOW
Impact on body image (1 uncontrolled, prospective observational study)									
Change from baseline in mean body image in transmales, measured using the BIS (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores represent a higher degree of body dissatisfaction.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=66	None	Baseline = 71.1 (SD 13.4) Follow-up = 52.9 (SD 16.8) No statistical analysis reported for this sub-group	Important	VERY LOW

Abbreviations: BIS: Body Image Scale; PHQ 9: Patient Health Questionnaire 9; SCARED: Screen for Child Anxiety Related Emotional Disorders; SD: standard deviation

1 Downgraded 1 level - the cohort study by Kuper et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).
2 Downgraded 1 level - the cohort study by Achille et al. 2020 was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).
3 Serious indirectness in Achille 2020- Approximately 30% of the full sample received puberty suppression alone or were receiving no treatment at final follow-up.

Table 14: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Outcomes controlled for concurrent counselling and medicines for mental health problems

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Impact on mental health (1 uncontrolled, retrospective observational study)									
Change from baseline in mean depression score in transfemales, measured using the CESD-R (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicate more depression.									
1 cohort study Achille et al. 2020	Serious limitations[1]	Serious indirectness[2]	No serious inconsistency	Not calculable	N=17	None	No statistically significant change from baseline (p=0.27) Numerical scores not reported	Critical	VERY LOW
Change from baseline in mean depression score in transmales, measured using the CESD-R (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicate more severe depression.									
1 cohort study Achille et al. 2020	Serious limitations[1]	Serious indirectness[2]	No serious inconsistency	Not calculable	N=33	None	No statistically significant change from baseline (p=0.43) Numerical scores not reported	Critical	VERY LOW
Change from baseline in depression score in transfemales, measured using the Patient Health Questionnaire Modified for Teens (PHQ 9_Modified for Teens) (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicate more severe depression.									
1 cohort study Achille et al. 2020	Serious limitations[1]	Serious indirectness[2]	No serious inconsistency	Not calculable	N=17	None	No statistically significant change from baseline (p=0.07) Numerical scores not reported	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Change from baseline in depression score in transmales, measured using the Patient Health Questionnaire Modified for Teens (PHQ 9_Modified for Teens) (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicate more severe depression.									
1 cohort study Achille et al. 2020	Serious limitations[1]	Serious indirectness[2]	No serious inconsistency	Not calculable	N=33	None	No statistically significant change from baseline (p=0.67) Numerical scores not reported	Critical	VERY LOW
Impact on quality of life (1 uncontrolled, retrospective observational study)									
Change from baseline in mean quality of life score in transfemales, measured using the QLES-Q-SF (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicated better quality of life.									
1 cohort study Achille et al. 2020	Serious limitations[1]	Serious indirectness[2]	No serious inconsistency	Not calculable	N=17	None	No statistically significant change from baseline (p=0.06)	Critical	VERY LOW
Change from baseline in mean quality of life score in transmales, measured using the QLES-Q-SF (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicated better quality of life.									
1 cohort study Achille et al. 2020	Serious limitations[1]	Serious indirectness[2]	No serious inconsistency	Not calculable	N=33	None	No statistically significant change from baseline (p=0.08)	Critical	VERY LOW
Psychosocial Impact (1 uncontrolled, retrospective observational study)									
Functioning in adolescent development: Progresses normatively in school/ work during the real-life phase – impact on need for mental health treatment before or during gender identity assessment									
1 cohort study Kaltiala et al. 2020	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=49	None	Needed mental health treatment: 47% (15/32) functioning well Did not need mental health treatment: 82% (14/17) functioning well Statistically significant difference p=0.02	Important	VERY LOW
Functioning in adolescent development: Is age-appropriately able to deal with matters outside of the home during the real-life phase – impact on need for mental health treatment before or during gender identity assessment									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
1 cohort study Kaltiala et al. 2020	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=49	None	Needed mental health treatment: 72% (23/32) managing well Did not need mental health treatment: 94% (16/17) managing well No statistically significant difference p=0.06	Important	VERY LOW
Functioning in adolescent development: Progresses normatively in school/ work during the real-life phase – impact on need for mental health treatment during the real-life phase									
1 cohort study Kaltiala et al. 2020	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=51	None	Needed mental health treatment: 42% (10/24) functioning well Did not need mental health treatment: 74% (20/27) functioning well Statistically significant difference p=0.02	Important	VERY LOW
Functioning in adolescent development: Is age-appropriately able to deal with matters outside of the home during the real-life phase – impact on need for mental health treatment during the real-life phase									
1 cohort study Kaltiala et al. 2020	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=51	None	Needed mental health treatment: 67% (16/24) managing well Did not need mental health treatment: 93% (25/27) managing well Statistically significant difference p=0.02	Important	VERY LOW

Abbreviations: CESD-R: Center for Epidemiologic Studies Depression; p: p-value; PHQ 9: Patient Health Questionnaire 9; QLES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire

1 Downgraded 1 level - the cohort study by Achille et al 2020 was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).
2 Serious indirectness in Achille 2020- Approximately 30% of the full sample received puberty suppression alone or were receiving no treatment at final follow-up.
3 Downgraded 1 level - the cohort study by Kaltiala et al. 2020 was assessed at high risk of bias (poor quality; lack of blinding and no control).

Table 15: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Tanner age

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Impact on mental health (1 uncontrolled, retrospective observational study)									
Change from baseline in mental health problems – depression, anxiety and anxiety-related symptoms (mean duration of gender-affirming hormone treatment was 10.9 months)									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=105	None	No difference in outcomes found by Tanner age. Numerical results, statistical analysis and information on specific outcomes not reported. It is unclear from the paper whether Tanner age is at initial assessment, start of GnRH analogues, start of gender-affirming hormones, or another timepoint	Critical	VERY LOW
Impact on body image (1 uncontrolled, prospective observational study)									
Change from baseline in mean body image, measured using the BIS (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores represent a higher degree of body dissatisfaction.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=105	None	No difference in body image score found by Tanner age. Numerical results, statistical analysis and information on specific outcomes not reported.	Important	VERY LOW

							It is unclear from the paper whether Tanner age is at initial assessment, start of GnRH analogues, start of gender-affirming hormones, or another timepoint		

Abbreviations: BIS: Body Image Scale

1 Downgraded 1 level - the cohort study by Kuper et al. 2020 was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).

Glossary

Ask Suicide-Screening Questions (ASQ)	ASQ is a four-item dichotomous (yes, no) response measure with high sensitivity, designed to identify risk of suicide. A patient is considered to have screened positive if they answered yes to any item. The authors of Allen et al. 2019 altered the fourth item of the ASQ ("Have you ever tried to kill yourself?") and prefaced it with "In the past few weeks . . ." as they were not investigating lifetime suicidality. A response of 'no' was scored as 0 and a response of 'yes' was scored as 1; each item was summed, generating an overall score for suicidality on a scale ranging from 0 to 4, with higher scores indicating greater levels of suicidal ideation.
Beck Depression Inventory-II (BDI-II)	The BDI-II is a tool for assessing depressive symptoms. There are no specific scores to categorise depression severity, but it is suggested that 0 to 13 is minimal symptoms, 14 to 19 is mild depression, 20 to 28 is moderate depression, and severe depression is 29 to 63.
Body Image Scale (BIS)	The BIS is used to measure body satisfaction. The scale consists of 30 body features, which the person rates on a 5-point scale. Each of the 30 items falls into one of 3 basic groups based on its relative importance as a gender-defining body feature: primary sex characteristics, secondary sex characteristics, and neutral body characteristics. A higher score indicates more dissatisfaction.
Bone mineral apparent density (BMAD)	BMAD is a size adjusted value of bone mineral density (BMD) incorporating bone size measurements using UK norms in growing adolescents.
Center for Epidemiologic Studies Depression scale (CESD-R)	The CESD-R is a valid, widely used tool to access depressive symptoms. The CESD-R asks about how frequently a person has felt or behaved in a certain way; with 20 questions scored from 0 score is calculated as a sum of 20 questions, ranging from 0 ("not at all or less than one day") to 3 ("5–7 days" and/or "nearly every day for 2 weeks"). Total score ranges from 0 to 60, with higher scores indicating more depressive symptoms.
Cisgender	Cisgender is a term for someone whose gender identity matches their birth-registered sex.
Family APGAR (Adaptability, Partnership, Growth, Affection and Resolve) test	The Family APGAR test is a 5-item questionnaire, with higher scores indicating better family functioning. The authors reported the following interpretation of the score: functional, 17-20 points; mildly dysfunctional, 16-13 points; moderately dysfunctional, 12-10 point; severely dysfunctional, <9 points.
Gender	The roles, behaviours, activities, attributes and opportunities that any society considers appropriate for girls and boys, and women and men.
Gender dysphoria	Discomfort or distress that is caused by a discrepancy between a person's gender identity (how they see themselves regarding their gender) and that person's sex assigned at birth (and the associated gender role, and/or primary and secondary sex characteristics).

General Well-Being Scale (GWBS) of the Pediatric Quality of Life Inventory score	The GWBS of the Pediatric Quality of Life Inventory uses uses a 5-point response scale, contains seven items, and measures two dimensions: general wellbeing (6 items) and general health (1 item). Each item is scored from 0 to 4, and the total score is linearly transformed to a 0 to 100 scale. High scores reflect fewer perceived problems and greater well-being.
GnRH analogue	GnRH analogues competitively block GnRH receptors to prevent the spontaneous release of two gonadotropin hormones, Follicular Stimulating Hormone (FSH) and Luteinising Hormone (LH) from the pituitary gland. The reduction in LH and FSH secretion reduces oestradiol secretion from the ovaries in those whose sex assigned at birth was female and testosterone secretion from the testes in those whose sex assigned at birth was male.
Patient Health Questionnaire Modified for Teens score (PHQ 9_Modified for Teens)	The PHQ 9_Modified for Teens is a validated tool to assess depression, dysthymia and suicide risk. The tool consists of 9 questions scored from 0 to 3 (total score 0 to 27), plus an additional 4 questions that are not scored. A score of 0 to 4 suggests no or minimal depressive symptoms, 5 to 9 mild, 10-14 moderate, 15-19 moderate and 20-27 severe symptoms.
Quick Inventory of Depressive Symptoms (QIDS)	Both the clinician- and self-reported QIDS are validated tools to assess depressive symptoms. The tool consists of 16 items, with the highest score for 9 items (sleep, weight, psychomotor changes, depressed mood, decreased interest, fatigue, guilt, concentration, and suicidal ideation) are added to give a total score ranging from 0 to 27. A score of 0 to 5 is suggestive of no depressive symptoms, 6 to 10 mild symptoms, 11 to 15 moderate symptoms, 16-20 severe symptoms and 21 to 27 very severe symptoms.
Quality of Life Enjoyment and Satisfaction Questionnaire (QLES-Q-SF)	QLES-Q-SF is a validated questionnaire, consisting of 15 questions that rate quality of life on a scale of 1 (poor) to 5 (very good).
Screen for Child Anxiety Related Emotional Disorders (SCARED) questionnaire	SCARED is a validated, 41-point questionnaire, with each item scored 0 to 2. A total score of 25 or more is suggestive of anxiety disorder, with scores above 30 being more specific. Certain scores for specific questions may indicate the presence of other anxiety-related disorders: A score of 7 or more in questions related to panic disorder or significant somatic symptoms may indicate the presence of these. A score of 9 or more in questions related to generalised anxiety disorder may indicate the presence of this. A score of 5 or more in questions related to separation anxiety may indicate the presence of this. A score of 8 or more in questions related to social anxiety disorder may indicate the presence of this. A score of 3 or more in questions related to significant school avoidance may indicate the presence of this.
State-Trait Anxiety Inventory (STAI) score	STAI is a validated and commonly used measure of state anxiety (current state of anxiety) and trait anxiety (general state of calmness, confidence and security). It has 40 items, the first 20 covering state anxiety, the second 20 covering trait anxiety. STAI

	can be used in clinical settings to diagnose anxiety and to distinguish it from depressive illness. Each subtest (state and trait) is scored between 20 and 80, with higher scores indicating greater anxiety. There is no published minimal clinically meaningful difference (MCID) for STAI or thresholds for anxiety severity.
Strengths and Difficulties Questionnaire (SDQ, Spanish version	The SDQ, Spanish version includes 25-items covering emotional symptoms, conduct problems, hyperactivity/ inattention, peer relationship problems and prosocial behaviour. The authors state that a score of more than 20 is considered indicative of risk of having a disorder (normal: 0-15; borderline: 16-19, abnormal: 20-40).
Tanner stage	Tanner staging is a scale of physical development.
Transgender (including transmale and transfemale)	Transgender is a term for someone whose gender identity is not congruent with their birth-registered sex. A transfemale is a person who identifies as female and a transmale is a person who identifies as male.
Utrecht Gender Dysphoria Scale (UGDS)	The UGDS is a validated screening tool for both adolescents and adults to assess gender dysphoria. It consists of 12 items, to be answered on a 1- to 5-point scale, resulting in a sum score between 12 and 60. Higher scores indicate higher levels of gender dysphoria.

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Socialstyrelsen
THE NATIONAL BOARD OF HEALTH AND WELFARE

Care of children and adolescents with gender dysphoria

Summary

Summary

The National Board of Health and Welfare (NBHW) has been commissioned by the Swedish government to update the national guidelines on care of children and adolescents with gender dysphoria, first published in 2015 [1]. Guidelines chapters are updated stepwise and this report contains revised guidance on psychosocial support and diagnostic assessment, and on puberty suppressing treatment with GnRH-analogues and gender-affirming hormonal treatment. This report thus replaces the corresponding chapters in the publication from 2015. Remaining chapters and the updated guidelines as a whole will be published later in 2022. In response to comments received during external review, two new chapters have been added, named *New recommendations on hormonal treatment – their reasons and consequences and Non-binary gender identity – current knowledge and a need for clarification*. Another difference compared to the guidelines from 2015 [1] is that the term "gender incongruence" is used alongside the term "gender dysphoria". For explanations of terms and abbreviations, see Appendix 2. For a description of the scientific evidence and clinical experience underlying the recommendations and the work process, see Appendices 3 and 4.

The guidelines apply to children and adolescents, i.e. people under 18 years of age. In the medical text sections, the term children (barn) refers to persons who have not yet entered puberty, while the term adolescents (ungdomar) refers to people whose puberty has started. In the text sections relating to juridical regulations, only the term children (barn) is used and denotes people younger than 18 years of age. Finally, the term "young people" (unga) is sometimes used in text sections addressing both children and adolescents.

Introductory comment

The summary that follows and the introductory chapter describe that the updated recommendations for puberty suppression with GnRH-analogues and gender-affirming hormonal treatment have become more restrictive compared to 2015, and the reasons that they have changed. The new recommendations entail that a larger

proportion than before, among adolescents with gender incongruence referred for diagnostic assessment of gender dysphoria, will need to be offered other care than hormonal treatments. Questions on how to ensure that all young people suffering from gender dysphoria be taken seriously and confirmed in their gender identity, well received and offered adequate care are becoming increasingly relevant, and will need to be answered during the ongoing restructuring of certain care for gender dysphoria into three national specialised medical care services (NBHW decision in December 2020). The care for children, adolescents and adults with gender dysphoria in these three national specialised units aims to improve equality in care, coordination and dialogue, and may enhance the implementation of national guidelines.

Recommendations and criteria for hormonal treatment

For adolescents with gender incongruence, the NBHW deems that the risks of puberty suppressing treatment with GnRH-analogues and gender-affirming hormonal treatment currently outweigh the possible benefits, and that the treatments should be offered only in exceptional cases. This judgement is based mainly on three factors: the continued lack of reliable scientific evidence concerning the efficacy and the safety of both treatments [2], the new knowledge that detransition occurs among young adults [3], and the uncertainty that follows from the yet unexplained increase in the number of care seekers, an increase particularly large among adolescents registered as females at birth [4].

A systematic review published in 2022 by the Swedish Agency for Health Technology Assessment and Assessment of Social Services [2] shows that the state of knowledge largely remains unchanged compared to 2015. High quality trials such as RCTs are still lacking and the evidence on treatment efficacy and safety is still insufficient and inconclusive for all reported outcomes. Further, it is not possible to determine how common it is for adolescents who undergo gender-affirming treatment to later change their perception of their gender identity or interrupt an ongoing treatment. An important difference compared to 2015 however, is that the occurrence of

detransition among young adults is now documented [3], meaning that the uncertain evidence that indicates a low prevalence of treatment interruptions or any aspects of regret is no longer unchallenged. Although the prevalence of detransition is still unknown, the knowledge that it occurs and that genderconfirming treatment thus may lead to a deteriorating of health and quality of life (i.e. harm), is important for the overall judgement and recommendation.

To minimize the risk that a young person with gender incongruence later will regret a gender-affirming treatment, the NBHW deems that the criteria for offering GnRH-analogue and gender-affirming hormones should link more closely to those used in the Dutch protocol, where the duration of gender incongruence over time is emphasized [5-7]. Accordingly, an early (childhood) onset of gender incongruence, persistence of gender incongruence until puberty and a marked psychological strain in response to pubertal development is among the recommended criteria. The publications that describe these criteria and the treatment outcomes when given in accordance [5, 6, 8] consitute the best available knowledge and should be used as guidance.

To ensure that new knowledge is gathered, the NBHW further deems that treatment with GnRH-analogues and sex hormones for young people should be provided within a research context, which does not necessarily imply the use of randomized controlled trials (RCTs). As in other healthcare areas where it is difficult to conduct RCTs while retaining sufficient internal validity, it is also important that other prospective study designs are considered for ethical review and that register studies are made possible. Until a research study is in place, the NBHW deems that treatment with GnRH-analogues and sex hormones may be given in exceptional cases, in accordance with the updated recommendations and criteria described in the guidelines. The complex multidisciplinary assessments will eventually be carried out in the three national units that are granted permission to provide highly specialized care services.

In accordance with the DSM-5, the recommendations in the guidelines from 2015 applied to young people with gender dysphoria in general, i.e. also young people with a non-binary gender identity. Another criterion within the Dutch protocol is that the child has had a binary ("cross-gender") gender identity since childhood [5, 6].

It has emerged during the review process, that the clinical experience and documentation of puberty-suppressing and hormonal treatment for young people with non-binary gender identity is lacking, and also that it is limited for adults. The NBHW still considers that gender dysphoria rather than gender identity should determine access to care and treatment. An urgent work thus remains, to clarify criteria under which adolescents with non-binary gender identity may be offered puberty-suppressing and gender-affirming hormonal treatment within a research framework.

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STM038:00/2020

Recommendation of the Council for Choices in Health Care in Finland (PALKO / COHERE Finland)

Medical Treatment Methods for Dysphoria Related to Gender Variance In Minors

Concepts

Suppression treatment	Pubertal suppression with GnRH analogues (drugs that inhibit gonadotropin-releasing hormone activity) to halt the development of secondary sex characteristics of the biological sex.
Cisgender/Cis person	A person whose gender identity matches the sex determined at birth (identifies, and is satisfied with, the sex determined at birth and generally expresses his/her gender accordingly).
Other gender identity	A person who does not identify as a man or a woman, but rather somewhere along the continuum or outside of it; genderless, nonbinary, or multigendered.
Transgender	A person whose gender identity differs from the legal and biological sex determined at birth but instead aligns with the opposite sex.

STM038:00/2020

Content

1. Basis for Preparing These Recommendations

As the number of patients, including minors, referred to the Helsinki University Hospital (HUS) and the Tampere University Hospital (TAYS) multidisciplinary outpatient clinics for assessment and treatment of gender dysphoria has increased, PALKO (Council for Choices in Healthcare in Finland / COHERE Finland) decided to prepare recommendations for medical treatments of gender dysphoria, i.e., distress which is associated with a minor's gender variance and impairs function. Gender variance refers to a spectrum of gender experience anywhere on the male-female identity continuum or outside it, and is not exclusively confined to the dichotomized male/female conception of gender. Not all patients with gender variance experience significant suffering or functional impairments, and not all seek medical treatment.

These recommendations are based on the legislation in force at the time of the adoption of the recommendation, the available research evidence, and the clinical experience of multidisciplinary teams with expertise in gender dysphoria assessment and treatment at HUS and TAYS. The knowledge base supporting these recommendations is detailed in a separate Preparatory Memorandum and appendices and includes a description of planning and implementation of medical treatments, a literature review of medical treatments, an extensive ethical analysis, and feedback following meetings with patients and the advocacy groups who represent them.

Finnish legislation defines the requirements for the legal gender recognition of transsexuals (Act on Legal Recognition of the Gender of Transsexuals (Trans Act) 536/2002). The detailed requirements for providing the assessment and treatment to enable legal gender recognition are spelled out further in a Decree of the Ministry of Social Affairs and Health (1053/2002). The Trans Act and the related Decree apply to adults. For those who are not of legal age, there are no laws governing the provision and needs of transgender healthcare; however, these are subject to the Health Care Act of Finland (1326/2010), in particular section 7 (criteria for integrated care), section 7a (criteria for treatment options), section 8 (evidence-based, high quality, safe and appropriate care) and section 10 (rationale for centralization); and also to the Constitution of Finland (731/1999)'s section 6 on equality and section 19 on the right to adequate social and healthcare services. Finland's Act on the Status and Rights of Patients, (785/1992), and especially sections 5, 6, and 7, are also relevant.

2. Recommendations' Target Population

These recommendations apply to minors suffering from dysphoria related to gender variance who are seeking a consultation regarding an evaluation of medical examination and treatment needs; the children and adolescents may identify with the opposite sex (transgender), or may identify as genderless, non-binary, or anywhere along or outside the male/female gender identity continuum (other gender).

3. Procedures Assessed

These recommendations focus on medical treatment procedures that aim to decrease suffering and functional impairment of gender-dysphoric minors.

4. Current Care

Cross-sex identification in childhood, even in extreme cases, generally disappears during puberty. However, in some cases, it persists or even intensifies. Gender dysphoria may also emerge or intensify at the onset of puberty. There is considerable variation in the timing of the onset of puberty in both sexes. The first-line treatment for gender dysphoria is psychosocial support and, as necessary, psychotherapy and treatment of possible comorbid psychiatric disorders.

Consultation appointments (for parents / caregivers) regarding pre-pubescent children's cross-sex identification or gender dysphoria are provided by the research group on the gender identity of minors at TAYS or HUS. However, ongoing support or other treatment of psychiatric disorders are provided through the local municipal services.

In clear cases of pre-pubertal onset of gender dysphoria that intensified during puberty, a referral can be made for an assessment by the research group at TAYS or HUS regarding the appropriateness for puberty suppression. If no contraindications to early intervention are identified, pubertal suppression with GnRH analogues (to suppress the effect of gonadotropin-releasing hormone) may be considered to prevent further development of secondary sex characteristics of the biological sex.

Adolescents who have already undergone puberty, whose gender dysphoria occurs in the absence of co-occurring symptoms requiring psychiatric treatment, and whose experience of transgender identity failed to resolve following a period of reflection, can be referred for assessment by the research group on the gender identity of minors at TAYS or HUS. Hormone therapy (testosterone/estrogen and anti-androgen) can be started after the diagnostic evaluations, but no earlier than age 16. Additionally, patients under 18 receive three to six months of GnRH analogue treatment prior to the initiation of cross-sex hormones in order to suppress the hormonal activity of the gonads. No gender confirmation surgeries are performed on minors.

5. Risks, Benefits and Uncertainty

The literature review identified two studies with the total of 271 persons diagnosed with childhood-onset gender identity disorder and associated gender or body dysphoria that intensified after the onset of puberty (Preparatory Memorandum Appendix 1, Tables 15 and 16, pages 46-48).

In a smaller study of 70 adolescents, puberty was suppressed with the GnRH analogue at the average age of 14.8 (12-18 years) and puberty blockade continued for an average of 2 years. During the treatment period, the adolescents' mood improved, and the risk of behavioral disorders diminished, but gender dysphoria itself did not diminish, and there were no changes in body image. In a larger study consisting of 201 adolescents, 101 patients with the average age of 15.5 (12-18 years) started an 18-month psychological supportive intervention, and, additionally at six months, pubertal development was suppressed by starting GnRH analogue treatment. The other cohort of 100 only received psychological supportive intervention for 18 months. In both groups, statistically significant increases in global psychosocial functioning were found at 12 and 18 months; among those having received psychological intervention alone, the improvement in global functioning was already significant at the 6-month mark. Both studies lack long-term treatment follow-up into adulthood.

A recent Finnish study, published after the completion of this literature review, reported on the effect of initiating cross-sex hormone therapy on functioning, progression of developmental tasks of adolescence, and psychiatric symptoms. This study found that during cross-sex hormone therapy, problems in these areas did not decrease.

Potential risks of GnRH therapy include disruption in bone mineralization and the as yet unknown effects on the central nervous system. In trans girls, early pubertal suppression inhibits penile growth, requiring the use of alternative sources of tissue grafts for a potential future vaginoplasty. The effect of pubertal suppression and cross-sex hormones on fertility is not yet known.

6. Ethical Assessment

Although the ethics analysis did not systematically address the issues pertaining to children and adolescents, they have been discussed in several areas in the related documents (Preparatory Memorandum pages 52-62; Appendix 5).

According to the Health Care Act (section 8), healthcare services must be based on evidence and recognized treatment and operational practices. As far as minors are concerned, there are no medical treatment that can be considered evidence-based. At the same time, the numbers of minors developing gender dysphoria has increased. In this situation, it is vital to assure that children and young people are able to talk about their feelings, and that their feelings are acknowledged. The opportunity to reflect on one's experience should be easily accessible through the local health system (i.e., school or student health care, primary care). A young

person's feelings should not be interpreted as immediately requiring specialized medical examinations or treatments.

In cases of children and adolescents, ethical issues are concerned with the natural process of adolescent identity development, and the possibility that medical interventions may interfere with this process. It has been suggested that hormone therapy (e.g., pubertal suppression) alters the course of gender identity development; i.e., it may consolidate a gender identity that would have otherwise changed in some of the treated adolescents. The reliability of the existing studies with no control groups is highly uncertain, and because of this uncertainty, no decisions should be made that can permanently alter a still-maturing minor's mental and physical development.

From the point of view of patient advocacy groups, halting puberty is providing young people with a period of reflection, rather than consolidating their gender identity. This is based on the premise that halting the development of one's permanent sex characteristics will improve the minor's social interactions, while allowing more time for diagnostic evaluations. Additionally, patient advocacy groups assert that early intervention with hormonal treatments will lead to improved outcomes for the patients who do eventually pursue gender reassignment. Professionals, for their part, consider it important to ensure that irreversible interventions, which may also have significant adverse effects, both physical and mental, are only performed on individuals who are able to understand the permanence of the changes and the potential for harm, and who are unlikely to regret such interventions. It is not known how the hormonal suppression of puberty affects young people's judgement and decision-making.

The Act on the Status and Rights of Patients (1992/785) states that the patient shall be provided with information about his/her state of health, the significance of the treatment, various alternative forms of treatment and their effects, and about other factors concerning treatment that have an effect on treatment decision-making. In a situation where a minor's identification with the opposite sex causes long-term and severe dysphoria, it is important to make sure that he/she understands the realistic potential of gender reassignment treatments to alter secondary sex characteristics, the reality of a lifelong commitment to medical therapy, the permanence of the effects, and the possible physical and mental adverse effects of the treatments. Although patients may experience regret, after reassignment treatments, there is no going back to the non-reassigned body and its normal functions. Brain development continues until early adulthood – about age 25, which also affects young people's ability to assess the consequences of their decisions on their own future selves for rest of their lives.

A lack of recognition of comorbid psychiatric disorders common among gender-dysphoric adolescents can also be detrimental. Since reduction of psychiatric symptoms cannot be achieved with hormonal and surgical interventions, it is not a valid justification for gender reassignment. A young person's identity and personality development must be stable so that they can genuinely face and discuss their gender dysphoria, the significance of their own feelings, and the need for various treatment options.

For children and adolescents, these factors are key reasons for postponing any interventions until adulthood.

7. Conclusions

The first-line intervention for gender variance during childhood and adolescent years is psychosocial support and, as necessary, gender-explorative therapy and treatment for comorbid psychiatric disorders. Uncertainty related to gender identity should be dealt with according to the severity of symptoms and the need for treatment and should be handled at the school / student health care, primary health care at the local level, or in specialty care.

In adolescents, psychiatric disorders and developmental difficulties may predispose a young person to the onset of gender dysphoria. These young people should receive treatment for their mental and behavioral health issues, and their mental health must be stable prior to the determination of their gender identity.

Clinical experience reveals that autistic spectrum disorders (ASD) are overrepresented among adolescents suffering from gender dysphoria; even if such adolescents are presenting with gender dysphoria, rehabilitative interventions for ASD must be properly addressed.

In light of available evidence, gender reassignment of minors is an experimental practice. Based on studies examining gender identity in minors, hormonal interventions may be considered before reaching adulthood in those with firmly established transgender identities, but it must be done with a great deal of caution, and no irreversible treatment should be initiated. Information about the potential harms of hormone therapies is accumulating slowly and is not systematically reported. It is critical to obtain information on the benefits and risks of these treatments in rigorous research settings.

At a minimum, a consultation for a pre- pubescent child at the specialist setting at the TAYS includes an extensive assessment appointment costing EUR 369. If necessary, a day-long outpatient consultation can be arranged, costing EUR 1,408.

The consultation and assessment process for minors at the specialist settings of TAYS or HUS costs EUR 4,300. If it is determined that this process would be untimely, the minimum cost is EUR 640. An initial assessment / consultation by phone costs EUR 100.

The planning and monitoring costs for pubertal suppression are EUR 2,000 for the first year, and EUR 1,200 for subsequent years. The costs for the planning and monitoring of hormone treatments are a minimum of EUR 400 per year.

These costs do not take into account the additional costs of psychosocial support provided in the local level, the possible need for psychiatric treatment, or hormone treatment medication costs.

8. Summary of the Recommendations

PALKO / COHERE maintains the following:

1. For the treatment of gender dysphoria due to variations in gender identity in minors, psychosocial support should be provided in school and student healthcare and in primary healthcare, and there must be sufficient competency to provide such support.
2. Consultation with a child or youth psychiatrist and the necessary psychiatric treatment and psychotherapy should be arranged locally according to the level of treatment needed.
3. If a child or young person experiencing gender-related anxiety has other simultaneous psychiatric symptoms requiring specialised medical care, treatment according to the nature and severity of the disorder must be arranged within the services of their own region, as no conclusions can be drawn on the stability of gender identity during the period of disorder caused by a psychiatric illness with symptoms that hamper development.

PALKO / COHERE considers that the consultation, periods of assessment, and treatments by the research group on the gender identity of minors at TAYS or HUS must be carried out according to the following principles:

1. Children who have not started puberty and are experiencing persistent, severe anxiety related to gender conflict and/or identification as the other sex may be sent for a consultation visit to the research group on the gender identity of minors at TAYS or HUS. Any need for support beyond the consultation visit or need for other psychiatric treatment should be addressed by local services according to the nature and severity of the problem.

2. If a child is diagnosed prior to the onset of puberty with a persistent experience of identifying as the other sex and shows symptoms of gender-related anxiety, which increases in severity in puberty, the child can be guided at the onset of puberty to the research group on the gender identity of minors at TAYS or HUS for an assessment of the need for treatment to suppress puberty. Based on these assessments, puberty suppression treatment may be initiated on a case-by-case basis after careful consideration and appropriate diagnostic examinations if the medical indications for the treatment are present and there are no contraindications. Therapeutic amenorrhea, i.e. prevention of menstruation, is also medically possible.

3. A young person who has already undergone puberty can be sent to the research clinic on the gender identity of minors at TAYS or HUS for extensive gender identity studies if the variation in gender identity and related dysphoria do not reflect the temporary search for identity typical of the development stage of adolescence and do not subside once the young person has had the opportunity to reflect on their identity but rather their identity and personality development appear to be stable.

4. Based on thorough, case-by-case consideration, the initiation of hormonal interventions that alter sex characteristics may be considered before the person is 18 years of age only if it can be ascertained that their identity as the other sex is of a permanent nature and causes severe dysphoria. In addition, it must be confirmed that the young person is able to understand the significance of irreversible treatments and the

benefits and disadvantages associated with lifelong hormone therapy, and that no contraindications are present.

5. If a young person experiencing gender-related anxiety has experienced or is simultaneously experiencing psychiatric symptoms requiring specialized medical care, a gender identity assessment may be considered if the need for it continues after the other psychiatric symptoms have ceased and adolescent development is progressing normally. In this case, a young person can be sent by the specialized youth psychiatric care in their region for an extensive gender identity study by the TAYS or HUS research group on the gender identity of minors, which will begin the diagnostic studies. Based on the results of the studies, the need for and timeliness of medically justified treatments will be assessed individually.

Surgical treatments are not part of the treatment methods for dysphoria caused by gender-related conflicts in minors. The initiation and monitoring of hormonal treatments must be centralized at the research clinics on gender identity at HUS and TAYS.

9. Additional Evidence Gathering and Monitoring the Effectiveness of Recommendations

Moving forward, the following information must be obtained about the patients diagnosed and receiving treatments in Finland before re-evaluating these recommendations:

- Number of new patient referrals
- Number of patients starting the assessment period, and numbers of new transgender (F64.0) vs “other gender” (F64.8) diagnoses
- Whether the diagnosis remains stable or changes during the assessment phase
- Number of patients discontinuing the assessment period and the reasons for the discontinuation
- Adverse effects of treatments (especially long-term effects and effect on fertility)
- Number of patients regretting hormone therapy
- Analysis of the effects of the assessment and the treatment period on gender dysphoria outcomes, as measured by the Gender Congruence and Life Satisfaction Scale (GCLS)
- Analysis of the effects of the assessment and the treatment period on functional capacity and quality of life
- The prevalence of co-occurring psychiatric diagnoses (especially neurodevelopmental diagnoses F80-F90) among those diagnosed with / seeking treatment for gender dysphoria, and whether the presence of these co-occurring diagnoses impacts the ability to achieve the desired outcome (e.g. decreased dysphoria) in the assessment or the treatment phase.
- Whether the assessment and treatment periods lead to a reduction of suicide attempts
- Whether the assessment and treatment periods lead to a reduction in depression and distress

10. Appendices

Preparatory Memorandum, with Appendices 1-5.

ACADÉMIE NATIONALE DE MÉDECINE

FONDÉE LE 20 DÉCEMBRE 1820

Medicine and gender transidentity in children and adolescents

Press release of the French National Academy of Medicine[1]

February 25, 2022

Gender transidentity is the strong sense, for more than 6 months, of identification with a gender different from that assigned at birth. This feeling can cause a significant and prolonged suffering, which can lead to a risk of suicide (a). No genetic predisposition has been found.

The recognition of this disharmony is not new, but a very strong increase in the demand for physicians for this reason has been observed (1, 2) in North America, then in the countries of northern Europe and, more recently, in France, particularly in children and adolescents. For example, a recent study within a dozen high schools in Pittsburgh revealed a prevalence that was much higher than previously estimated in the United States (3): 10% of students declared themselves to be transgender or non-binary or of uncertain gender (b). In 2003, the Royal Children's Hospital in Melbourne had diagnosed gender dysphoria in only one child, while today it treats nearly 200.

Whatever the mechanisms involved in the adolescent – overuse of social networks, greater social acceptability, or example in the entourage - this epidemic-like phenomenon results in the appearance of cases or even clusters in the immediate surroundings (4). This primarily social problem is based, in part, on a questioning of an excessively dichotomous vision of gender identity by some young people.

The medical demand is accompanied by an increasing supply of care, in the form of consultations or treatment in specialized clinics, because of the distress it causes rather than a mental illness per se. Many medical specialties in the field of pediatrics are concerned. First of all psychiatry, then, if the transidentity appears real or if the malaise persists, endocrinology gynecology and finally surgery are concerned.

However, a great medical caution must be taken in children and adolescents, given the vulnerability, particularly psychological, of this population and the many undesirable effects, and even serious complications, that some of the available therapies can cause. In this respect, it is important to recall the recent decision (May 2021) of the Karolinska University Hospital in Stockholm to ban the use of hormone blockers.

Although, in France, the use of hormone blockers or hormones of the opposite sex is possible with parental authorization at any age, the greatest reserve is required in their use, given the

[1] This Press release, adopted by the French Academy of Medicine on February 25, 2022, by 59 votes for, 20 against and 13 abstentions, was approved, in its revised version, by the Board of Directors on February 28, 2022.

side effects such as impact on growth, bone fragility, risk of sterility, emotional and intellectual consequences and, for girls, symptoms reminiscent of menopause.

As for surgical treatments, in particular mastectomy, which is authorized in France from the age of 14, and those involving the external genitalia (vulva, penis), their irreversible nature must be emphasized.

Therefore, faced with a request for care for this reason, it is essential to provide, first of all, a medical and psychological support to these children or adolescents, but also to their parents, especially since there is no test to distinguish a "structural" gender dysphoria from transient dysphoria in adolescence. Moreover, the risk of over-diagnosis is real, as shown by the increasing number of transgender young adults wishing to "detransition". It is therefore advisable to extend as much as possible the psychological support phase.

The National academy of medicine draws the attention of the medical community to the increasing demand for care in the context of gender transidentity in children and adolescents and recommends:

- A psychological support as long as possible for children and adolescents expressing a desire to transition and their parents;

- In the event of a persistent desire for transition, a careful decision about medical treatment with hormone blockers or hormones of the opposite sex within the framework of Multi-disciplinary Consultation Meetings;

- The introduction of an appropriate clinical training in medical studies to inform and guide young people and their families;

- The promotion of clinical and biological as well as ethical research, which is still too rare in France on this subject.

- The vigilance of parents in response to their children's questions on transidentity or their malaise, underlining the addictive character of excessive consultation of social networks which is both harmful to the psychological development of young people and responsible, for a very important part, of the growing sense of gender incongruence.

Glossary:

a. Gender dysphoria is the medical term used to describe the distress resulting from the incongruence between the felt gender and the gender assigned at birth (5).

b. A non-binary person is a person whose gender identity is neither male nor female.

c. A transgender person adopts the appearance and lifestyle of a sex different from that assigned at birth. Whether born male or female, the transgender persons changes, or even rejects, their original gender identity. The sex registered on his or her civil status does not correspond to the appearance he or she sends back. This does not necessarily lead to a therapeutic approach.

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Recognising and addressing the mental health needs of people experiencing Gender Dysphoria / Gender Incongruence

August 2021

Position statement 103

Summary

This position statement developed by the Royal Australian and New Zealand College of Psychiatrists (RANZCP) provides an overview of Gender Dysphoria and highlights the importance of respecting an individual's gender identity.

Purpose

This position statement developed by the Royal Australian and New Zealand College of Psychiatrists (RANZCP) provides an overview of Gender Dysphoria and highlights the importance of respecting an individual's gender identity. This statement offers insight into the key issues relevant to the mental health needs of people experiencing Gender Dysphoria and guidance is provided on how psychiatrists and mental health services can support individuals constructively. People experiencing Gender Dysphoria may experience a disproportionate level of mental illness and psychological distress. This position statement makes recommendations for enhancing the mental health sector's responsiveness to these needs.

Key messages

- Gender Dysphoria is associated with significant distress.
- There are polarised views and mixed evidence regarding treatment options for people presenting with gender identity concerns, especially children and young people. It is important to understand the different factors, complexities, theories, and research relating to Gender Dysphoria.
- It is important that there is adequate, person-centred care, for the mental health needs of people experiencing Gender Dysphoria.
- Psychiatrists play a crucial role in caring for the mental health needs of people experiencing Gender Dysphoria.
- Psychiatrists should act in a manner which is supportive, ethical, and non-judgmental.
- Comprehensive assessment is crucial. Assessment and treatment should be evidence-informed, fully explore the patient's gender identity, the context in which this has arisen, other features of mental illness

and a thorough assessment of personal and family history. This should lead to a formulation. The assessment will be always responsive to and supportive of the person's needs.
- Psychiatrists must have regard to the relevant laws and professional standards in relation to assessing capacity and obtaining consent, including the RANZCP Code of Ethics.
- Gender Dysphoria is an emerging field of research and, at present, there is a paucity of evidence. Better evidence in relation to outcomes, especially for children and adolescents is required.

Definition

Gender Dysphoria, as defined in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), refers to marked incongruence between one's experienced or expressed gender and one's assigned gender, associated with clinically significant distress or impairment in functioning.[1] Gender Incongruence is defined in the International Classification of Diseases 11th revision (ICD-11) as is 'a marked and persistent incongruence between an individual's experienced gender and the assigned sex'.[2]

Terminology

The RANZCP acknowledges the importance of using appropriate terminology when discussing issues of sexual, sex and gender identity.[3] Inclusive language engenders respect and promotes visibility for important issues, and this is integral to improving the health of LGBTIQ+ people.[4] The key terminology section below provides an overview of some key terms used in Australia and New Zealand.

It is important to be mindful of the importance of individual terminology preferences when talking about someone's sexual orientation or gender identity. Using the individual's preferred terms, especially pronouns, is very important for trans, gender diverse and non-binary people. Healthcare providers should not refer to someone using terms or pronouns that are against the individual's wishes. For example, an individual may wish to be referred to by the pronouns 'they and them' so as to avoid the gendered pronouns 'she' and 'he', and this should be respected. It is important to also be aware of the rapidity with which language and terminology can change and develop in this area, and to consider additional research or inquiry with relevant organisations as appropriate (please refer to the list of resources below for more information).

Key Terminology

- **Transphobia** encompasses a range of negative attitudes and feelings such as hatred, disgust, contempt, prejudice and fear towards people who are gender variant.
- **Trans,** or **TGD (trans and gender diverse)** are commonly used to describe a broad range of non-conforming gender identities or expressions including **transgender, agender** (having no gender), **bigender** (identifying as both a woman and a man), or **non-binary** (neither woman nor man). Some people may describe themselves as **MTF/M2F** (male-to-female), **FTM/F2M** (female-to-male), **AFAB** (assigned female at birth) or **AMAB** (assigned male at birth). The term **genderqueer** is used to refer to gender identity that does not conform to sociocultural norms. **Gender fluid** is used to refer to gender identity which shifts over time.
- For **TGDNB** (trans, gender diverse and non-binary) people, preferred pronouns may include 'he/him', 'she/her', 'they/them' or neopronouns like 'zi/zim'.
- Some Aboriginal and Torres Strait Islander peoples use the term **sistergirl** to refer to sex assigned at birth males who live partly or fully as women and **brotherboy** to refer to sex assigned at birth females who live partly or fully as men.[3]
- **Takatāpui** as a self-descriptor is often used by Māori to describe non-binary gender and/or sexual identity. Specific meaning can vary depending on context.[5] There are several Māori words for transgender people, including whakawahine (trans woman) and **whakatāne** (trans man).[6]

- In Pacific Island cultures, there are a number of gender-diverse identities including the Samoan **fa'afafine** and Tongan **fakaleiti**.[7]

Background

People experiencing Gender Dysphoria should be supported by mental health services to navigate their experience in a constructive way. Gender Dysphoria can emerge in a variety of ways. Each case should be assessed by a mental health professional, which will frequently be a psychiatrist, with the person at the centre of care. It is important the psychological state and context in which Gender Dysphoria has arisen is explored to assess the most appropriate treatment.

The views about whether psychiatric diagnosis is warranted for people who experience incongruence of gender identity are changing.[8] While 'Gender Dysphoria' is classified as a mental disorder in DSM-5, ICD-11 classifies the condition 'Gender Incongruence' not as a 'mental, behavioural and neurodevelopmental disorder' but as a 'condition related to sexual health'.[1, 2] ICD-11 has undergone significant revisions to ensure that disorders relating to sexuality and gender identity reflect contemporary evidence while appropriately distinguishing between health conditions and private behaviours.[9]

Gender Dysphoria continues to be widely debated across jurisdictions in Australia and New Zealand. The RANZCP has developed this position statement from the perspective of psychiatry.

Supporting people experiencing Gender Dysphoria/Gender Incongruence

There is evidence that people who experience incongruence between their gender identity and assigned gender have higher levels of mental illness than the general population.[10] In a retrospective study, Reisner et al (2015) found higher rates of depression, anxiety, suicidal ideation and self-harm in youth who identified as transgender.[11]

Data suggest that the number of people seeking help for gender identity issues has increased worldwide, with referrals to gender clinics increasing across age groups, including amongst children and adolescents.[12, 13] Clinics seeing young people have also reported an increasing preponderance of sex assigned at birth females among those seeking intervention and a co-occurrence of autism spectrum disorder and Gender Dysphoria. [14, 15]

Gender Dysphoria emerges in many different ways and is associated with significant distress for those who experience it. However, Gender Incongruence is not in and of itself pathological. There are polarised views and mixed evidence regarding treatment options for people presenting with gender identity concerns, especially children and young people.

The World Professional Association for Transgender Health (WPATH) uses the terminology "real life experience" defining it as "the act of fully adopting a new or evolving gender role or gender presentation in everyday life".[16] Real life experience allows transgender individuals who wish to permanently change their gender role, to transition from imagined experience to a lived experience. This experience can differ between individuals, for some the experience is liberating, whereas others can experience disappointment due to transition not living up to the desired expectation.[17]

A major challenge for clinicians working with children and adolescents who present for treatment of Gender Dysphoria is the impact of polarised socio-political discourse on clinical assessment and decision-making. Polarised views can be unhelpful and can make the task of clinicians assisting young people presenting with complex presentations more difficult.[18] Whilst these debates must be acknowledged, the most important goal currently is to ensure that there is adequate care available to meet the mental health needs of people experiencing Gender Dysphoria.

Role of psychiatrists

There are a number of guidelines and resources available which relate to Gender Dysphoria. [19-27] The RANZCP does not preference any specific guidelines. The RANZCP encourages psychiatrists to be aware there are multiple perspectives and views.

There is some evidence to suggest positive psychosocial outcomes for those who are supported in their gender identity.[28] However, evidence and professional opinion is divided as to whether an affirmative approach should be taken in relation to treatment of transgender children or whether other approaches are more appropriate.[24]

A gender affirmative approach endorses the belief system that children should be able to 'live in the gender that feels most real or comfortable to that child and to express that gender with freedom from restriction, aspersion, or rejection' therefore the child's statements regarding their gender identity should not be questioned, but instead accepted.[29] Affirmative approaches may include consideration of the need for medical treatments including gender affirming hormones, gonadotrophin releasing hormone analogues (GnRH) (in children and adolescents) and surgery. Approaches which don't include medical treatments may focus on utilising psychotherapy to aid individuals with Gender Dysphoria in exploring their gender identity, and aid alleviation of any co-existing mental health concerns identified in screening and assessment.[24]

The RANZCP endorses practice which supports and validates the identity, strength, and experience of the individual, recognising that all experiences of gender are equally healthy and valuable. In all cases, clinicians have a crucial role in empathetically supporting the individual and family/whānau assertions and lived experiences. The RANZCP acknowledges the dynamic changes in a child or adolescent's identity and brain development, appreciating the inherent complexities in the clinical care and assessment of the individual.

Mental health professionals should acknowledge the concerns of children, adolescents, and their families whilst not expressing any negative attitudes towards experiences of Gender Dysphoria. Acceptance, and alleviation of secrecy can provide relief to individuals experiencing Gender Dysphoria as well as their families.[24]

Psychiatric assessment and treatment should be both based on available evidence and allow for full exploration of the person's gender identity.[20] The RANZCP emphasises the importance of the psychiatrist's role to undertake thorough assessment and evidence-based treatment ideally as part of a multidisciplinary team, especially highlighting co-existing issues which may need addressing and treating. Psychiatric assessment and treatment must also occur in accordance with professional standards, and in a way which is person-centred, responsive to and supportive of the person's needs. Psychosocial support should be continuously offered and provided to people and their families before, during and after any treatment to maximise positive mental health outcomes.[20] If appropriate, psychiatrists can additionally facilitate the assessment of eligibility, preparation and referral for treatment.[24]

Mental health professionals including psychiatrists should maintain a collaborative and multidisciplinary approach to the treatment of Gender Dysphoria. Psychiatrists should discuss progress and obtain peer consultation from other professionals competent in the assessment and treatment of Gender Dysphoria, within both mental health and other medical disciplines.[24]

Health professionals should also be aware of ethical and medicolegal dilemmas in relation to medical and surgical treatment for people experiencing Gender Dysphoria. Psychiatrists should practise within the relevant laws and accepted professional standards in relation to assessing capacity and obtaining consent, including the RANZCP Code of Ethics.[30] Consent and authorisation for children and adolescents to commence GnRH and gender affirming hormones are subject to specific legislation in Australia and New Zealand. The legal position is rapidly changing, with the implications for policy and practice differing by jurisdiction. It is important that psychiatrists are aware of the policies and practices within the jurisdiction in which they work.

Given the complexity of these issues, it is essential that sufficient information is provided to people (and their family/whānau, or carer where relevant) to enable informed consent.[31] Further, evidence for clinical decisions about whether a child or adolescent is capable and competent to consent to treatment should be clearly recorded. In all cases, the risks and benefits of different treatments must be carefully assessed and balanced by the multidisciplinary team providing care and support to the person experiencing Gender Dysphoria.

Research on Gender Dysphoria is still emerging. At present, there is a paucity of quality evidence on the outcomes of those presenting with Gender Dysphoria. In particular, there is a need for better evidence in relation to outcomes for children and young people.[20] The RANZCP supports further research being undertaken into the long-term effects of medical and surgical affirming treatment in all age groups, including children and adolescents. Findings from the

Australian Trans20 longitudinal cohort study and Gender identity Longitudinal Experience (GENTLE) cohort study are expected to improve our understanding.[32, 33] Such research is crucial in ensuring that individuals can safely access evidence-based therapies for Gender Dysphoria/Gender Incongruence as needed.[34, 35]

Recommendations

The RANZCP recommends the following actions to support the mental health needs of people experiencing Gender Dysphoria/Gender Incongruence:

- Psychiatrists should engage with people experiencing Gender Dysphoria in a way which is person-centred, non-judgmental and cares for their mental health needs.
- Assessment and treatment should be based on the best available evidence and fully explore the person's gender identity and the biopsychosocial context from which this has emerged.
- Health services should take steps to accommodate the needs and ensure the cultural safety of people experiencing Gender Dysphoria/Gender Incongruence.
- Further research should be supported and funded in relation to wellbeing and quality of life during and after medical and surgical interventions for Gender Dysphoria/Gender Incongruence.

Further reading

Royal Australian and New Zealand College of Psychiatrists Position Statement 83: Recognising and addressing the mental health needs of the LGBTIQ+ population

Responsible committee: Practice, Policy and Partnerships Committee

References ›

DEFENDANT'S EXHIBIT 15

Neutral Citation Number: [2020] EWHC 3274 (Admin)

Case No: CO/60/2020

IN THE HIGH COURT OF JUSTICE
ADMINISTRATIVE COURT
DIVISIONAL COURT

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 01/12/2020

Before :

THE PRESIDENT OF THE QUEEN'S BENCH DIVISION
LORD JUSTICE LEWIS
MRS JUSTICE LIEVEN

- -

Between :

(1) QUINCY BELL
(2) MRS A

Claimants

and

THE TAVISTOCK AND PORTMAN NHS FOUNDATION TRUST

Defendant

NATIONAL HEALTH SERVICE COMMISSIONING BOARD (NHS ENGLAND)

Interested Party

(1) UNIVERSITY COLLEGE LONDON HOSPITALS NHS FOUNDATION TRUST
(2) LEEDS TEACHING HOSPITALS NHS TRUST
(3) TRANSGENDER TREND LTD

Interveners

Mr Jeremy Hyam QC and Mr Alasdair Henderson (instructed by **Sinclairslaw**) for the **Claimants**
Ms Fenella Morris QC and Ms Nicola Kohn (instructed by **DAC Beachcroft**) for the **Defendant**
The Interested Party did not appear and was not represented
Mr John McKendrick QC (instructed by **Hempsons**) for the **First and Second Interveners**
Mr Paul Skinner and Mr Aidan Wills (instructed by **Ai Law)** for the **Third Intervener**
Hearing dates: **7 and 8 October 2020**

- -

Approved Judgment

I direct that pursuant to CPR PD 39A para 6.1 no official shorthand note shall be taken of this Judgment and that copies of this version as handed down may be treated as authentic.

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THE PRESIDENT OF THE QUEEN'S BENCH DIVISION
LORD JUSTICE LEWIS
MRS JUSTICE LIEVEN

Dame Victoria Sharp P., Lord Justice Lewis, Lieven J.

SECTION A: INTRODUCTION AND BACKGROUND

1. This is the judgment of the court.

2. This is a claim for judicial review of the practice of the defendant, the Tavistock and Portman NHS Foundation Trust, through its Gender Identity Development Service (GIDS) and the first and second Interveners (the Trusts) of prescribing puberty-suppressing drugs to persons under the age of 18 who experience gender dysphoria.

3. Gender dysphoria or GD is a condition where persons experience distress because of a mismatch between their perceived identity and their natal sex, that is, their sex at birth. Such persons have a strong desire to live according to their perceived identity rather than their natal sex.

4. Those with gender dysphoria may be referred to GIDS. GIDS may, in turn, refer them to one of two NHS Trusts (the first and second Interveners) whose clinicians may be prepared to undertake medical interventions in relation to those with gender dysphoria. We are concerned in this case with the administration of gonadotropin-releasing hormone agonists (GnRHa) which are hormone or puberty blocking drugs (also called PBs) to suppress the physical developments that would otherwise occur during puberty.

5. Puberty blocking drugs can in theory be, and have in practice been, prescribed for gender dysphoria through the services provided by the defendant to children as young as 10. It is the practice of the defendant, through GIDS, to require the informed consent of those children and young persons to whom such drugs are prescribed.

6. The issue at the heart of this claim is whether informed consent in the legal sense can be given by such children and young persons.

7. The claimants' case is that children and young persons under 18 are not competent to give consent to the administration of puberty blocking drugs. Further, they contend that the information given to those under 18 by the defendant is misleading and insufficient to ensure such children or young persons are able to give informed consent. They further contend that the absence of procedural safeguards, and the inadequacy of the information provided, results in an infringement of the rights of such children and young persons under Article 8 of the European Convention for the Protection of Human Rights and Fundamental Freedoms (the Convention).

8. In our view, it is appropriate to consider first, whether a child under 16, or a young person between 16 and 18, can give the requisite consent; and secondly, if, in principle, they can do so, whether the information provided by the defendant and the Trusts is adequate for achieving informed consent.

9. The court in this case is concerned with the legal requirements of the process of obtaining consent for the carrying out of medical treatment. In considering this issue the court has had to consider evidence on the use of PBs, their impact on the patients, both in the short and long term, and the evidence of the efficacy of their use. The court is not deciding on the benefits or disbenefits of treating children with GD with PBs, whether in the long or short term. The court has been given a great deal of evidence

about the nature of GD and the treatments that may or may not be appropriate. That is not a matter for us. The sole legal issue in the case is the circumstances in which a child or young person may be competent to give valid consent to treatment in law and the process by which consent to the treatment is obtained.

10. We have had placed before us written evidence from a wide variety of those engaged in issues surrounding GD and a number of individuals who have been treated or are still being treated with PBs.

11. On behalf of the defendant and the Trusts there are statements from Dr Polly Carmichael, Director of GIDS, Professor Gary Butler, Consultant in Paediatric Endocrinology at University College Hospital London, and Dr Nurus-Sabah Alvi, Consultant in Paediatric Endocrinology at Leeds General Infirmary and Clinical Lead for Endocrine Liaison Clinics of the GIDS, Leeds. These witnesses describe the process that the children and young people go through at GIDS and at the Trusts. The court has also had a wide range of evidence from a variety of people concerned with the treatment of those under 18 with PBs. We will refer to that evidence and its sources as appropriate below. Our references to a child or children will be to those under the age of 16, and to young person(s) to anyone under the age of 18, save where it is clear from the context that we are referring to anyone under the age of 18.

Gender Dysphoria

12. Gender dysphoria is defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) which provides for one overarching diagnosis of gender dysphoria with separate specific criteria for children and for adolescents and adults:

> "In adolescents and adults gender dysphoria diagnosis involves a difference between one's experienced gender and assigned gender, and significant distress or problems functioning. It lasts at least six months and is shown by at least two of the following:
>
> 1. A marked incongruence between one's experienced / expressed gender and primary and / or secondary sex characteristics
>
> 2. A strong desire to be rid of one's primary and / or secondary sex characteristics
>
> 3. A strong desire for the primary and / or secondary sex characteristics of the other gender
>
> 4. A strong desire to be of the other gender
>
> 5. A strong desire to be treated as the other gender
>
> 6. A strong conviction that one has the typical feelings and reactions of the other gender.
>
> In children, gender dysphoria diagnosis involves at least six of the following and an associated significant distress or impairment in function, lasting at least six months:

1. A strong desire to be of the other gender or an insistence that one is the other gender

2. A strong preference for wearing clothes typical of the other gender

3. A strong preference for cross-gender roles in make-believe play or fantasy play

4. A strong preference for toys, games or activities stereotypically used or engaged in by the other gender

5. A strong preference for playmates of the other gender

6. A strong rejection of toys, games and activities typical of one's assigned gender

7. A strong dislike of one's sexual anatomy

8. A strong desire for the physical sex characteristics that match one's experienced gender."

Gender Identity Development Service (GIDS)

13. The defendant is an NHS Foundation Trust employing specialist staff including child psychologists, psychotherapists, psychiatrists, social workers, family therapists and nurses. Since 1989 it has provided a gender identity development service, a specialised service providing care to patients up to the age of 18 suffering from GD. GIDS is commissioned by the National Health Service Commissioning Board. The statutory mechanism is that under section 3B of the NHS Act 2006, the Secretary of State has the power to require NHS England to arrange services or facilities as may be prescribed by regulations. The Secretary of State has exercised that power (pursuant to Regulation 11 of the National Health Service Commissioning Board and Clinical Commissioning Groups (Responsibilities and Standing Rules) Regulations 2012/2296, which concerns specified services for rare and very rare conditions) that NHS England must arrange for the provision of services including, pursuant to para 56 of Schedule 4, a gender identity development service specifically for children and adolescents in addition to gender dysphoria services more generally (para 57).

14. Schedule 2, Part A of the NHS Standard Contract, pursuant to which GIDS is provided, sets out the Service Specification which establishes the context of the service, its aims and objectives and the manner in which it will be delivered. As set out in the Service Specification, the service is commissioned to provide specialist assessment, consultation and care including psychological support and physical treatments. The purpose of the treatment is *"to help reduce the distressing feelings of a mismatch between their natal (assigned) sex and their gender identity."* The service also provides support to family and carers of children and young persons so affected.

15. GIDS recognises three stages of physical intervention that may be appropriate in cases of GD. Stage 1 is the administration of GnRHa (one form of puberty blocker). This is clinically appropriate for children and young people who have reached Tanner Stage 2

of puberty and above. Tanner Stage 2 marks the beginning of the physical development of puberty. In natal girls this is the start of development of the breasts, and in boys the testicles and scrotum begin to get larger. Stage 2 of the treatment is the administration of cross-sex hormones (CSH) which can only be prescribed from around the age of 16. Stage 3 is gender reassignment surgery which is only available via adult services to people aged over 18.

16. GIDS takes referrals from across England and Wales and from a wide range of professionals in the health, social services and education sectors, and the voluntary sectors. When a referral is made, the case will be discussed with the relevant regional team. If the intake is successful, then the child will then progress to the GIDS waiting list.

17. As at November 2019 the waiting time for a first assessment at GIDS was between 22-26 months. When a young person reaches the top of the waiting list, they will be invited to the first of a number of assessment appointments at GIDS. The assessment process laid out in the Service Specification anticipates that the assessment process will typically span three to six sessions over 6 months or longer. Most young people will have more sessions than this, and the younger the age the more sessions are likely.

18. Dr Carmichael said that during assessments young persons will be asked, for example, about: the onset of their gender dysphoria; the consistency of their feelings about their gender; how they identify (cross-gender, non-binary, etc); their relationships with peers and family members; their social functioning in general, thoughts about or experience of puberty; their relationship to their bodies; their attractions or romantic relationships as appropriate based on their age and maturity; and their hopes and expectations for the future.

19. As this case is brought by way of judicial review of the GIDS policy and practice, rather than a challenge to an individual treatment decision, it is not possible to give a detailed analysis of the facts of an individual case and the degree to which all the matters referred to by Dr Carmichael were explored in the particular case. We refer at paras 78 to 89 below to the evidence of the experience of the first claimant and some of the other patients of the GIDS service.

20. Dr Carmichael sets out the broad range of professionals who work within GIDS, their specialism in working with young people with GD and the care that is taken when discussing the young person's expression of their gender identity.

21. At the end of the assessment period the clinicians will agree a care plan with the young person and their family. Where the young person fulfils the criteria in the Service Specification and has reached at least Tanner Stage 2 of puberty, they will be referred by GIDS to the first and second Interveners for consultation and/or physical assessment with endocrinologists with a view to being prescribed PBs. Dr Carmichael explains that before any referral to the Trusts, GIDS clinicians discuss the treatment with the young person, including explaining side effects.

The Age and Patient Group for Puberty Blockers

22. Until 2011 PBs were only available at GIDS for those aged 16 or older. In 2011 PBs started to be prescribed for those aged 12-15 and in mid-puberty. This was first done between 2011-14 at University College London Hospital (UCLH) under an approved research study known as the Early Intervention Study. The Study took an uncontrolled treatment cohort of 12-15 year olds with established and persistent GD in England. The Study recruited children for 3 years, but there was then a period until February 2019 when the last cohort member began the next stage of therapy (cross-sex hormones).

23. One of the issues raised in these proceedings is the non-existent or poor evidence base, as it is said to be, for the efficacy of such treatment for children and young persons with GD.

24. In that context, we note that though this research study was commenced some 9 years ago, at the time of the hearing before us the results of this research had yet to be published. Dr Carmichael says in her witness statement dated 2 February 2020 that a paper is now being finalised for publication. At the hearing we were told that that this paper had been submitted for peer-review but that Professor Viner, one of the authors of it, had yet to respond to issues raised by the reviewers, as he has been otherwise engaged in working on issues relating to the coronavirus pandemic.

25. The court was however provided with a paper entitled *"The Early Intervention Study. An evaluation of early pubertal suppression in a carefully selected group of adolescents with "Gender Identity Disorder". A statement and update on the Early Intervention Study (dated 2020)".* We refer further to this paper at para 73 below.

26. There are now two types of endocrine clinic: a clinic for under 15s, referred to as the early intervention clinic, and a clinic for over 15s. The Service Specification states that the early intervention clinic will continue to follow the 2011 Protocol, save that PBs will now be considered for any children *under the age of 12* if they are in established puberty.

27. The age distribution of those treated with PBs in each year between 2011 and 2020 was not provided to the court. Although the defendant and the Trusts said that such data was available, in the sense that the ages of the children are known, the data has not been collated for each year. However, Ms Ailsa Swarbrick, the Divisional Director of Gender Services at the Trust, has presented evidence in relation to patients referred to endocrinology services in 2019-20 and those treated in earlier years but who were discharged from GIDS in 2019-2020. This work was done in response to recommendations in the GIDS Review Action Plan 2019 (a Review commissioned by the Trust following a report by Dr David Bell) that data would help to inform clinical and service developments and a process of continuous improvement.

28. We note here that we find it surprising that such data was not collated in previous years given the young age of the patient group, the experimental nature of the treatment and the profound impact that it has.

29. As it is, for the year 2019/2020, 161 children were referred by GIDS for puberty blockers (a further 10 were referred for other reasons). Of those 161, the age profile is as follows:

> 3 were 10 or 11 years old at the time of referral;
>
> 13 were 12 years old;
>
> 10 were 13 years old;
>
> 24 were 14 years old;
>
> 45 were 15 years old;
>
> 51 were 16 years old;
>
> 15 were 17 or 18 years old.

For the year 2019/20, therefore, 26 of the 161 children referred were 13 or younger; and 95 of the 161 (well over 50%) were under the age of 16.

30. It follows from the information that the court does have on age distribution that some young people could be on PBs for a number of years, in the most extreme case for 5 years between the age of 10 and when they start CSH at 16.

31. Apart from the age distribution, there are other aspects of the patient group which are relevant to this case. The number of referrals to GIDS has increased very significantly in recent years. In 2009, 97 children and young people were referred. In 2018 that number was 2519.

32. Further, in 2011 the gender split was roughly 50/50 between natal girls and boys. However, in 2019 the split had changed so that 76 per cent of referrals were natal females. That change in the proportion of natal girls to boys is reflected in the statistics from the Netherlands (Brik et al "*Trajectories of Adolescents Treated with Gonadotropin-Releasing Hormone Analogues for Gender Dysphoria"* 2018). The defendant did not put forward any clinical explanation as to why there had been this significant change in the patient group over a relatively short time.

33. It is recorded in the GIDS Service Specification and the wider literature that a significant proportion of those presenting with GD have a diagnosis of Autistic Spectrum Disorder (ASD). The Service Specification says:

> "There seems to be a higher prevalence of autistic spectrum disorder (ASD) conditions in clinically referred, gender dysphoric adolescents than in the general adolescent population. Holt, Skagerberg & Dunsford (2014) found that 13.3% of referrals to the service in 2012 mentioned comorbid ASD (although this is likely to be an underestimate). This compares with 9.4% in the Dutch service; whereas in the Finnish service, 26% of adolescents were diagnosed to be on the autism spectrum (Kaltiala-Heino et al. 2015)."

34. The court asked for statistics on the number or proportion of young people referred by GIDS for PBs who had a diagnosis of ASD. Ms Morris said that such data was not available, although it would have been recorded on individual patient records. We therefore do not know the proportion of those who were found by GIDS to be *Gillick* competent who had ASD, or indeed a mental health diagnosis.

35. Again, we have found this lack of data analysis – and the apparent lack of investigation of this issue - surprising.

The process of taking consent

36. The position taken by GIDS is that they will only refer a young person for PBs if they determine that person is competent to give consent, i.e. is *Gillick* competent within the meaning of competence identified in the decision of the House of Lords in *Gillick v West Norfolk and Wisbech Health Authority* [1986] AC 112.

37. Dr Carmichael explained that GIDS takes consent from the young person to their case being referred to the Trusts for treatment; however the consent for the actual prescription of the PBs is taken separately by the clinicians working for the Trusts. She set out the careful process by which GIDS gives information to the young persons and to their parents in order to seek to ensure that the young person is in a position to give valid consent. The court was taken through the statements of Dr Carmichael and Professor Butler and various documents to show the level of information and dialogue that was involved in achieving lawful consent to the treatment. The Service Specification includes Section 3.2 on "Informed Consent". This states *"The consequences of treatment decisions can be significant and life-changing"* and states:

> "All efforts will be made to ensure that clients are aware of the longer term consequences of the endocrine treatments, including implications for fertility, and the decision of the competence of the client will be jointly made by the endocrine and psychological members of the Service's integrated team.
>
> The current context of treatment decisions about cross sex hormones in adolescence is that there is limited scientific evidence for the long-term benefits versus the potential harms of the intervention. There are also concerns that it is uncertain whether or not a young person will continue to identify as transgender in the future, given that some subsequently identify in a different way."

38. The defendant has recently adopted a Standard Operating Procedure for the taking of consent in GIDS. This has taken 2 years to develop and is dated 31 January 2020. Dr Carmichael says at para 33 of her first statement:

> "In advance of any referral by the Trust of a young person for consideration by an endocrinologist for GnRHa treatment, GIDS clinicians discuss treatment with the young person. This includes, checking that the young person's hopes for treatment are realistic, explaining what the treatment can and cannot do, discussing any potential

> side-effects, discussing fertility and potential impact on genital development for birth registered males. We have developed visual aids to support this process.
>
> UCLH and LTH have collated extensive written information to help young people and their parents further understand the nature of the drugs, their limitations and the possible side effects. These written documents are given to young people at their first endocrine clinic visit. The written documents act as a reference point for patients with questions whilst they contemplate whether they would like to go ahead with the referral, and subsequently with treatment. In particular, informational slides titled "Have you thought about having children in the future?" explains the impact GnRHa treatment can have on fertility in explicit terms. Young people and their families are encouraged to raise any questions with their GIDS clinicians or at their next endocrine clinic visit."

39. Ms Morris emphasised that the process of ensuring that consent could validly be given was a discursive and iterative one that involved multiple discussions and answering any questions the young people or their parents might raise. Dr Carmichael said at para 35: "*The GIDS clinicians make it very clear to children and young people that there are both known and unknown risks associated with GnRHa treatment."* Further, she said at para 41: "*In my experience, those young people we see who are recommended for GnRHa treatment understand the implications and limitations of treatment with GnRHa treatment and are able to consent to this stage of treatment."*

40. Professor Butler described the approach to consent at the Trusts as follows:

> "For those under 15 years of age all the pre-assessment consultations are individual and occur with a consultant or senior clinical fellow on at least two visits. Parental support (or that of their guardian or social services where appropriate) is a pre-requisite for the under 15 year stream. On occasions, a young person is not deemed, on clinical examination, to be at an appropriate stage of puberty so further follow-up visits are arranged thereafter at 6-12 monthly intervals until a person is deemed at an appropriate physical stage for intervention and taking of consent. This also gives the opportunity to judge the level of emotional cognitive and psychosocial maturity, and capacity.
>
> The decisions at UCLH and Leeds do not automatically follow on from those made at the GIDS Tavistock. They are a reassessment of physical maturity and cognitive capacity in their own right. They may be at odds with the Tavistock formulation (an infrequent event) and thus would be returned to the Tavistock MDT for reconsideration."

41. Professor Butler said that in his clinic they are careful to ensure that the force behind the decision to seek treatment comes from the young person themselves and is not a consequence of pressure upon them from others around them. The Trusts work closely

with parents to reach a solution that is satisfactory to all and meets the best interests of the child. His clinic has never sought to apply to the Court under its inherent jurisdiction "against" parental opinions because he is concerned that would cause familial frictions. Equally, he suggested UCLH would not wish to have to apply to the court for consent on behalf of the child because it would delay treatment and put an additional burden on GIDS and the Trusts; and because "*it would also increase the distress suffered by the young people themselves, finding that their right to autonomous decision making had been removed from them.*"

42. Professor Butler said a full written information package is provided to older adolescents. For those under 15 there is an initial individual consultation because of the need for "*individualising the approach for very young people, taking special care to assess their level of knowledge and understanding and they are given the written information package then.*" In relation to impacts on fertility and sexual functioning he says:

> "It is also relevant for the consultation purposes that matters of fertility are discussed and counselling by the team takes place, and the option of meeting a fertility specialist is offered, and often taken up. The options of fertility preservation are discussed with all the young people and it is a requirement of the consent process that they fully understand this at an age appropriate level. This understanding must include that they are unable to have the typical sexual relationship of their identified gender with another person on account of their biological sex organ development, and that other surgical procedures may be necessary later on to achieve this possibility."

43. He then said: "*it is an absolute requirement before starting any treatment that a young person can fully understand this effect on fertility and sexual functioning according to their age and level of maturation.*"

44. The court asked for statistical material on the number, if any, of young people who had been assessed to be suitable for PBs but who were *not* prescribed them because the young person was considered not to be *Gillick* competent to make the decision, whether at GIDS or the Trusts. Ms Morris could not produce any statistics on whether this situation had ever arisen. She suggested that in the main, GIDS would work with the young person to give them further information, discuss the matter further and in some cases wait until they had achieved further maturity. The court gained the strong impression from the evidence and from those submissions that it was extremely unusual for either GIDS or the Trusts to refuse to give PBs on the ground that the young person was not competent to give consent. The approach adopted appears to be to continue giving the child more information and to have more discussions until s/he is considered *Gillick* competent or is discharged.

45. Relevant to the evidence of consent is the evidence of Professor Scott (Director of University College London's Institute of Cognitive Neuroscience). She *"seeks to explain, from a neuroscientific point of view, why I have significant doubts about the ability of young people under the age of 18 years old to adequately weigh and*

appreciate the significant consequences that will result from the decision to accept hormonal treatment for gender dysphoria."

46. She explained the neurological development of adolescents' brains that leads to teenagers making different, more risky decisions than adults. She said further that this is backed up by behavioural studies showing that when decision making is "hot" (i.e. more emotional), under 18 year olds make less rational decisions than when the responses are made in a colder, less emotional context. Her conclusion was that:

> "11. … given the risk of puberty blocking treatment, and the fact that these will have irreversible effects, that have life-long consequences, it is my view that even if the risks are well explained, that in the light of the scientific literature, that it is very possible for an adolescent to be unable to fully grasp the implications of puberty-blocking treatment. All the evidence we have suggests that the complex, emotionally charged decisions required to engage with this treatment are not yet acquired as a skill at this age, both in terms of brain maturation and in terms of behaviour."

Parental consent

47. If a child cannot give consent for treatment because they are not *Gillick* competent then the normal position in law would be that someone with parental responsibility could consent on their behalf. Mr Hyam sought at one point to argue that a decision as to giving PBs would fall outside the scope of parental responsibility because of the nature of the treatment concerned. However, the GIDS practice in relation to acting on parental consent alone is quite clear. In the response to the pre-action protocol letter the defendant said:

> "36. There is a fundamental misunderstanding in your letter, which states that parents can consent to pubertal suspension on behalf of a child who is not capable of doing so. This is not the case for this service, as is clear from the above. Although the general law would permit parent(s) to consent on behalf of their child, GIDS has never administered, nor can it conceive of any situation where it would be appropriate to administer blockers on a patient without their consent. The Service Specification confirms that this is the case."

It follows that is not necessary for us to consider whether parents could consent to the treatment if the child cannot lawfully do so because this is not the policy or practice of the defendant and such a case could not currently arise on the facts.

The effect of Puberty Blockers

48. PBs have been used for many years to stop precocious puberty. This is a condition experienced largely by children aged 7 or under when puberty commences at a very early age. This condition is seen more often in natal girls but sometimes in natal boys. PBs are used to stop this early onset of puberty and the use of them ceases when the child reaches an appropriate age for puberty. As can be seen from the evidence this use of PBs does not interfere with the onset of puberty at a normal biological age and, as such, will not interfere with normal development of puberty through adolescence.

49. The use of PBs in cases of GD is quite different. We have some evidence of the history of this treatment and the meaning of puberty from Professor Hruz (Associate Professor of Paediatrics, Endocrinology and Diabetes at Washington University, St Louis, USA) on behalf of the claimants.

50. In summary, PBs were first used for such treatment at a Dutch gender clinic in the late 1990s. That clinic developed a protocol, often referred to as the Dutch protocol. The Dutch protocol was published in the European Journal of Endocrinology in 2006 and called for puberty suppression to begin at the age of 12 after a diagnosis of GD. Puberty is understood in medicine or biology as a process of physiological change involving the process of maturation of the gonads. Hormones in a part of the brain secrete a gonadotropin-releasing hormone which, in turn, stimulates the pituitary gland to secrete other hormones. These stimulate the growth of the gonads, that is ovaries in females and testes in males. Further hormones are secreted which contribute to the further development of the primary sex characteristics, the uterus in females and the penis and scrotum in males. The hormones contribute to the development of secondary sex characteristics including breasts and wider hips in girls and wider shoulders, deeper voices and increased muscle mass in boys. Further growth hormones are released, which stimulate growth. With regular injection of the PBs there is no progression of puberty and some regression of the first stages of already developed sexual characteristics. This means that in girls *"breast tissue will become weak and may disappear completely"* and in boys *"testicular volume will regress to a lower volume."*

51. Under the Dutch protocol, the introduction of CSH starts at age 16. As Professor Hruz explained:

> "29. Then, starting at age 16, cross-sex hormones are administered while GnRH analogue treatment continues, in order to induce something like the process of puberty that would normally occur for members of the opposite sex. In female-to-male patients, testosterone administration leads to the development of "a low voice, facial and body hair growth, and a more masculine body shape" as well as to clitoral engagement and further atrophying of breast tissue. In patients seeking a male-to-female transition, the administration of estrogens will result in "breast development and a female-appearing body shape." Cross-sex hormone administration for these patients will be prescribed for the rest of their lives."

52. There is some dispute as to the purpose of prescribing PBs. According to Dr Carmichael, the primary purpose of PBs is to give the young person time to think about their gender identity. This is a phrase which is repeated on a number of the GIDS and Trust information documents. The Health Research Authority carried out an investigation into the Early Intervention Study in 2019. Its report was somewhat critical of the description of the purpose and said:

> "The research team described the purpose of pubertal suppression as 'to induce a sex hormone-neutral environment to provide young people with space to decide whether to progress further with gender reassignment treatment as an adult.' This phrase appears to have caused confusion as it has been interpreted by some that the puberty suppression was for use in

> any children presenting to the clinic, that there would be no change in the course of any gender identity dysphoria during this time, and that the child could then choose to progress to cross-sex hormone treatment or to stop treatment with subsequent onset of puberty in the birth gender. It has been noted that the participants in this study and other research involving early puberty suppression have progressed to cross-sex hormones. This has raised concerns that the treatment might be responsible for generating persistence, rather than 'creating space to decide'.
>
> It would have reduced confusion if the purpose of the treatment had been described as being offered specifically to children demonstrating a strong and persistent gender identity dysphoria at an early stage in puberty, such that the suppression of puberty would allow subsequent cross-sex hormone treatment without the need to surgically reverse or otherwise mask the unwanted physical effects of puberty in the birth gender. The present study was not designed to investigate the implications on persistence or desistence of offering puberty suppression to a wider range of patients, it was limited to a group that had already demonstrated persistence and were actively requesting puberty blockers."

53. Professor Butler said that PBs:

> "may have some help or advantage in the support of transgender adolescents in some aspects of mental health functioning, in particular with reducing the risk of reduction of suicidal ideation and actual suicidal actions themselves."

54. See further the reference at para 73 below to the paper presented by Dr Carmichael and Professor Viner in 2014, referring to the Early Intervention Study and the limited evidence of psychological benefit.

55. As is clear from the literature and referred to by the HRA, the other purpose of giving PBs is stopping the development of the physical effects of puberty (something that obviously varies depending on at what age and stage in pubertal development the PBs are commenced) because slowing or preventing the early development of secondary sex characteristics during puberty can make a later transition (both medical and social) to living as the opposite sex easier.

The relationship between Puberty Blockers and Cross-Sex Hormones (CSH)

56. GIDS and the Trust place reliance on the fact that Stage 1 treatment with PBs and Stage 2 treatment (CSH) are separate. Thus, so it is said, it is possible for a young person to come off the PBs at any point and not proceed to taking CSH. On one view, this is correct. However, the evidence that we have on this issue clearly shows that practically all children / young people who start PBs progress on to CSH.

57. No precise numbers are available from GIDS (as to the percentage of patients who proceed from PBs to CSH). There was some evidence based on a random sample of those who in 2019-2020 had been discharged or had what is described as a closing summary from GIDS. However the court did have the evidence of Dr de Vries. Dr de Vries is a founding board member of EPATH (European Professional Association for Transgender Health) and a member of the WPATH (World Professional Association for Transgender Health) Committee on Children and Adolescents and its Chair between 2010 and 2016, and leads the Centre of Expertise on Gender Dysphoria at the Amsterdam University Medical Centre in the Netherlands (CEGD). This is the institution which has led the way in the use of PBs for young people in the Netherlands; and is the sole source of published peer reviewed data (in respect of the treatment we are considering) produced to the court. She says that of the adolescents who started puberty suppression, only 1.9 per cent stopped the treatment and did not proceed to CSH.

58. We were told that the defendant did not have any data recording the proportion of those on puberty blockers who progress to cross-sex hormones. We were told that in part this resulted from the fact that some would have progressed to adult services and would not be recorded by the defendant. Ms Swarbrick had carried out an analysis of a random sample of 312 of 1648 files of patients discharged from GIDS from 1st March 2019 to 4th March 2020. Dr Carmichael summarised this as:

> "…based on a random sample of those referred to GIDS who had been discharged or had a closing summary from GIDS in 19-20 (analysis B) 16% of patients (49 individuals) had accessed the endocrinology service during their time with GIDS. Of those 16%, 55% (27 individuals) were subsequently approved for or accessed cross-sex hormones during their time with GIDS. This number represents 8.7% of all the patients discharged from GIDS that year. We also know that of the 49 patients who were referred to endocrinology for GnRHa whilst at GIDS, two did not commence GnRHa treatment, and a further five were discharged from GIDS without being referred on to another gender service."

59. We find it surprising that GIDS did not obtain full data showing the figures and the proportion of those on puberty blockers who remain within GIDS and move on to cross-sex hormones. Although neither Dr Carmichael nor Professor Butler could give the equivalent figures in the United Kingdom to those from the Netherlands, the language used in their witness statements suggests that a similarly high proportion of children and young people in the United Kingdom move from PBs onto CSH.

The impact of Puberty Blockers and their reversibility

60. Both WPATH and the Endocrine Society in their documentation describe PBs as fully reversible. Professor Butler says that "*we do not know everything about the blocker and as far as we know it is a safe reversible treatment with a well-established history."* Dr Alvi also referred to the history of the use of PBs as showing that they are fully reversible. However, it is important to note that apart from the Amsterdam study, the history of the use of PBs relied upon in this context is *from the treatment of precocious*

puberty which is a different condition from GD, and where PBs are used in a very different way.

61. Dr de Vries was somewhat more nuanced in her evidence. She said:

> "Puberty blocking treatment is fully reversible (see for example section 2.0 of the Endocrine Society's Clinical Practice Guidelines…). By fully reversible I mean that the administration of puberty blockers in young people has no irreversible physical consequences, for example for fertility, voice deepening or breast growth".

62. At para 20 of her evidence she said:

> "Ethical dilemmas continue to exist around … the uncertainty of apparent long-term physical consequences of puberty blocking on bone density, fertility, brain development and surgical options."

63. The GIDS Early Intervention Young Person Information Sheet states:

> "What are the possible benefits of starting on hormone blockers?
>
> We have looked at other countries who have given this treatment **and the results** suggest that:
>
> - Hormone blockers which block the body's natural sex hormones may improve the way you feel about yourself.
> - If you decide to stop the hormone blockers early **your physical development** will return as usual in your natal gender. **As far as we are aware**, the hormone blockers will not harm your physical or psychological development.
> - Hormone blockers will make you feel less worried about growing up in the wrong body and will give you more time and space to think about your gender identity.
>
> What are the possible disadvantages and risks of the hormone blockers?
>
> - Possible side effects from the hormone blockers are hot flushes, headache, nausea and weight gain.
> - A short term effect is that your bone strength is shown not to grow as fast as it usually would whilst you are on hormone blockers. However, this will resume once your body is exposed to hormones again. That is why we have to do a bone scan every year to check the thickness of your bones. **We do not fully know how hormone blockers will affect bone strength, the development of your sexual organs, body shape or your final adult height. There**

> **could be other long-term effects of hormone blockers in early puberty that we don't yet know about.**
>
> - Hormone blockers could affect your memory, your concentration or the way you feel about your gender and how likely you are to change your mind about your gender identity.
>
> - Hormone blockers could affect your ability to have a baby. It could take 6 to 12 months longer after stopping the hormone blockers before natal boys start making sperm again or natal girls start maturing eggs in their ovaries. However, hormone blockers do not work as a contraceptive. If you are sexually active, please ask your doctor for advice about birth control." (emphasis added)

64. A number of aspects of this asserted reversibility are raised by the claimants. PBs stop the physical changes in the body when going through puberty. But in reliance on the evidence of Professor Levine (Clinical Professor of Psychiatry at Western Reserve University, Ohio) and Professor Hruz, the claimants assert that neurological and psychological changes occurring in puberty are less well understood than the physiological changes. Further, the degree to which neurological differences are caused by biological factors like hormones and genes are matters of debate. Professor Levine set out evidence on the degree to which young people mature through adolescence through both social and personal experiences. For young people on PBs that maturing process is stopped or delayed with potential social and psychological impacts which could be described as non-reversible.

65. Thus, the central point made by the claimants is that although most of the physical consequences of taking PBs may be reversible if such treatment is stopped, the child or young person will have missed a period, however long, of normal biological, psychological and social experience through adolescence; and that missed development and experience, during adolescence, can never be truly be recovered or "reversed".

66. It is to be noted that prior to June 2020, the NHS website on PBs said:

> "The effects of treatment with GnRH analogues are considered to be fully reversible, so treatment can usually be stopped at any time."

67. In June 2020 this section was updated to read as follows:

> "**Little is known about the long-term side effects of hormone or puberty blockers in children with gender dysphoria.**
>
> Although the Gender Identity Development Service (GIDS) advises that is a physically reversible treatment if stopped, **it is not known what the psychological effects may be.**

> **It's also not known whether hormone blockers affect the development of the teenage brain or children's bones**. Side effects may also include hot flushes, fatigue and mood alterations." (emphasis added)

68. A second key part of the argument about reversibility turns on the relationship between PBs and CSH and the degree to which commencing PBs in practice puts a young person on a virtually inexorable path to taking CSH. CSH are to a very significant degree not reversible. As is set out above at para 57 above, a very high proportion of those who start PBs move on to CSH and thus in statistical terms once a child or young person starts on PBs they are on a very clear clinical pathway to CSH.

Evidence base to support the use of Puberty Blockers for Gender Dysphoria

69. The claimants submit that the treatment of PBs for GD is properly described as (i) experimental (ii) a treatment with a very limited evidence base, and (iii) as a highly controversial treatment. The claimants rely on witness statements from a number of undoubted experts in various relevant fields and from academic institutions in the United Kingdom, the USA, Sweden and Australia who refer to the controversial nature of the treatment and its limited evidential support.

70. It is not however the court's role to judge the weight to be given to various different experts in a judicial review. In our view, more important is the evidence from the defendant and the evidence base *it* relies upon for the use of PBs. In the USA the treatment of GD is not an FDA approved use and as such PBs can only be used "off-label". That does not prevent clinicians, whether in the USA or the United Kingdom, from using PBs for this purpose, as long as their use falls within the clinician's professional expertise. Professor Butler explained that it is very common for paediatric medicines to be used off-label and that this factor does not render the treatment in any sense experimental.

71. However, the lack of a firm evidence base for their use is evident from the very limited published material as to the effectiveness of the treatment, however it is measured.

72. Paul Jenkins, Chief Executive of the defendant said:

> "…it is correct that in recent years, some clinicians [at the Trust] have raised their concerns about the use of GnRHa for young people presenting with gender dysphoria. Indeed, some have called for the Trust to alter its practices and have done so in a variety of ways. We are keenly aware that the subject of gender dysphoria raises complex issues and that many have strong opinions about it."

73. The Evaluation Paper on the Early Intervention Study at GIDS, referred to in para 25 above, gives some (albeit limited) material on the outcome of that study. It summarised a meeting paper presented by Dr Carmichael and Professor Viner in 2014 (but not published in a peer review journal) as follows:

> "The reported qualitative data on early outcomes of 44 young people who received early pubertal suppression. It noted that 100% of young people stated that they wished to continue on GnRHa, that 23 (52%) reported an improvement in mood since starting the blocker but that 27% reported a decrease in mood. **Noted that there was no overall improvement in mood or psychological wellbeing using standardized psychological measures**." (emphasis added)

74. Ms Morris submitted it is not for this court to determine clinical disagreements between experts about the efficacy of a treatment. We agree. That is a matter for the relevant NHS and regulatory bodies to oversee and to decide. However the degree to which the treatment is experimental and has, as yet, an unknown impact, does go to the critical issue of whether a young person can have sufficient understanding of the risks and benefits to be able lawfully to consent to that treatment.

Persistence

75. The claimants submit that there is good evidence that for a significant proportion of young people presenting with GD, the condition resolves itself through adolescence without treatment with PBs. Further, that PBs serve to increase the likelihood of GD, and, as such, can be positively harmful to the child or young person's long-term health. According to DSM5: "*in natal males, persistence of [gender dysphoria] has ranged from 2.2% to 30%. In natal females, persistence has ranged from 12% to 50%."* These figures need to be treated with some caution because it may be that the cohort whose persistence was being considered in these statistics was at a lower age and with less clearly established GD than the young people being treated at GIDS.

76. The Dutch study argued that adolescents who show established GD rarely identify as their biological sex. Professor Hruz suggested there may be two reasons for this. It may be that the clinicians made sound diagnoses of persistent GD. Alternatively, it may be that the very fact of the diagnosis and the course of treatment which affirmed that diagnosis (that is, both gender affirmative psychotherapy and the use of PBs) solidified the feeling of cross-gender identification and led the young people to commit to sex reassignment more strongly than they would have done if there had been a different diagnosis and treatment.

77. As already indicated, it is not our role to adjudicate on the reasons for persistence or otherwise of GD. However, the nature of this issue highlights the highly complex and unusual nature of this treatment and the great difficulty there is in fully understanding its implications for the individual young person. In short, the treatment may be supporting the persistence of GD in circumstances in which it is at least possible that without that treatment, the GD would resolve itself.

SECTION B: EVIDENCE OF THE CLAIMANTS AND OTHER INDIVIDUALS

78. The first claimant was born a female. In her witness statement in these proceedings she set out her experience of being prescribed PBs and then CSH. It should be noted that some of the details relating to her treatment and the information she was given (at GIDS and the first defendant) is disputed. This case is a judicial review of the GIDS policy,

not a tort action relating to the specific facts surrounding the first claimant's treatment and it is not necessary therefore to resolve any factual dispute. We simply record the first claimant's account. She describes a highly traumatic childhood. From the age of 4 or 5 she displayed gender non-conformity, associating more with male games and clothes. She felt highly alienated at secondary school and took birth control pills to stop her periods. She felt disgusted by her body and became depressed and highly anxious. From the age of 14 she began actively to question her gender identity and started to look at YouTube videos and do research on the internet about gender identity disorder and the transition process. She said: "*I thought I had finally found the answer as to why I felt so masculine, uncomfortable with my female body and why I was so much more similar to a stereotypical boy than to a stereotypical girl in physical expression and interests."*

79. When she was 15, the first claimant was referred to GIDS. When she was at the local Children and Adolescent Mental Health Services clinic she remembered: *"the psychiatrist attempted to talk of the gender spectrum as a way of persuading me to not pursue medical transition. I took this as a challenge to how serious I was about my feelings and what I wanted to do and it made me want to transition more. Now I wish I had listened to her."* She was first seen at GIDS aged 16 and had a number of appointments spread out over 1 year and 9 months. She was referred to UCLH in June 2013 and after three appointments commenced PBs. She was given advice about the impact on her fertility, but her priority was to move on to testosterone. She said that at 16, she was not thinking about children and, in any event, egg storage was not available on the NHS.

80. In April 2014 she was referred to an adult Gender Identity Clinic to discuss surgery. She "*was visualising myself becoming a tall, physically strong young man where there was virtually no difference between me and a biological boy."* After commencing testosterone at 17, changes to her body commenced rapidly: these changes included genital changes, her voice dropping and the growth of facial and body hair. She was on testosterone for 3 years but increasingly began to doubt the process of transition:

> "27. I started to have my first serious doubts about transition. These doubts were brought on by for the first time really noticing how physically different I am to men as a biological female, despite having testosterone running through my body. There were also a lot of experiences I could not relate to when having conversations with men due to being biologically female and socialised in society as a girl. There was an unspoken "code" a lot of the time that I felt I was missing. I remember telling a close male friend at the time about these transition doubts, who responded by telling me that I was being silly and I believed him. This was reinforced by the online forums that I browsed where the consensus was that most transsexual people have doubts and that that is a normal part of transitioning, so the doubts should be ignored. I continued on, pushing the doubts in the far back of my mind and no more doubts creeped in for a while."

81. Despite these doubts, when she was 20, she had a double mastectomy. In the year following this:

> "31. … I started to realise that the vision I had as a teenager of becoming male was strictly a fantasy and that it was not possible. My biological make-up was still female and it showed, no matter how much testosterone was in my system or how much I would go to the gym. I was being perceived as a man by society, but it was not enough. I started to just see a woman with a beard, which is what I was. I felt like a fraud and I began to feel more lost, isolated and confused than I did when I was pre-transition."

82. She described facing the reality of taking a regular dose of drugs for the rest of her life to maintain her male appearance; and the need to have a hysterectomy if she remained a man because of the atrophy of her reproductive organs if she continued to take testosterone.

83. From January 2019 the first claimant stopped taking testosterone. She now wishes to identify as a woman and is seeking to change her legal sex back to that on her original birth certificate. She said:

> "39. … It is only until recently that I have started to think about having children and if that is ever a possibility, I have to live with the fact that I will not be able to breastfeed my children. I still do not believe that I have fully processed the surgical procedure that I had to remove my breasts and how major it really was. I made a brash decision as a teenager, (as a lot of teenagers do) trying to find confidence and happiness, except now the rest of my life will be negatively affected. I cannot reverse any of the physical, mental or legal changes that I went through. Transition was a very temporary, superficial fix for a very complex identity issue."

84. The defendant submits the first claimant was given the fullest possible information after a large number of consultations (at least 10) and that she was *Gillick* competent to make the decision to take PBs. Further, the defendant produced witness statements from a number of children and young people who are strongly supportive of the treatment they have received.

85. J is a 20 year old transgender man who received PBs in 2012 at the age of 12 followed by CSH in 2015. He described how he felt a strong need to become a boy from an early age and how he was bullied at school for his behaviour. He found the onset of female puberty horrifying and unbearable. After a number of sessions at GIDS he was prescribed PBs from the age of 12.

86. According to J he was given the fullest possible information from the clinicians at GIDS as to the benefits and disbenefits of the treatment. The clinicians strongly challenged his desire to transition and why he had chosen to express his gender identity as male. He was advised as to the impact on fertility if he chose to go on to CSH and surgery. He said: "*I made the decision to proceed with pubertal suppression without pursuing egg preservation. It was a difficult decision to make because I did not know whether I would want biological children in adulthood, but I was certain I would never want to*

carry a child and give birth. Ultimately, I made the decision because I had a poor quality of life and without immediate treatment I did not feel I had a future at all." He says: "*We discussed sex and I told them the idea of it disgusted me. I knew I would be unable to consider having a sexual relationship as an adult with my body so wrongly formed."* He ended his witness statement by saying that he is thankful that his pubertal development was halted as it removed the distress caused by continued development, but he wishes that the PBs were started earlier which would have prevented the need for breast surgery later.

87. S is a 13 year old trans boy who is on the waiting list at GIDS. He was told that he would have to wait for approximately 24 months to be seen and with his parents decided to see a private provider, GenderGP, where he has been prescribed PBs. We note at this point that the GP in question was removed from the professional register and now operates from outside the United Kingdom. S in his witness statement said:

> "13. … I haven't really thought about parenthood – I have been asked about it by the gender identity specialist I have mentioned but I just have no idea what me in the future is going to think. I haven't had a romantic relationship and it's just not a thing that is really on my radar at the moment."

88. N, an 18 year old trans woman, who was prescribed PBs when she was 17 years old said:

> "12. The treatment of hormone blockers may very well have saved my life. In the period of my life that I was prescribed them my mental health was spiralling due to my dysphoria and this impacting on my daily life, learning and social interactions. While the first injections of gonapeptyl were slow to take effect they eventually began to alleviate my dysphoria in very real ways. I had to shave less and I didn't have to fear pubertal development anymore. I had the time necessary to think about my situation and decide on further courses of action. This also helped my mental health as it gave me significantly less issues overall allowing me to focus and concentrate on aspects in my life alongside my gender identity rather than my fears of puberty and development overtaking everything else in my life."

89. The second claimant, Mrs A, is the mother of a 15 year old girl who has ASD. The daughter has a history of mental health and behavioural problems. She "*is desperate to run away from all that made her female"* and has been referred to CAMHS (Child and Adolescent Mental Health Services). Mrs A is very concerned that her daughter would be referred to GIDS and prescribed PBs. However the daughter has not currently been referred to GIDS and having regard to the defendant's current practice, would not meet the criteria for PBs because her parents would not support that treatment. Mrs A's interest in this action is therefore largely theoretical.

SECTION C: SUBMISSIONS

90. The claimants' primary case is that children or young persons under the age of 18 are not capable of giving consent to the administration of PBs. Their secondary case is that the information given by the defendant and the Interested Party is misleading and inadequate to form the basis for informed consent to be given. In their statement of issues, the claimants put issue one as the adequacy of the information and issue two whether children and young people are capable of giving consent. In our view, the first issue must be whether *Gillick* competence can be achieved, and the secondary or alternative issue, whether the information being given is adequate. We deal with the arguments in that order.

91. Mr Hyam also raised a third issue (at least in writing). This was a submission that if any young person under the age of 18 is prescribed PBs, their case should be referred to the Court of Protection. In oral argument he accepted that the Court of Protection, being a creature of statute, would have no jurisdiction to consider such referrals. We think that the substance of issue three falls within the terms of issue one.

92. Mr Hyam stressed that the claimants were not calling into question that GD existed. Nor were they questioning that it could cause extreme distress or that PBs should never be given to people under 18 or that it was never in their best interests for it to be prescribed. The central issue was whether those under 18 could give informed consent.

93. Mr Hyam submitted that a child still going through puberty is not capable of properly understanding the nature and effect of PBs and weighing the consequences and side effects properly. He pointed to the evidence of the individuals, including that put forward on behalf of the defendant, to show that children of this age cannot understand the implications of matters such as the loss of the ability to orgasm, the potential need to construct a neo-vagina, or the loss of fertility. He argued that the use of PBs to address GD does not have an adequate evidence base to support it and thus should properly be described as experimental treatment. There is evidence that PBs can have significant side effects and there is strong evidence that once a child commences on PBs they will progress to CSH which will cause irreversible changes to the child's body with lifelong medical, psychological and emotional implications for the child. He relies on the harm potentially caused to these vulnerable young people as evidenced by the witness statement of the first claimant.

94. He submitted that the advice given to the children and young persons is misleading because they are told that the PBs are fully reversible when the current evidence on reversibility or the long term implications of the treatment is limited and unclear. He said further, that the reality is that PBs pave the way for CSH which do have irreversible impacts. Further, the information provided by GIDS fails to tell the child that there are no proven benefits to this treatment in either physical or psychological terms. The information is misleading as to the reversibility of PBs, their purpose and their benefits.

95. In those circumstances he submitted that the court should be guided by the approach of the Court of Protection in its *Practice Guidance (Court of Protection: Serious Medical Treatment)* [2020] 1 WLR 641 which sets out those decisions relating to medical treatment where an application should be made to the Court of Protection.

96. Paras 10 and 11 of that Guidance state:

> "10. In any case which is not about the provision of life-sustaining treatment, but involves the serious interference with the person's rights under the ECHR, it is:
>
> "highly probable that, in most, if not all, professionals faced with a decision whether to take that step will conclude that it is appropriate to apply to the court to facilitate a comprehensive analysis of [capacity and] best interests, with [the person] having the benefit of legal representation and independent expert advice."
>
> This will be so even where there is agreement between all those with an interest in the person's welfare.
>
> 11. Examples of cases which may fall into paragraph 10 above will include, but are not limited to: (a) where a medical procedure or treatment is for the primary purpose of sterilisation; (b) where a medical procedure is proposed to be performed on a person who lacks capacity to consent to it, where the procedure is for the purpose of a donation of an organ, bone marrow, stem cells, tissue or bodily fluid to another person; (c) a procedure for the covert insertion of a contraceptive device or other means of contraception; (d) where it is proposed that an experimental or innovative treatment to be carried out; (e) a case involving a significant ethical question in an untested or controversial area of medicine."

97. The defendant and the first and second Interveners make common cause. Ms Morris argued that the care and treatment provided at GIDS fell within the terms of the Service Specification laid down by NHS England (NHSE) as required in accordance with the international frameworks of WPATH and the Endocrine Society and by the domestic regulatory frameworks of the General Medical Council and the Care Quality Commission. The NHSE is currently undertaking a review of the efficacy of treatment for GD (the Cass Review) which will report in due course, and its findings will be reflected in the Service Specification.

98. She argued that the process at GIDS was "deeply *Montgomery* compliant" (i.e. it met the requirements for informed consent identified by the Supreme Court in *Montgomery v Lanarkshire Health Board* [2015] AC 1430) having regard to the frequent consultations, discussions and the provision of detailed, but age appropriate, information. The "vast majority" of the children referred for PBs are 15 or older she said, and the information given is varied depending on the age and maturity of the child or young person. Where the assessment is that the individual is not initially *Gillick* competent, time is taken to see if their understanding develops and competency can be achieved. The information that is given is what is salient for that individual at that age.

99. As to those between the ages of 16-18, if the young person, the parents and the clinicians are agreed then she submitted there is no justiciable issue and the court has no jurisdiction.

100. Mr McKendrick for the first and second Interveners argued that the child or young person did not need to understand the impact of CSH on their fertility because that did

not fall to be decided at the stage of prescribing PBs. The PBs provided the space for the person to think about further stages. In appropriate cases, a natal girl or young person's eggs could be harvested and preserved in order to preserve their fertility. The critical thing for the child was that s/he had GD and that there was no alternative physical treatment to PBs. Once the child or young person had reached the Endocrine Clinic at the Trust, there was no alternative psychological treatment available because that was a matter within the purview of GIDS and GIDS had referred the child for PBs, although ongoing psychological treatment is provided at GIDS alongside treatment with PBs. Therefore, the Trust clinicians were faced with a child in acute distress with no alternative treatment options. The purpose of the treatment was to alleviate distress and that, according to Mr McKendrick, had been achieved.

101. When asked by the court what evidence there was that the PBs did achieve the purpose of alleviating distress, in the light of the lack of published research, Mr McKendrick pointed to the evidence of experienced endocrinologists in both Trusts who could see the real benefits of the treatment.

102. Like Ms Morris, Mr McKendrick said the current practice was not to proceed only on parental consent. However, he did argue that if the child's consent was rendered invalid, the treatment would continue to be lawful if the parents had consented.

103. The third Intervener is Transgender Trend Ltd., an organisation that provides evidence-based information and resources for parents and schools concerning children with GD. Ms Davies-Arai is the director of that organisation and she has filed a witness statement in these proceedings. She set out concerns about the lack of evidence as to the impacts and effectiveness of PBs and in relation to which patients it is most likely to help. Much of her evidence focused on the increase of referrals to GIDS of teenage natal girls and the cultural factors, including material on the internet and social media, which may play a part in this. She said that GIDS does not offer young people with GD a range of ways to interpret their experience, and the GIDS pathway offers a minimal challenge to the beliefs and ideas of the young person.

104. Mr Skinner on behalf of Transgender Trend said the case was particularly important because it concerned the deliberate provision by the State of medical treatment to children and young people which may cause harm. The court should be anxious to ensure that vulnerable children, for example those with ASD, are provided with the full protection of the law.

SECTION D: THE LAW

105. In *Gillick v West Norfolk and Wisbech Health Authority* [1986] AC 112, the House of Lords considered the lawfulness of the Secretary of State's policy on giving contraceptive advice to children without parental consent. The House of Lords held by a majority that a doctor could lawfully give contraceptive advice and treatment to a girl aged under 16 if she had sufficient maturity and intelligence to understand that nature and implications of the proposed treatment and provided that certain conditions were satisfied.

106. Lord Fraser at p. 169B-E said:

> "It seems to me verging on the absurd to suggest that a girl or boy aged 15 could not effectively consent, for example, to have a medical examination of some trivial injury to his body or even to have a broken arm set. Of course the consent of the parents should normally be asked, but they may not be immediately available. Provided the patient, whether the boy or a girl, is capable of understanding what is proposed, and of expressing his or her own wishes, I see no good reason for holding that he or she lacks the capacity to express them validly and effectively and to authorise the medical man to make the examination or give the treatment which he advises. After all, a minor under the age of 16 can, with certain limits, enter into a contract. He or she can also sue and be sued, and can give evidence on oath. …."
>
> Accordingly, I am not disposed to hold now, for the first time, that a girl less than 16 lacks the power to give valid consent to contraceptive advice or treatment, merely on account of her age."

107. Lord Scarman at p. 186A-D said:

> "The law relating to parent and child is concerned with the problems of the growth and maturity of the human personality. If the law should impose upon the process of "growing up" fixed limits where nature knows only a continuous process, the price would be artificiality and a lack of realism in an area where the law must be sensitive to human development and social change. If certainty be thought desirable, it is better that the rigid demarcations necessary to achieve it should be laid down by legislation after a full consideration of all the relevant factors than by the courts confined as they are by the forensic process to the evidenced adduced by the parties and to whatever may properly fall within the judicial notice of judges. Unless and until Parliament should think fit to intervene, the courts should establish a principle flexible enough to enable justice to be achieved by its application to the particular circumstances proved by the evidence placed before them."

And at p.189C-E:

> "When applying these conclusions to contraceptive advice and treatment it has to be borne in mind there is much that has to be understood by a girl under the age of 16 if she is to have legal capacity to consent to such treatment. It is not enough that she should understand the nature of the advice which is being given: she must also have a sufficient maturity to understand what is involved. There are moral and family questions, especially her relationship with her parents; long-term problems associated with the emotional impact of pregnancy and its termination; and there are the risks to health of sexual intercourse at her age, risks which contraception may diminish but cannot eliminate. It follows that a doctor will have to satisfy himself that she is able to appraise these factors

> before he can safely proceed upon the basis that she has at law capacity to consent to contraceptive treatment. And it further follows that ordinarily the proper course will be for him, as the guidance lays down, first to seek to persuade the girl to bring her parents into consultation and, if she refuses, not to prescribe contraceptive treatment unless he is satisfied that her circumstances are such that he ought to proceed without parental knowledge and consent."

And p. 191C-D:

> "The truth may well be that the rights of parents and children in this sensitive area are better protected by the professional standards of the medical profession than by "a priori" legal lines of division between capacity and the lack of capacity to consent since any such general dividing line is sure to produce in some cases injustice, hardship, and injury to health."

108. In *R (Axon) v Secretary of State for Health (Family Planning Association Intervening)* [2006] QB 539 Silber J considered *Gillick* in the context of Article 8 of the Convention, the United Nations Convention on the Rights of the Child (UNCRC) and the increasing emphasis on the autonomy of the child. He held that the principles set out in *Gillick* continued to apply, see para 152.

109. There are two cases dealing with children aged 16 or over who refused medical treatment in circumstances where clinicians considered it was clinically indicated. The issue in each was whether the court could nevertheless, authorise the treatment. *Re W (a Minor) (Medical Treatment: Court's Jurisdiction)* [1993] Fam. 64, concerned the case of a 16 year old girl with anorexia nervosa. The local authority applied under the inherent jurisdiction of the High Court to give medical treatment to W without her consent and against her wishes. W relied on section 8 of the Family Law Reform Act 1969, which states:

> "Section 8 is in these terms:
>
> (1) The consent of a minor who has attained the age of 16 years to any surgical, medical or dental treatment which, in the absence of consent, would constitute a trespass to his person, shall be as effective as it would be if he were of full age; and where a minor has by virtue of this section given an effective consent to any treatment it shall not be necessary to obtain any consent for it from his parent or guardian. (2) In this section 'surgical, medical or dental treatment' includes any procedure undertaken for the purposes of diagnosis, and this section applies to any procedure which is ancillary to any treatment as it applies to that treatment. (3) Nothing in this section shall be construed

> as making ineffective any consent which would have been effective if this section had not been enacted."

110. The Court of Appeal held that section 8 did not confer on a minor an absolute right to determine whether or not she received medical treatment but protected the medical practitioner from an action in trespass. Lord Donaldson analysed *Gillick* and said that Lord Scarman would necessarily have considered that the purpose of section 8 was to provide the medical practitioners treating the child with a defence to either criminal assault or a civil claim for trespass, see pages 76G-H and 78D-F. Lord Donaldson described the effect of the section as being a *"legal flak jacket",* whereby the 16-17 year old is conclusively proved to be *Gillick* competent but this did not mean that someone else who has parental responsibility cannot give consent for the treatment.

111. When applying his analysis to the facts of W's case, Lord Donaldson said at p. 80G-81B:

> "I have no doubt that the wishes of a 16 or 17-year-old child or indeed of a younger child who is "Gillick competent" are of the greatest importance both legally and clinically, but I do doubt whether Thorpe J was right to conclude that W was of sufficient understanding to make an informed decision. I do not say this on the basis that I consider her approach irrational. I personally consider that religious or other beliefs which bar any medical treatment or treatment of particular kinds are irrational, but that does not make minors who hold those beliefs any the less "Gillick competent". They may well have sufficient intelligence and understanding fully to appreciate the treatment proposed and the consequences of their refusal to accept that treatment. What distinguishes W from them, and what with all respect I do not think that Thorpe J took sufficiently into account (perhaps because the point did not emerge as clearly before him as it did before us), is that it is a feature of anorexia nervosa that it is capable of destroying the ability to make an informed choice. It creates a compulsion to refuse treatment or only to accept treatment which is likely to be ineffective. This attitude is part and parcel of the disease and the more advanced the illness, the more compelling it may become. Where the wishes of the minor are themselves something which the doctors reasonably consider need to be treated in the minor's own best interests, those wishes clearly have a much reduced significance."

112. Lord Donaldson concluded at p. 84A-B that:

> "No minor of whatever age has power by refusing consent to treatment to override a consent to treatment by someone who has parental responsibility for the minor and a fortiori a consent by the court. Nevertheless such a refusal is a very important consideration in making clinical judgments and for parents and the courts in deciding whether themselves to give consent. Its importance increases with the age and maturity of the minor."

113. Balcombe LJ at p. 87G-H agreed with Lord Donaldson that the parents of a 16 and 17 year old retained the right to consent to treatment even if she did not consent, and that the court could continue to exercise its inherent jurisdiction. Nolan LJ did not express a view as to whether parents could consent to treatment where the child had refused, but considered that the court under its inherent jurisdiction could continue to do so. He said, at p. 94D-E:

> "To take it a stage further, if the child's welfare is threatened by a serious or imminent risk that the child will suffer grave and irreversible mental or physical harm, then once again the court when called upon has a duty to intervene. It makes no difference whether the risk arises from the action or inaction of others, or from the action or inaction of the child. Due weight must be given to the child's wishes, but the court is not bound by them. In the present case, Thorpe J was apparently satisfied on the evidence before him that such a risk existed. In my judgment, he was fully entitled to take this view. By the time the matter came to this court, it was impossible to take any other view. For these reasons, I would dismiss the appeal save to the extent of making the necessary variation of the order of Thorpe J."

114. We were taken to two cases concerning the application of *Gillick* in particularly difficult medical and ethical situations, which are of some assistance in the present case. In *Re L (Medical Treatment: Gillick Competency*) [1998] 2 F.L.R. 810 Sir Stephen Brown P. considered the case of a 14 year old girl with a life threatening condition involving the possibility of a blood transfusion. L was a Jehovah's Witness and would not consent to the blood transfusion. The court ordered that the medical treatment should take place without her consent. The expert clinician appointed by the Official Solicitor is recorded as giving the following evidence:

> "He makes the point that the girl's view as to having no blood transfusion is based on a very sincerely, strongly held religious belief which does not in fact lend itself in her mind to discussion. It is one that has been formed by her in the context of her own family experience and the Jehovah's Witness meetings where they all support this view. He makes the point that there is a distinction between a view of this kind and the constructive formulation of an opinion which occurs with adult experience. That has not happened of course in the case of this young girl."

115. Sir Stephen Brown then concluded at p. 813:

> "It is, therefore, a limited experience of life which she has – inevitably so – but this is in no sense a criticism of her or of her upbringing. It is indeed refreshing to hear of children being brought up with the sensible disciplines of a well-conducted family. But it does necessarily limit her understanding of matters which are as grave as her own present situation. It may be that because of her belief she is willing to say, and to mean it, 'I am willing to accept death rather than to have a blood transfusion', but it is quite clear in this case that she has not been able to be given all the

> details which it would be right and appropriate to have in mind when making such a decision.
>
> I do not think that in this case this young girl is 'Gillick competent'. I base that upon all the evidence that I have heard. She is certainly not 'Gillick competent' in the context of all the necessary details which it would be appropriate for her to be able to form a view about."

116. *Re S (A Child) (Child Parent: Adoption Consent)* [2019] 2 Fam 177 also concerned a child under 16. In that case Cobb J considered the competence of a mother under the age of 16 to consent to her baby being placed for adoption. Cobb J held that it was appropriate and helpful in determining *Gillick* competence to read across and borrow from the relevant concepts and language in the Mental Capacity Act 2005 but cognisant of some fundamental differences, in particular that the assumption of capacity in section 1(2) of that Act did not apply and there was no requirement for any diagnostic characteristic as there is in section 2(1) of the Mental Capacity Act 2005, see paras 15,16 and 60.

117. At paras 34 to 37 Cobb J considered what test he should apply to the information that S needed to understand and then set out the information that would be relevant for the decision in question:

> "34. Macur J in *LBL v RYJ and VJ* [2011] 1 FLR 1279, para 24 held that it would not be necessary for a decision-maker to be able to comprehend "all the peripheral detail" in the assessment of capacity to make the relevant decision; in a case concerning residence and the provision of education, Macur J went on to say, at para 58:
>
> "In [the expert's] view it is unnecessary for his determination of RYJ's capacity that she should understand all the details within the statement of special educational needs. It is unnecessary that she should be able to give weight to every consideration that would otherwise be utilised in formulating a decision objectively in her 'best interests'. I agree with his interpretation of the test in section 3 which is to the effect that the person under review must comprehend and weigh the salient details relevant to the decision to be made. To hold otherwise would place greater demands upon RYJ than others of her chronological age/commensurate maturity and unchallenged capacity."
>
> 35. In the same vein, Baker J remarked in *H v A Local Authority* [2011] EWHC 1704 at [16(xi)]: "[the] courts must guard against imposing too high a test of capacity to decide issues such as residence because to do so would run the risk of discriminating against persons suffering from a mental disability."
>
> 36. Although not cited in argument, I further remind myself of the comments of Chadwick LJ in the Court of Appeal in *Masterman-Lister v Brutton & Co (Nos 1 and 2)* [2003] 1 WLR 1511, para 79: "a person should not be held unable to understand the information relevant to a

> decision if he can understand the explanation of that information in broad terms and simple language…" So, says Ms Dolan, it is not necessary for S to understand all the peripheral and non-salient information in the adoption consent form in order to be declared capacitous. Nor does she even need to fully understand the legal distinctions between placement for adoption under a placement order and not under a placement order. Indeed, Ms Dolan herself relies in this regard on *In re A (Adoption: Agreement: Procedure)* [2001] 2 FLR 455, para 43 where Thorpe LJ observes that the differences between freeing and adoption are "complex in their inter-relationship and it is not to be expected that social workers should have a complete grasp of the distinction between the two, or always to signify the distinction in their discussion with the clients" (my emphasis)." If social workers are not expected to understand the complexities of the legislation (or its predecessor) or explain the distinction accurately to the parents with whom they are working asks Ms Dolan, why should a person under the age of 16 be expected to be able to grasp them in order to be able to be declared capacitous?
>
> 37. Accordingly, argues the local authority, the salient or "sufficient" information which is required to be understood by the child parent regarding extra-familial adoption is limited to the fundamental legal consequences of the same. The factors discussed at the hearing include: (i) your child will have new legal parents, and will no longer be your son or daughter in law, (ii) adoption is final, and non-reversible; (iii) during the process, other people (including social workers from the adoption agency) will be making decisions for the child, including who can see the child, and with whom the child will live; (iv) you may obtain legal advice if you wish before taking the decision; (v) the child will live with a different family forever; you will (probably) not be able to choose the adopters; (vi) you will have no right to see your child or have contact with your child; it is highly likely that direct contact with your child will cease, and any indirect contact will be limited; (vii) the child may later trace you, but contact will only be re-established if the child wants this; (viii) there are generally two stages to adoption; the child being placed with another family for adoption, and being formally adopted; (ix) for a limited period of time you may change your mind; once placed for adoption, your right to change your mind is limited, and is lost when an adoption order is made."

118. Cobb J's conclusions were these:

> "60… It follows that in order to satisfy the Gillick test in this context the child parent should be able to demonstrate "sufficient" understanding of the "salient" facts around adoption; she should understand the essential "nature and quality of the transaction" (per Munby J in *Sheffield City Council v E* [2005] Fam 326, para 19) and should not need to be concerned with the peripheral.

> 61. It will, however, be necessary for the competent child decision-maker to demonstrate a "full understanding" of the essential implications of adoption when exercising her decision-making, for the independent CAFCASS officer to be satisfied that the consent is valid. If consent is offered under section 19 and/or section 20 of the 2002 Act, it will be necessary for a form to be signed, even if not in the precise format of that identified by Practice Direction 5A. I accept that on an issue as significant and life-changing as adoption, there is a greater onus on ensuring that the child understands and is able to weigh the information than if the decision was of a lesser magnitude: see Baker J in *CC v KK and STCC* [2012] COPLR 627, para 69. This view is consistent with the Mental Capacity Act 2005 Code of Practice, which provides, at paragraph 4.19:
>
> "a person might need more detailed information or access to advice, depending on the decision that needs to be made. If a decision could have serious or grave consequences, it is even more important that a person understands the information relevant to that decision.""

119. In determining the level of understanding that the child needs to have to consent to PBs, Mr Hyam attached considerable importance to the decision of the Supreme Court in *Montgomery v Lancashire Health Board*. That case concerned an action in negligence brought by a mother on behalf of her child. The child was disabled as a result of complications during delivery and the mother argued that she should have been advised as to the possibility of delivery by elective caesarean. The central issue for present purposes was the information that the doctor needed to have given the patient in order to establish that she had given informed consent for the treatment.

120. Lord Kerr set out the requirements placed on a doctor in providing information on risks of injury from treatment in the following terms at para 87:

> "An adult person of sound mind is entitled to decide which, if any, of the available forms of treatment to undergo, and her consent must be obtained before treatment interfering with her bodily integrity is undertaken. The doctor is therefore under a duty to take reasonable care to ensure that the patient is aware of any material risks involved in any recommended treatment, and of any reasonable alternative or variant treatments. The test of materiality is whether, in the circumstances of the particular case, a reasonable person in the patient's position would be likely to attach significance to the risk, or the doctor is or should reasonably be aware that the particular patient would be likely to attach significance to it."

121. Mr Hyam submitted that in determining whether a child is *Gillick* competent the court should consider what would a *"reasonable person in the patient's position understand",* and in asking that question, he submitted that the "reasonable person" is one with adult knowledge.

122. Ms Morris went to the opposite extreme. She submitted that when deciding what information needs to be given to the patient and understood by them, the test is a reasonable person in that individual's position, i.e. a reasonable 12 year old (or other

age) with GD. She said that the "salient" information that needs to be provided is what that reasonable patient would attach importance to. She said that seeking consent, certainly for treatment with lifelong implications such as sterilisation will always involve some *"act of imagination"*. Many patients facing life changing treatment, such as the loss of fertility in cancer treatment or endometriosis, will not have had experience of what they are foregoing, for example, fertility. She submitted that the court ought not to be pronouncing on hypothetical cases: rather, it should or could consider the facts of one specific case as and when it arises.

123. Mr McKendrick submitted that the correct approach in deciding what information was material was to assume a reasonable child of the individual's age.

124. Mr Skinner pointed out that *Montgomery* concerned an adult and therefore the presumption of capacity in the Mental Capacity Act 2005 applied. That presumption is inapplicable in a case concerning *Gillick* competency where the very issue is whether the child is competent to make the decision. The decision in *Montgomery* was of limited assistance, therefore, in the present case. In determining competence, the child must have sufficient understanding of the factors that are not just relevant to him or her now but which on an objective basis ought to be given weight in the future.

125. In our view, the following principles can be derived from the cases to which we have referred:

126. First, the question as to whether a person under the age of 16 is *Gillick* competent to make the relevant decision will depend on the nature of the treatment proposed as well as that person's individual characteristics. The assessment is necessarily an individual one. Where the decision is significant and life changing then there is a greater onus to ensure that the child understands and is able to weigh the information, see *Re S* at para 60.

127. Secondly, however, that does not mean that it is not possible for the court to draw some lines. The Trusts themselves accept that a 7 year old being treated with PBs for precocious puberty cannot give informed consent and his or her parents must give that consent because of the young age of the child concerned and the nature of the treatment.

128. Thirdly, efforts should be made to allow the child or young person to achieve *Gillick* competency where that is possible. Clinicians should therefore work with the individual to help them understand the treatment proposed and its potential implications in order to help them achieve competence.

129. Fourthly, however, that does not mean that every individual under 16 can achieve *Gillick* competence in relation to the treatment proposed. As we discuss below, where the consequences of the treatment are profound, the benefits unclear and the long-term consequences to a material degree unknown, it may be that *Gillick* competence cannot be achieved, however much information and supportive discussion is undertaken.

130. Fifthly, in order to achieve *Gillick* competence it is important not to set the bar too high. It is not appropriate to equate the matters that a clinician needs to explain, as set out in *Montgomery*, to the matters that a child needs to understand to achieve *Gillick* competence. The consequence of Mr Hyam's approach would be significantly to raise

the bar for competence and capacity, which would be contrary both to the common law and to a child's Article 8 rights and the importance of supporting individual autonomy.

131. We adopt the language of Chadwick LJ in *Masterman-Lister v Brutton and Co (Nos 1 and 2)* [2003] 1 WLR 151: a person should be able to "*understand an explanation of that information in broad terms and simple language"*, see *Re S* at para 36. Although this was said in a case that concerned an adult's capacity, in our judgment the same approach should be applied to a case concerning *Gillick* competence. The child or young person needs to be able to demonstrate sufficient understanding of the salient facts, see *Re S* at para 60.

132. Sixthly, we agree with Mr Skinner, that in deciding what facts are salient and what level of understanding is sufficient, it is necessary to have regard to matters which are those which objectively ought to be given weight in the future although the child might be unconcerned about them now. On the facts of this case there are some obvious examples, including the impact on fertility and on future sexual functioning.

SECTION E: CONCLUSIONS

133. The principal issue before this court is in some ways a narrow one. Can a child or young person under the age of 16 achieve *Gillick* competence in respect of the decision to take PBs for GD? The legal position of 16 and 17 year olds is different, and we deal with that below.

134. The starting point is to consider the nature of the treatment proposed. The administration of PBs to people going through puberty is a very unusual treatment for the following reasons. Firstly, there is real uncertainty over the short and long-term consequences of the treatment with very limited evidence as to its efficacy, or indeed quite what it is seeking to achieve. This means it is, in our view, properly described as experimental treatment. Secondly, there is a lack of clarity over the purpose of the treatment: in particular, whether it provides a "pause to think" in a "hormone neutral" state or is a treatment to limit the effects of puberty, and thus the need for greater surgical and chemical intervention later, as referred to in the Health Research Authority report. Thirdly, the consequences of the treatment are highly complex and potentially lifelong and life changing in the most fundamental way imaginable. The treatment goes to the heart of an individual's identity, and is thus, quite possibly, unique as a medical treatment.

135. Furthermore, the nature and the purpose of the medical intervention must be considered. The condition being treated, GD, has no direct physical manifestation. In contrast, the treatment provided for that condition has direct physical consequences, as the medication is intended to and does prevent the physical changes that would otherwise occur within the body, in particular by stopping the biological and physical development that would otherwise take place at that age. There is also an issue as to whether GD is properly categorised as a psychological condition, as the DSM-5 appears to do, although we recognise there are those who would not wish to see the condition categorised in that way. Be that as it may, in our judgment for the reasons already identified, the clinical intervention we are concerned with here is different in kind to other treatments or clinical interventions. In other cases, medical treatment is used to remedy, or alleviate the symptoms of, a diagnosed physical or mental condition, and

the effects of that treatment are direct and usually apparent. The position in relation to puberty blockers would not seem to reflect that description.

136. Indeed the consequences which flow from taking PBs for GD and which must be considered in the context of informed consent, fall into two (interlinking) categories. Those that are a direct result of taking the PBs themselves, and those that follow on from progression to Stage 2, that is taking cross-sex hormones. The defendant and the Trusts argue that Stage 1 and 2 are entirely separate; a child can stop taking PBs at any time and that Stage 1 is fully reversible. It is said therefore the child needs only to understand the implications of taking PBs alone to be *Gillick* competent. In our view this does not reflect the reality. The evidence shows that the vast majority of children who take PBs move on to take cross-sex hormones, that Stages 1 and 2 are two stages of one clinical pathway and once on that pathway it is extremely rare for a child to get off it.

137. The defendant argues that PBs give the child "time to think", that is, to decide whether or not to proceed to cross-sex hormones or to revert to development in the natal sex. But the use of puberty blockers is not itself a neutral process by which time stands still for the child on PBs, whether physically or psychologically. PBs prevent the child going through puberty in the normal biological process. As a minimum it seems to us that this means that the child is not undergoing the physical and consequential psychological changes which would contribute to the understanding of a person's identity. There is an argument that for some children at least, this may confirm the child's chosen gender identity at the time they begin the use of puberty blockers and to that extent, confirm their GD and increase the likelihood of some children moving on to cross-sex hormones. Indeed, the statistical correlation between the use of puberty blockers and cross-sex hormones supports the case that it is appropriate to view PBs as a stepping stone to cross-sex hormones.

138. It follows that to achieve *Gillick* competence the child or young person would have to understand not simply the implications of taking PBs but those of progressing to cross-sex hormones. The relevant information therefore that a child would have to understand, retain and weigh up in order to have the requisite competence in relation to PBs, would be as follows: (i) the immediate consequences of the treatment in physical and psychological terms; (ii) the fact that the vast majority of patients taking PBs go on to CSH and therefore that s/he is on a pathway to much greater medical interventions; (iii) the relationship between taking CSH and subsequent surgery, with the implications of such surgery; (iv) the fact that CSH may well lead to a loss of fertility; (v) the impact of CSH on sexual function; (vi) the impact that taking this step on this treatment pathway may have on future and life-long relationships; (vii) the unknown physical consequences of taking PBs; and (viii) the fact that the evidence base for this treatment is as yet highly uncertain.

139. It will obviously be difficult for a child under 16 to understand and weigh up such information. Although a child may understand the concept of the loss of fertility for example, this is not the same as understanding how this will affect their adult life. A child's attitude to having biological children and their understanding of what this really means, is likely to change between childhood and adulthood. For many children, certainly younger children, and some as young as 10 and just entering puberty, it will not be possible to conceptualise what not being able to give birth to children (or conceive children with their own sperm) would mean in adult life. Similarly, the

meaning of sexual fulfilment, and what the implications of treatment may be for this in the future, will be impossible for many children to comprehend.

140. Ms Morris submitted that many decisions about complex and long-lasting medical treatment will involve the patient having, to some degree, to imagine themselves into an uncertain future of which they have no experience. However, for the reasons that we have explained in para 135 above we consider the treatment in this case to be in entirely different territory from the type of medical treatment which is normally being considered.

141. Some of the children and young people who have been treated at GIDS say in their witness statements that the thought of sex disgusted them, or they did not really think about fertility. These normal reactions do not detract from the difficulties surrounding consent and treatment with PBs. That adolescents find it difficult to contemplate or comprehend what their life will be like as adults and that they do not always consider the longer-term consequences of their actions is perhaps a statement of the obvious.

142. These various difficulties are compounded by the particular difficulties prevalent in the cohort of children treated at GIDS. On the defendant's case, they suffer considerable psychological distress by reason of their GD and are highly vulnerable. In those circumstances, the consequences of taking PBs on their fertility for example, or on their sexual life, may be viewed as a relatively small price to pay for what may be perceived as a solution to their immediate and real psychological distress. It would not follow however that their weighing of risks and benefits when they might start taking PBs would prevail in the longer-term.

143. The difficulty of achieving informed consent in these circumstances is further exacerbated by the lack of evidence as to the efficacy of PBs in treating GD and the long-term outcomes of taking it. We entirely accept that the fact that a treatment is experimental, or that the long-term outcomes are not yet known, does not of itself prevent informed consent being given. Otherwise no experimental treatment could ever be consented to. However, the combination here of lifelong and life changing treatment being given to children, with very limited knowledge of the degree to which it will or will not benefit them, is one that gives significant grounds for concern.

144. We do not think that the answer to this case is simply to give the child more, and more detailed, information. The issue in our view is that in many cases, however much information the child is given as to long-term consequences, s/he will not be able to weigh up the implications of the treatment to a sufficient degree. There is no age appropriate way to explain to many of these children what losing their fertility or full sexual function may mean to them in later years.

145. *Gillick* makes clear that any decision is treatment and person specific. However, for the reasons that we have set out above, we think that it is appropriate in this case to give clear guidance as to the application of the *Gillick* tests to the treatment and cohort of children in question. The conclusion we have reached is that it is highly unlikely that a child aged 13 or under would ever be *Gillick* competent to give consent to being treated with PBs. In respect of children aged 14 and 15, we are also very doubtful that a child of this age could understand the long-term risks and consequences of treatment in such a way as to have sufficient understanding to give consent. However, plainly the

increased maturity of the child means that there is more possibility of achieving competence at the older age.

146. In respect of a young person aged 16 or over, the legal position is different. There is a presumption of capacity under section 8 of the Family Law Reform Act 1969. As is explained in *Re W*, that does not mean that a court cannot protect the child under its inherent jurisdiction if it considers the treatment not to be in the child's best interests. However, so long as the young person has mental capacity and the clinicians consider the treatment is in his/her best interests, then absent a possible dispute with the parents, the court generally has no role. We do not consider that the court can somehow adopt an intrusive jurisdiction in relation to one form of clinical intervention for which no clear legal basis has been established.

147. We do however recognise that in the light of the evidence that has emerged, and the terms of this judgment, clinicians may well consider that it is not appropriate to move to treatment, such as PBs or CSH, without the involvement of the court. We consider that it would be appropriate for clinicians to involve the court in any case where there may be any doubt as to whether the long-term best interests of a 16 or 17 year old would be served by the clinical interventions at issue in this case.

148. We express that view for these reasons. First, the clinical interventions involve significant, long-term and, in part, potentially irreversible long-term physical, and psychological consequences for young persons. The treatment involved is truly life changing, going as it does to the very heart of an individual's identity. Secondly, at present, it is right to call the treatment experimental or innovative in the sense that there are currently limited studies/evidence of the efficacy or long-term effects of the treatment.

149. The position of the defendant and the Trusts is that they consider it would be an intrusion into the child or young person's autonomy if a decision about treatment with PBs were to be made by the court not by the patient. They are concerned about the use of NHS and court resources if these decisions have to be made by the court. We do not consider that this is the correct approach. In principle, a young person's autonomy should be protected and supported; however, it is the role of the court to protect children, and particularly a vulnerable child's best interests. The decisions in respect of PBs have lifelong and life-changing consequences for the children. Apart perhaps from life-saving treatment, there will be no more profound medical decisions for children than whether to start on this treatment pathway. In those circumstances we consider that it is appropriate that the court should determine whether it is in the child's best interests to take PBs. There is a real benefit in the court, almost certainly with a child's guardian appointed, having oversight over the decision. In any case, under the inherent jurisdiction concerning medical treatment for those under the age of 18, there is likely to be a conflict between the support of autonomy and the protective role of the court. As we have explained above, we consider this treatment to be one where the protective role of the court is appropriate.

150. The claimants' alternative ground is that the information provided by the defendant and the Trusts is inadequate to form the basis of informed consent. We accept that the defendant and the Trusts have in their written information, to children, young people and their parents and carers, tried hard to explain the potential consequences of PBs, including that of moving on to CSH, and to give full information. They have also

attempted to do this in an age appropriate manner. The problem is not the information given, but the ability of the children and young people, to understand and most importantly weigh up that information. The approach of the defendant appears to have been to work on the assumption that if they give enough information and discuss it sufficiently often with the children, they will be able to achieve *Gillick* competency. As we have explained above, we do not think that this assumption is correct.

OVERALL CONCLUSION

151. A child under 16 may only consent to the use of medication intended to suppress puberty where he or she is competent to understand the nature of the treatment. That includes an understanding of the immediate and long-term consequences of the treatment, the limited evidence available as to its efficacy or purpose, the fact that the vast majority of patients proceed to the use of cross-sex hormones, and its potential life changing consequences for a child. There will be enormous difficulties in a child under 16 understanding and weighing up this information and deciding whether to consent to the use of puberty blocking medication. It is highly unlikely that a child aged 13 or under would be competent to give consent to the administration of puberty blockers. It is doubtful that a child aged 14 or 15 could understand and weigh the long-term risks and consequences of the administration of puberty blockers.

152. In respect of young persons aged 16 and over, the legal position is that there is a presumption that they have the ability to consent to medical treatment. Given the long-term consequences of the clinical interventions at issue in this case, and given that the treatment is as yet innovative and experimental, we recognise that clinicians may well regard these as cases where the authorisation of the court should be sought prior to commencing the clinical treatment.

153. We have granted a declaration to reflect the terms of this judgment.

Decision Memo for GENDER Dysphoria and GENDER REASSIGNMENT SURGERY (CAG-00446N)

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Decision Summary

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on a case-by-case basis. We received a complete, formal request to make a national coverage determination on surgical remedies for gender identity disorder (GID), now known as gender dysphoria. The Centers for Medicare & Medicaid Services (CMS) is not issuing a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria because the clinical evidence is inconclusive for the Medicare population.

In the absence of a NCD, coverage determinations for gender reassignment surgery, under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements, will continue to be made by the local MACs on a case-by-case basis. To clarify further, the result of this decision is not national non-coverage rather it is that no national policy will be put in place for the Medicare program. In the absence of a national policy, MACs will make the determination of whether or not to cover gender reassignment surgery based on whether gender reassignment surgery is reasonable and necessary for the individual beneficiary after considering the individual's specific circumstances. For Medicare beneficiaries enrolled in Medicare Advantage (MA) plans, the initial determination of whether or not surgery is reasonable and necessary will be made by the MA plans.

Consistent with the request CMS received, the focus of this National Coverage Analysis (NCA) was gender reassignment surgery. Specific types of surgeries were not individually assessed. We did not analyze the clinical evidence for counseling or hormone therapy treatments for gender dysphoria. As requested by several public commenters, we have modified our final decision memorandum to remove language that was beyond the scope of the specific request. We are not making a national coverage determination related to counseling, hormone therapy treatments, or any other potential treatment for gender dysphoria.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

Decision Memo

To: Administrative File: CAG #00446N

From: Tamara Syrek Jensen, JD
Director, Coverage and Analysis Group

Joseph Chin, MD, MS
Deputy Director, Coverage and Analysis Group

James Rollins, MD, PhD
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Analyst

Subject: Final Decision Memorandum on Gender Reassignment Surgery for Medicare Beneficiaries with Gender Dysphoria

Date: August 30, 2016

I. Decision

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on a case-by-case basis. We received a complete, formal request to make a national coverage determination on surgical remedies for gender identity disorder (GID), now known as gender dysphoria. The Centers for Medicare & Medicaid Services (CMS) is not issuing a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria because the clinical evidence is inconclusive for the Medicare population.

In the absence of a NCD, coverage determinations for gender reassignment surgery, under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements, will continue to be made by the local MACs on a case-by-case basis. To clarify further, the result of this decision is not national non-coverage rather it is that no national policy will be put in place for the Medicare program. In the absence of a national policy, MACs will make the determination of whether or not to cover gender reassignment surgery based on whether gender reassignment surgery is reasonable and necessary for the individual beneficiary after considering the individual's specific circumstances. For Medicare beneficiaries enrolled in Medicare Advantage (MA) plans, the initial determination of whether or not surgery is reasonable and necessary will be made by the MA plans.

Consistent with the request CMS received, the focus of this National Coverage Analysis (NCA) was gender reassignment surgery. Specific types of surgeries were not individually assessed. We did not analyze the clinical evidence for counseling or hormone therapy treatments for gender dysphoria. As requested by several public commenters, we have modified our final decision memorandum to remove language that was beyond the scope of the specific request. We are not making a national coverage determination related to counseling, hormone therapy treatments, or any other potential treatment for gender dysphoria.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

II. Background

Below is a list of acronyms used throughout this document.

AHRQ - Agency for Healthcare Research and Quality
AIDS - Acquired Immune Deficiency Syndrome
ANOVA - Analysis of Variance

APA - American Psychiatric Association
APGAR - Adaptability, Partnership Growth, Affection, and Resolve test
BIQ - Body Image Questionnaire
BSRI - Bem Sex Role Inventory
CCEI - Crown Crips Experimental Index
CDC – Centers for Disease Control
CHIS - California Health Interview Survey
CI - Confidence Interval
CMS - Centers for Medicare & Medicaid Services
DAB - Departmental Appeals Board
DSM - Diagnostic and Statistical Manual of Mental Disorders
EMBASE - Exerpta Medica dataBASE
FBeK - Fragebogen zur Beurteilung des eigenen Korpers
FDA - Food and Drug Administration
FPI-R - Freiburg Personality Inventory
FSFI - Female Sexual Function Index
GAF - Global Assessment of Functioning
GID - Gender Identity Disorder
GIS - Gender Identity Trait Scale
GRS - Gender Reassignment Surgery
GSI - Global Severity Indices
HADS - Hospital Anxiety Depression Scale
HHS - U.S. Department of Health and Human Services
HIV - Human Immunodeficiency Virus
IIP - Inventory of Interpersonal Problems
IOM - Institute of Medicine
KHQ - King's Health Questionnaire
LGB - Lesbian, Gay, and Bisexual
LGBT - Lesbian, Gay, Bisexual, and Transgender
MAC - Medicare Administrative Contractor
MMPI - Minnesota Multiphasic Personality Inventory
NCA - National Coverage Analysis
NCD - National Coverage Determination
NICE - National Institute for Health Care Excellence
NIH - National Institutes of Health
NZHTA - New Zealand Health Technology Assessment
PIT - Psychological Integration of Trans-sexuals
QOL - Quality of Life
S.D. - Standard Deviation
SADS - Social Anxiety Depression Scale
SCL-90R - Symptom Check List 90-Revised
SDPE - Scale for Depersonalization Experiences
SES - Self Esteem Scale
SF - Short Form
SMR - Standardized Mortality Ratio SOC – Standards of Care
STAI-X1 - Spielberger State and Trait Anxiety Questionnaire
STAI-X2 - Spielberger State and Trait Anxiety Questionnaire
TSCS - Tennessee Self-Concept Scale
U.S. - United States
VAS - Visual Analog Scale
WHOQOL-BREF - World Health Organization Quality of Life - Abbreviated version of the WHOQOL-100
WPATH - World Professional Association for Transgender Health

A. Diagnostic Criteria

The criteria for gender dysphoria or spectrum of related conditions as defined by the American Psychiatric Association (APA) in the Diagnostic and Statistical Manual of Mental Disorders (DSM) has changed over time (See Appendix A).

Gender dysphoria (previously known as gender identity disorder) is a classification used to describe persons who experience significant discontent with their biological sex and/or gender assigned at birth. Although there are other therapeutic options for gender dysphoria, consistent with the NCA request, this decision only focuses on gender reassignment surgery.

B. Prevalence of Transgender Individuals

For estimates of transgender individuals in the U.S., we looked at several studies.

The Massachusetts Behavior Risk Factor Surveillance Survey (via telephone) (2007 and 2009) identified 0.5% individuals as transgender (Conron et al., 2012).

Derivative data obtained from the 2004 California Lesbian Gay Bisexual and Transgender (LGBT) Tobacco Survey (via telephone) and the 2009 California Health Interview Survey (CHIS) (via telephone) suggested the LGB population constitutes 3.2% of the California population and that transgender subjects constitute approximately 2% of the California LGBT population and 0.06% of the overall California population (Bye et al., 2005; CHIS 2009; Gates, 2011).

Most recently, the Williams Institute published a report that utilized data from the Centers for Disease Control's (CDC) Behavioral Risk Factor Surveillance System (BRFSS). Overall, they found that 0.6% or 1.4 million U.S. adults identify as transgender. The report further estimated 0.7% of adults between the ages of 18-25 identify as transgender, 0.6% of adults between the ages of 25-65 identify as transgender, and 0.5% of adults age 65 or older identify as transgender (Flores et al., 2016).

In a recent review of Medicare claims data, CMS estimated that in calendar year 2013 there were at least 4,098 transgender beneficiaries (less than 1% of the Medicare population) who utilized services paid for by Medicare, of which 90% had confirmatory diagnosis, billing codes, or evidence of a hormone therapy prescription. The Medicare transgender population is racially and ethnically diverse (e.g., 74% White, 15% African American) and spans the entire country. Nearly 80% of transgender beneficiaries are under age 65, including approximately 23% ages 45-54. (CMS Office of Minority Health 2015).

For international comparison purposes, recent estimates of transgender populations in other countries are similar to those in the United States. New Zealand researchers, using passport data, reported a prevalence of 0.0275% for male-to-female adults and 0.0044% female-to-male adults (6:1 ratio) (Veale, 2008). Researchers from a centers of transgender treatment and reassignment surgery in Belgium conducted a survey of regional plastic surgeons and reported a prevalence of 0.008% male-to-female and 0.003% female-to-male (ratio 2.7:1) surgically reassigned transsexuals in Belgium (De Cuypere et al., 2007). Swedish researchers, using national mandatory reporting data on those requesting reassignment surgery, reported secular changes over time in that the number of completed reassignment surgeries per application increased markedly in the 1990s; the male-to- female/female-to-male sex ratio changed from 1:1 to 2:1; the age of male-to-female and female-to-male applicants was initially similar, but increased by eight years for male-to-female applicants; and the proportion of foreign born applicants increased (Olsson and Moller 2003).

III. History of Medicare Coverage

Date	Action
August 1, 1989	CMS published the initial NCD, titled "140.3, Transsexual Surgery" in the Federal Register. (54 Fed. Reg. 34,555, 34,572)
May 30, 2014	The HHS Departmental Appeals Board (DAB) determined that the NCD denying coverage for all transsexual surgery was not valid. As a result, MACs determined coverage on a case-by-case basis.

CMS does not currently have a NCD on gender reassignment surgery.

A. Current Request

On December 3, 2015, CMS accepted a formal complete request from a beneficiary to initiate a NCA for gender reassignment surgery.

CMS opened this National Coverage Analysis (NCA) to thoroughly review the evidence to determine whether or not gender reassignment surgery may be covered nationally under the Medicare program.

B. Benefit Category

Medicare is a defined benefit program. For an item or service to be covered by the Medicare program, it must fall within one of the statutorily defined benefit categories as outlined in the Act. For gender reassignment surgery, the following are statutes are applicable to coverage:

Under §1812 (Scope of Part A) Under §1832 (Scope of Part B)
Under §1861(s) (Definition of Medical and Other Health Services)
Under §1861(s)(1) (Physicians' Services)

This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

Timeline of Medicare Coverage Policy Actions for Gender Reassignment Surgery

Date	Action
December 3, 2015	CMS accepts an external request to open a NCD. A tracking sheet was posted on the web site and the initial 30 day public comment period commenced.
January 2, 2016	Initial comment period closed. CMS received 103 comments.
June 2, 2016	Proposed Decision Memorandum posted on the web site and the final 30 day public comment period commenced.
July 2, 2016	Final comment period closed. CMS received 45 comments.

V. FDA Status

Surgical procedures per se are not subject to the Food and Drug Administration's (FDA) approval.

Inflatable penile prosthetic devices, rigid penile implants, testicular prosthetic implants, and breast implants have been approved and/or cleared by the FDA.

VI. General Methodological Principles

In general, when making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. (§ 1862 (a)(1)(A)). The evidence may consist of external technology assessments, internal review of published and unpublished studies, recommendations from the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC), evidence-based guidelines, professional society position statements, expert opinion, and public comments.

The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) specific clinical question relevant to the coverage request can be answered conclusively; and 2) the extent to which we are confident that the intervention will improve health outcomes for patients.

A detailed account of the methodological principles of study design the agency staff utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, blinding of readers of the index test, and reference test results.

VII. Evidence

A. Introduction

Below is a summary of the evidence we considered during our review, primarily articles about clinical trials published in peer- reviewed medical journals. We also considered articles cited by the requestor, articles identified in public comments, as well as those found by a CMS literature review. Citations are detailed below.

B. Literature Search Methods

CMS staff extensively searched for primary studies for gender dysphoria. The emphasis focused less on specific surgical techniques and more on functional outcomes unless specific techniques altered those types of outcomes.

The reviewed evidence included articles obtained by searching literature databases and technology review databases from PubMed (1965 to current date), EMBASE, the Agency for Healthcare Research and Quality (AHRQ), the Blue Cross/Blue Shield Technology Evaluation Center, the Cochrane Collection, the Institute of Medicine, and the National Institute for Health and Care Excellence (NICE) as well as the source material for commentary, guidelines, and formal evidence-based documents published by professional societies. Systematic reviews were used to help locate some of the more obscure publications and abstracts.

Keywords used in the search included: Trans-sexual, transgender, gender identity disorder (syndrome), gender

dysphoria and/or hormone therapy, gender surgery, genital surgery, gender reassignment (surgery), sex reassignment (surgery) and/or quality of life, satisfaction-regret, psychological function (diagnosis of mood disorders, psychopathology, personality disorders), suicide (attempts), mortality, and adverse events-reoperations. After the identification of germane publications, CMS also conducted searches on the specific psychometric instruments used by investigators.

Psychometric instruments are scientific tools used to measure individuals' mental capabilities and behavioral style. They are usually in the form of questionnaires that numerically capture responses. These tools are used to create a psychological profile that can address questions about a person's knowledge, abilities, attitudes and personality traits. In the evaluation of patients with gender dysphoria, it is important that both validity and reliability be assured in the construction of the tool (validity refers to how well the tool actually measures what it was designed to measure, or how well it reflects the reality it claims to represent, while reliability refers to how accurately results of the tool would be replicated in a second identical piece of research). Reliability and validity are important because when evaluating patients with gender dysphoria most of the variables of interest (e.g., satisfaction, anxiety, depression) are latent in nature (not directly observed but are rather inferred) and difficult to quantify objectively.

Studies with robust study designs and larger, defined patient populations assessed with objective endpoints or validated test instruments were given greater weight than small, pilot studies. Reduced consideration was given to studies that were underpowered for the assessment of differences or changes known to be clinically important. Studies with fewer than 30 patients were reviewed and delineated, but excluded from the major analytic framework. Oral presentations, unpublished white papers, and case reports were excluded. Publications in languages other than English were excluded. The CMS initial internal search for the proposed decision memorandum was limited to articles published prior to March 21, 2016. The CMS internal search for the final decision memorandum continued through articles published prior to July 22, 2016.

Included studies were limited to those with adult subjects. Review and discussion of the management of children and adolescents with the additional considerations of induced pubertal delay are outside the scope of this NCD. In cases where the same population was studied for multiple reasons or where the patient population was expanded over time, the latest and/or most germane sections of the publications were analyzed. The excluded duplicative publications are delineated.

CMS also searched Clinicaltrials.gov to identify relevant clinical trials. CMS looked at trial status including early termination, completed, ongoing with sponsor update, and ongoing with estimated date of completion. Publications on completed trials were sought. For this final decision, CMS also reviewed all evidence submitted via public comment.

C. Discussion of Evidence

The development of an assessment in support of Medicare coverage determinations is based on the same general question for almost all national coverage analyses (NCAs): "Is the evidence sufficient to conclude that the application of the item or service under study will improve health outcomes for Medicare patients?" For this specific NCA, CMS is interested in answering the following question:

Is there sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria?

The evidence reviewed is directed towards answering this question.

1. Internal Technology Assessment

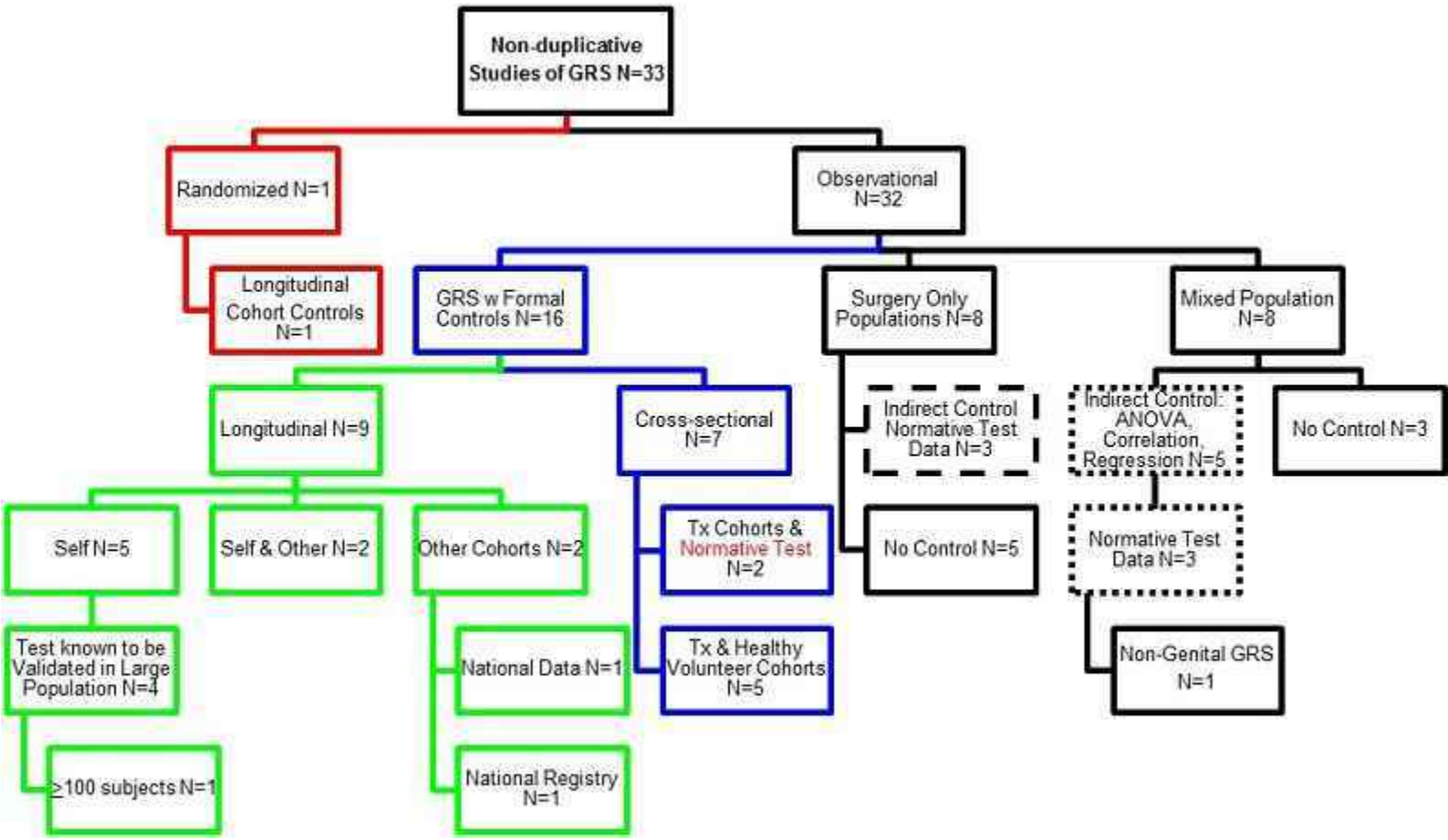
CMS conducted an extensive literature search on gender reassignment related surgical procedures and on facets of gender dysphoria that provide context for this analysis. The latter includes medical and environmental conditions.

CMS identified numerous publications related to gender reassignment surgery. A large number of these were case reports, case series with or without descriptive statistics, or studies with population sizes too small to conduct standard parametric statistical analyses. Others addressed issues of surgical technique.

CMS identified and described 36 publications on gender reassignment surgery that included health outcomes. Because the various investigators at a site sometimes conducted serial studies on ever-enlarging cohort populations, studied sub-populations, studied different outcomes, or used different tools to study the same outcomes, not all study populations were unique. To reduce bias from over-lapping populations, only the latest or most germane publication(s) were described. Subsumed publications were delineated.

Of these 36 publications, two publications used different assessment tools on the same population, and, so for the purposes of evaluation, were classified as one study (Udeze et al., 2008; Megeri and Khoosal, 2007). A total of 33 studies were reviewed (See Figure 1). Appendices C, D, and F include more detail of each study. The publications covered a time span from 1979 to 2015. Over half of the studies were published after 2005.

Figure 1. Studies of Gender Reassignment Surgery (GRS)



ANOVA=Analysis of Variance Normative=Psychometric Tests with known normative for large populations

Figure 1 Legend: The studies in Figure 1 are categorized into three groups. The first group, depicted by the colored

boxes (red, blue, and green), had explicit controls. There was a single randomized study. The remainder in the first group were observational studies. These were subdivided into longitudinal studies and cross-sectional studies. The second group, depicted by black boxes (starting with the surgery only population box) consisted of surgical series. The third group, depicted by black boxes (starting with mixed population), was composed of patients whose treatment could involve a variety of therapeutic interventions, but who were not stratified by that treatment.

When looking at the totality of studies, the 33 studies could be characterized by the following research design groups:

a. Observational, mixed population of surgical and non-surgical patients without stratification

Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol. 2011 Apr;164(4):635-42. Epub 2011 Jan 25.

Asscheman et al. conducted a retrospective, non-blinded, observational study of mortality using a longitudinal design to assess a mixed population treated with hormones, as well as, reassignment surgery in comparison to a population-based cohort. The study was not designed to assess the specific impact of gender reassignment surgery on clinical outcomes.

The investigators assessed mortality in patients who (a) were from a single-center, unspecified, Dutch university specialty clinic, (b) had initiated cross-sex hormone treatment prior to July 1, 1997, and (c) had been followed (with or without continued hormone treatment) by the clinic for at least one year or had expired during the first year of treatment. The National Civil Record Registry (Gemeentelijke Basis Administratie) was used to identify/confirm deaths of clinic patients. Information on the types or hormones used was extracted from clinic records, and information on the causation of death was extracted from medical records or obtained from family physicians. Mortality data for the general population were obtained through the Central Bureau of Statistics of the Netherlands (Centraal Bureau voor Statistiek). Mortality data from Acquired Immune Deficiency Syndrome (AIDS) and substance abuse were extracted from selected Statistics Netherlands reports. The gender of the general Dutch population comparator group was the natal sex of the respective gender dysphoric patient groups.

A total of 1,331 patients who met the hormone treatment requirements were identified (365 female-to-male [27.4%]; 966 male- to-female [72.6%]; ratio 1:2.6). Of these, 1,177 (88.4%) underwent reassignment surgery (343 [94.0% of female-to-male entrants]; 834 [86.3% of male-to-female entrants]; ratio difference 1:2.4 with a p-value $p<0.0001$). Later calculations did not distinguish between those with hormone therapy alone versus those with hormone therapy plus reassignment surgery. The mean age at the time of hormone initiation in female-to-male and male-to-female patients was 26.1±7.6 (range 16–56) years and 31.4±11.4 (range 16–76) years respectively, although the male-to-female subjects were relatively older ($p<0.001$). The mean duration of hormone therapy in female-to-male and male-to-female patients was 18.8±6.3 and 19.4±7.7 years respectively.

There were a total of 134 deaths in the clinic population using hormone therapy with or without surgical reassignment. Of these patients, 12 (3.3%) of the 365 female-to-male patients and 122 (12.6%) of the 966 male-to-female patients died. All-cause mortality for this mixed population was 51% higher and statistically significant (Standardized Mortality Ratio [SMR] 95% confidence interval [CI]) 1.47-1.55) for males-to-females when compared to males in the general Dutch population. The increase in all-cause mortality (12%) for females-to-males when compared to females in the general Dutch population was not statistically significant (95% CI 0.87-1.42).

Ischemic heart disease was a major disparate contributor to excess mortality in male-to-female patients but only in older patients (n=18, SMR 1.64 [95% CI 1.43-1.87]), mean age [range]: 59.7 [42-79] years. Current use of a

particular type of estrogen, ethinyl estradiol, was found to contribute to death from myocardial infarction or stroke (Adjusted Hazard Ratio 3.12 [95% CI 1.28-7.63], p=0.01). There was a small, but statistically significant increase in lung cancer that was thought to possibly be related to higher rates of smoking in this cohort.

Other contributors to the mortality difference between male-to-female patients and the Dutch population at large were completed suicide (n=17, SMR 5.70 [95% CI 4.93-6.54]), AIDS (n=16, SMR 30.20 [95% CI 26.0-34.7]), and illicit drug use (n=5, SMR 13.20 [95% CI 9.70-17.6]). An additional major contributor was "unknown cause" (n=21, SMR 4.00 [95% CI 3.52-4.51]). Of the 17 male-to-female hormone treated patients who committed suicide, 13 (76.5%) had received prior psychiatric treatment and six (35.3%) had not undergone reassignment surgery because of concerns about mental health stability.

Overall mortality, and specifically breast cancer and cardiovascular disease, were not increased in the hormone-treated female-to-male patients. Asscheman et al. reported an elevated SMR for illicit drug use (n=1, SMR 25 [6.00-32.5]). This was the cause of one of the 12 deaths in the cohort.

This study subsumes earlier publications on mortality (Asscheman et al. 1989 [n=425]; Van Kesteren et al. 1997 [n=816]).

Gómez-Gil E, Zubiaurre-Elorza L, Esteva I, Guillamon A, Godás T, Cruz Almaraz M, Halperin I, Salamero M. Hormone-treated transsexuals report less social distress, anxiety and depression. Psychoneuroendocrinology. 2012 May;37(5):662-70. Epub 2011 Sep 19.

Gómez-Gil et al. conducted a prospective, non-blinded observational study using a cross-sectional design and non-specific psychiatric distress tools in Spain. The investigators assessed anxiety and depression in patients with gender dysphoria who attended a single-center specialty clinic with comprehensive endocrine, psychological, psychiatric, and surgical care. The clinic employed World Professional Association for Transgender Health (WPATH) guidelines. Patients were required to have met diagnostic criteria during evaluations by 2 experts. Investigators used the Hospital Anxiety and Depression Scale (HADS) and the Social Anxiety and Distress Scale (SADS) instruments. The SADS total score ranges from 0 to 28, with higher scores indicative of more anxiety. English language normative values are 9.1±8.0. HAD-anxiety and HAD-depression total score ranges from 0 to 21, with higher scores indicative of more pathology. Scores less than 8 are normal. ANOVA was used to explore effects of hormone and surgical treatment.

Of the 200 consecutively selected patients recruited, 187 (93.5% of recruited) were included in the final study population. Of the final study population, 74 (39.6%) were female-to-male patients; 113 (60.4%) were male-to-female patients (ratio 1:1.5); and 120 (64.2%) were using hormones. Of those using hormones, 36 (30.0%) were female-to-male; 84 (70.0%) were male-to-female (ratio 1:2.3). The mean age was 29.87±9.15 years (range 15-61). The current age of patients using hormones was 33.6±9.1 years (n=120) and older than the age of patients without hormone treatment (25.9±7.5) (p=0.001). The age at hormone initiation, however, was 24.6±8.1 years.

Of those who had undergone reassignment surgery, 29 (36.7%) were female-to-male; 50 (63.3%) were male-to-female (ratio 1:1.7). The number of patients not on hormones and who had undergone at least one gender-related surgical procedure (genital or non-genital) was small (n=2). The number of female-to-male patients on hormones who had undergone such surgery (mastectomy, hysterectomy, and/or phalloplasty) was 28 (77.8%). The number of male-to-female patients on hormones who had undergone such surgery (mammoplasty, facial feminization, buttock feminization, vaginoplasty, orchiectomy, and/or vocal feminization (thyroid chondroplasty) was 49 (58.3%).

Analysis of the data revealed that although the mean scores HAD-Anxiety, HAD-Depression, and SADS were statistically lower (better) in those on hormone therapy than in those not on hormone therapy, the mean scores for

HAD-Depression and SADS were in the normal range for gender dysphoric patients not using hormones. The HAD-Anxiety score was 9 in transsexuals without hormone treatment and 6.4 in transsexuals with hormone treatment. The mean scores for HAD-Anxiety, HAD- Depression, and SADS were in the normal range for gender dysphoric patients using hormones. ANOVA revealed that results did not differ by whether the patient had undergone a gender related surgical procedure or not.

Gómez-Gil E, Zubiaurre-Elorza L, de Antonio I, Guillamon A, Salamero M. Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. Qual Life Res. 2014 Mar;23(2):669-76. Epub 2013 Aug 13.

Gómez-Gil et al. conducted a prospective, non-blinded observational study using a non-specific quality of life tool. There were no formal controls for this mixed population ± non-genital reassignment surgery undergoing various stages of treatment.

The investigators assessed quality of life in the context of culture in patients with gender dysphoria who were from a single-center (Barcelona, Spain), specialty and gender identity clinic. The clinic used WPATH guidelines. Patients were required to have met diagnostic criteria during evaluations by both a psychologist and psychiatrist. Patients could have undergone non-genital surgeries, but not genital reassignment surgeries (e.g., orchiectomy, vaginoplasty, or phalloplasty). The Spanish version of the World Health Organization Quality of Life-Abbreviated version of the WHOQOL-100 (WHOQOL- BREF) was used to evaluate quality of life, which has 4 domains (environmental, physical, psychological, and social) and 2 general questions. Family dynamics were assessed with the Spanish version of the Family Adaptability, Partnership Growth, Affection, and Resolve (APGAR) test. Regression analysis was used to explore effects of surgical treatment.

All consecutive patients presenting at the clinic (277) were recruited and, 260 (93.9%) agreed to participate. Of this number, 59 of these were excluded for incomplete questionnaires, 8 were excluded for prior genital reassignment surgery, and 193 were included in the study (the mean age of this group was 31.2±9.9 years (range 16-67). Of these, 74 (38.3%) were female-to-male patients; 119 (61.7%) were male-to-female patients (ratio1:1.6). Of these, 120 (62.2%) were on hormone therapy; 29 (39.2%) of female-to-male patients had undergone at least 1 non-genital, surgical procedure (hysterectomy n=19 (25.7%); mastectomy n=29 (39.2%)); 51 (42.9%) of male-to-female patients had undergone at least one non-genital surgical procedure with mammoplasty augmentation being the most common procedure, n=47 (39.5%), followed by facial feminization, n=11 (9.2%), buttocks feminization, n=9 (7.6%), and vocal feminization (thyroid chondroplasty), n=2 (1.7%).

WHOQOL-BREF domain scores for gender dysphoric patients with and without non-genital surgery were: "Environmental" 58.81±14.89 (range 12.50-96.88), "Physical" 63.51±17.79 (range 14.29-100), "Psychological" 56.09+16.27 (range 16.67- 56.09), "Social" 60.35±21.88 (range 8.33-100), and "Global QOL and Health" 55.44+27.18 (range 0-100 with higher score representing better QOL). The mean APGAR family score was 7.23±2.86 (range 0-10 with a score of 7 or greater indicative of family functionality).

Regression analysis, which was used to assess the relative importance of various factors to WHOQOL-BREF domains and general questions, revealed that family support was an important element for all four domains and the general health and quality- of-life questions. Hormone therapy was an important element for the general questions and for all of the domains except "Environmental." Having undergone non-genital reassignment surgery, age, educational levels, and partnership status, did not impact domain and general question results related to quality of life.

Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A. Psychiatric comorbidity in gender identity disorder. J Psychosom Res. 2005 Mar;58(3):259-61.

Hepp et al. conducted a single-site (Zurich, Switzerland) prospective, non-blinded, observational study using a cross-sectional design. There was some acquisition of retrospective data. The investigators assessed current and lifetime psychiatry co-morbidity using structured interviews for diagnosis of Axis 1 disorders (clinical syndromes) and Axis 2 disorders (developmental or personality disorders) and HADS for dimensional evaluation of anxiety and depression. Statistical description of the cohort and intra-group comparisons was performed. Continuous variables were compared using t-tests and ANOVA.

A total of 31 patients with gender dysphoria participated in the study: 11 (35.5%) female-to-male; 20 (64.5%) male-to-female (ratio 1:1.8). The overall mean age was 32.2±10.3 years. Of the participants, seven had undergone reassignment surgery, 10 pre- surgical patients had been prescribed hormone therapy, and 14 pre-surgical patients had not been prescribed hormone therapy. Forty five and one half percent of female-to-male and 20% of male-to-female patients did not carry a lifetime diagnosis of an Axis 1 condition. Sixty three and six tenths percent of female-to-male and 60% of male-to-female patients did not carry a current diagnosis of an Axis 1 condition. Lifetime diagnosis of substance abuse and mood disorder were more common in male-to-female patients (50% and 55% respectively) than female-to-male patients (36.4% and 27.3% respectively). Current diagnosis of substance abuse and mood disorder were present in male-to-female patients (15% and 20% respectively) and absent in female-to-male patients. One or more personality disorders were identified 41.9%, but whether this was a current or lifetime condition was not specified. Of the patients, five (16.1%) had a Cluster A personality disorder (paranoid-schizoid), seven (22.6%) had a Cluster B personality disorder (borderline, anti-social, histrionic, narcissistic), six (19.4%) had a Cluster C personality disorder (avoidant, dependent, obsessive-compulsive), and two (6.5%) were not otherwise classified.

HADS scores were missing for at least one person. The HADS test revealed non-pathologic results for depression (female-to-male: 6.64±5.03; male-to-female: 6.58±4.21) and borderline results for anxiety (female-to-male: 7.09±5.11; male-to-female: 7.74±6.13, where a result of 7-10 = possible disorder). There were no differences by natal gender. The investigators reported a trend for less anxiety and depression as measured by HADS in the patients who had undergone surgery.

Johansson A, Sundbom E, Höjerback T, Bodlund O. A five-year follow-up study of Swedish adults with gender identity disorder. Arch Sex Behav. 2010 Dec;39(6):1429-37. Epub 2009 Oct 9.

Johansson et al. conducted a two center (Lund and Umeå, Sweden) non-blinded, observational study using a semi-cross-sectional design (albeit over an extended time interval) using a self-designed tool and Axis V assessment. The study was prospective except for the acquisition of baseline Axis V data. There were no formal controls in this mixed population with and without surgery.

The investigators assessed satisfaction with the reassignment process, employment, partnership, sexual function, mental health, and global satisfaction in gender-reassigned persons from two disparate geographic regions. Surgical candidates were required to have met National Board of Health and Welfare criteria including initial and periodic psychiatric assessment, ≥1 year of real-life experience in preferred gender, and ≥1 year of subsequent hormone treatment. In addition, participants were required to have been approved for reassignment five or more years prior and/or to have completed surgical reassignment (e.g., sterilization, genital surgery) two or more years prior. The investigators employed semi-structured interviews covering a self-designed list of 55 pre-formulated questions with a three or five point ordinal scale. Clinician assessment of Global Assessment of Functioning (GAF; Axis V) was also conducted and compared to initial finding during the study. Changes or differences considered to be biologically significant were not pre- specified except for GAF, which pre-specified a difference to mean change ≥5 points. Statistical corrections for multiple comparisons were not included. There was no stratification by treatment.

Of the pool of 60 eligible patients, 42 (70.0% of eligible) (17 [40.5 %] female-to-male; 25 [59.5%] male-to-female;

ratio 1:1.5) were available for follow-up. Of these, 32 (53.3% of eligible) (14 [43.8%] female-to-male; 18 [56.2%] male-to-female [ratio 1:1.3]) had completed genital gender reassignment surgery (not including one post mastectomy), five were still in the process of completing surgery, and five (one female-to-male; four male- to-female; ratio 1:4) had discontinued the surgical process prior to castration and genital surgery.

The age (ranges) of the patients at entry into the program, reassignment surgery, and follow-up were 27.8 (18-46), 31.4 (22- 49), and 38.9 (28-53) years in the female-to-male group respectively and 37.3 (21-60), 38.2 (22-57), and 46.0 (25.0-69.0) years in the male- to-female group respectively. The differences in age by cohort group were statistically significant. Of participants, 88.2% of all enrolled female-to-male versus 44.0% of all enrolled female-to-male patients had cross-gender identification in childhood (versus during or after puberty) ($p<0.01$).

Although 95.2% of all enrolled patients self-reported improvement in GAF, in contrast, clinicians determined GAF improved in 61.9% of patients. Clinicians observed improvement in 47% of female-to-male patients and 72% of male-to- female patients. A ≥5 point improvement in the GAF score was present in 18 (42.9%). Of note, three of the five patients who were in the process of reassignment and five of the five who had discontinued the process were rated by clinicians as having improved.

Of all enrolled 95.2% (with and without surgery) reported satisfaction with the reassignment process. Of these 42 patients, 33 (79%) identified themselves by their preferred gender and nine (21%) identified themselves as transgender. None of these nine (eight male-to-female) had completed reassignment surgery because of ambivalence secondary to lack of acceptance by others and dissatisfaction with their appearance. Of the patients who underwent genital surgery (n=32) and mastectomy only (n=one), 22 (66.7%) were satisfied while four (three female-to-male) were dissatisfied with the surgical treatment.

Regarding relationships after surgery, 16 (38.1%) (41.2% of female- to-male; 36.0% of male-to-female patients) were reported to have a partner. Yet more than that number commented on partner relationships: (a) 62.2 % of the 37 who answered (50.0% of female- to- male; 69.6% of male-to-female patients) reported improved partner relationships (five [11.9%] declined to answer.); (b) 70.0% of the 40 who answered (75.0% of female-to-male; 66.7% of male-to-female patients) reported an improved sex life. Investigators observed that reported post-operative satisfaction with sex life was statistically more likely in those with early rather than late cross-gender identification. In addition 55.4% self-reported improved general health; 16.1% reported impaired general health; 11.9% were currently being treated with anti-depressants or tranquilizers.

This study subsumes earlier work by Bodlund et al. (1994, 1996). The nationwide mortality studies by Dhejne et al. (2011) may include all or part of this patient population.

Leinung M, Urizar M, Patel N, Sood S. Endocrine treatment of transsexual persons: extensive personal experience. Endocr Pract. 2013 Jul-Aug;19(4):644-50. (United States study)

Leinung et al. conducted a single-center (Albany, New York) a partially prospective, non-blinded, observational study using a cross-sectional design and descriptive statistics. There were no formal controls. The investigators assessed employment, substance abuse, psychiatric disease, mood disorders, Human Immunodeficiency Virus (HIV) status in patients who had met WPATH guidelines for therapy, and who had initiated cross-sex hormone treatment.

A total of 242 patients treated for gender identity disorder in the clinic from 1992 through 2009 inclusive were identified. The number of those presenting for therapy almost tripled over time. Of these patients, 50 (20.7%) were female-to-male; 192 (79.3%) male-to-female (ratio 1:3.8).

The age of female-to-male and male-to-female patients with gender dysphoria at the time of clinic presentation was 29.0 and 38.0 years respectively.

The female-to-male and male-to-female patients with gender dysphoria at the time of hormone initiation were young: 27.5 and 35.5 years old respectively ($p<0.5$). Of the male-to-female cohort, 19 (7.8%) had received hormone therapy in the absence of physician supervision; Of the patient population, 91 (37.6%) had undergone gender-reassignment surgery (32 female-to-male [64.0% of all female-to- male; 35.2% of all surgical patients]; 59 male-to-female [30.7% of all male-to-female; 64.8% of all surgical patients]; ratio 1:1.8).

Psychiatric disease was more common in those who initiated hormone therapy at an older age (>32 years) 63.9% versus 48.9% at a younger age and by natal gender (48.0% of female-to-male; 58.3% male-to-female). Mood disorders were more common in those who initiated hormone therapy at an older age (>32 years) 52.1% versus 36.0% at a younger age and this finding did not differ by natal gender (40.0% of female-to-male; 44.8% male-to-female). The presence of mood disorders increased the time to reassignment surgery in male-to-female patients.

Motmans J , Meier P, Ponnet K, T'Sjoen G. Female and male transgender quality of life: socioeconomic and medical differences. J Sex Med. 2012 Mar;9(3):743-50. Epub 2011 Dec 21.

Motmans et al., conducted a prospective, non-blinded, observational study using a cross-sectional design and a non-specific quality of life tool. No concurrent controls were used in this study. Quality of life in this Dutch-speaking population was assessed using the Dutch version of a SF-36 (normative data was used). Participants included subjects who were living in accordance with the preferred gender and who were from a single Belgian university specialty clinic at Ghent. The Dutch version of the SF-36 questionnaire along with its normative data were used. Variables explored included employment, pension status, ability to work, being involved in a relationship. Also explored, was surgical reassignment surgery and the types of surgical interventions. Intragroup comparisons by transgender category were conducted, and the relationships between variables were assessed by analysis of variance (ANOVA) and correlations.

The age of the entire cohort (n=140) was 39.89±10.21 years (female-to-male: 37.03±8.51; male-to-female: 42.26±10.39). Results of the analysis revealed that not all female-to-male patients underwent surgical reassignment surgery and, of those who did, not all underwent complete surgical reassignment. The numbers of female-to-male surgical interventions were: mastectomy 55, hysterectomy 55, metaoidplasty eight (with five of these later having phalloplasty), phalloplasty 40, and implantation of a prosthetic erectile device 20. The frequencies of various male-to-female surgical interventions were: vaginoplasty 48, breast augmentation 39, thyroid cartilage reduction 17, facial feminization 14, and hair transplantation three.

The final number of subjects with SF-36 scores was 103 (49 [47.6%] female-to-male; 54 [52.4%] male-to-female; ratio 1:1.1). For this measure, the scores for the vitality and mental health domains for the final female-to-male cohort (n= 49 and not limited to those having undergone some element of reassignment surgery) were statistically lower: 60.61±18.16 versus 71.9±18.31 and 71.51±16.40 versus 79.3±16.4 respectively. Scores were not different from the normative data for Dutch women: vitality: 64.3±19.7 or mental health 73.7±18.2. None of the domains of the SF-36 for the final male-to-female cohort (n=54 and not limited to those having undergone some element of reassignment surgery) were statistically different from the normative data for Dutch women.

Analysis of variance indicated that quality of life as measured by the SF-36 did not differ by whether female-to-male patients had undergone genital surgery (metaoidoplasty or phalloplasty) or not. Also, ANOVA indicated that quality of life as measured by the SF-36 did not differ by whether male-to-female patients had undergone either breast augmentation or genital surgery (vaginoplasty) or not.

Whether there is overlap with the Ghent populations studied by Heylens et al. or Weyers et al. is unknown.

Newfield E, Hart S, Dibble S, Kohler L. Female-to-male transgender quality of life. Qual Life Res. 2006 Nov;15(9):1447-57. Epub 2006 Jun 7. (United States study)

Newfield et al. conducted a prospective, observational internet self-report survey of unknown blinding status using a cross- sectional design and a non-specific quality of life tool in a mixed population with and without hormone therapy and/or reassignment surgery. There were no formal controls.

The investigators recruited natal female participants identifying as male using email, internet bulletin boards, and flyers/postcards distributed in the San Francisco Bay Area. Reduction of duplicate entries by the same participant was limited to the use of a unique user name and password.

The investigators employed the Short-Form 36 (SF-36) Version 2 using U.S. normative data. They reported using both male and female normative data for the comparator SF-36 cohort. Data for the eight domains were expressed as normative scoring. The Bonferroni correction was used to adjust for the risk of a Type 1 error with analyses using multiple comparisons.

A total of 379 U.S. respondents classified themselves as males-or-females to males with or without therapeutic intervention. The mean age of the respondents who classified themselves as male or female-to-male was 32.6±10.8 years. Of these 89% were Caucasian, 3.6% Latino, 1.8% African American, 1.8% Asian, and 3.8% other. Of these, 254 (67.0%) reported prior or current testosterone use while 242 (63.8%) reported current testosterone use. In addition, 136 (36.7%) reported having had "top" surgery and 11 (2.9%) reported having "bottom" surgery.

Complete SF-36 data were available for 376 U.S. respondents. For the complete, non-stratified U.S. cohort the Physical Summary Score (53.45±9.42) was statistically higher (better) than the natal gender unspecified SF-36 normative score (50±10) (p=<0.001), but was within one standard deviation of the normative mean. The Mental Summary Score (39.63±12.2) was statistically lower (worse) than the natal gender unspecified SF-36 normative score (50±10) (p<0.001), but was well within two standard deviations of the normative mean. Subcomponents of this score: Mental Health (42.12±10.2), Role Emotional (42.42±11.6), Social Functioning (43.14±10.9), and Vitality (46.22±9.9) were statistically lower (worse) than the SF-36 normative sub-scores, but well within one standard deviation of the normative sub- score means. Interpretive information for these small biologic differences in a proprietary assessment tool was not provided.

Additional intragroup analyses were conducted, although the data were not stratified by type of therapeutic intervention (hormonal, as well as, surgical). Outcomes of hormone therapy were considered separately and dichotomously from reassignment surgery. The Mental Summary Score was statistically higher (better) in those who had "Ever Received Testosterone" (41.22±11.9) than those with "No Testosterone Usage" (36.08±12.6) (p=0.001). The Mental Summary Scores showed a trend towards statistical difference between those who "Ever Received Top Surgery" (41.21±11.6) and those without "Top Surgery" (38.01±12.5) (p=0.067). These differences were well within one standard deviation of the normative mean. Interpretive information for these small biologic differences in a proprietary assessment tool was not provided.

b. Observational, surgical series, without concurrent controls

Blanchard R, Steiner BW, Clemmensen LH. Gender dysphoria, gender reorientation, and the clinical management of transsexualism. J Consult Clin Psychol. 1985 Jun; 53(3):295-304.

Blanchard et al. conducted a single-center (Ontario, Canada), prospective, non-blinded, cross-sectional study using a self-designed questionnaire and a non- specific psychological symptom assessment with normative data. The investigators assessed social adjustment and psychopathology in patients with gender dysphoria and who were at least one year post gender reassignment surgery. Reassignment surgery was defined as either vaginoplasty or mastectomy/construction of male chest contour with or without nipple transplants, but did not preclude additional procedures. Partner preference was determined using Blanchard's Modified Androphilia-Gynephilia Index, and the nature and extent of any psychopathology was determined with the Symptom Check List 90-Revised (SCL-90R). Differences in test scores considered to be biologically significant were not pre-specified in the methods.

Of the 294 patients (111 natal females and 183 natal males, ratio: 1:1.65) initially evaluated, 263 were diagnosed with gender dysphoria. Of these 79 patients participated in the study (38 female-to-male; 32 male-to-female with male partner preference; 9 male-to-female with female partner preference). The respective mean ages for these 3 groups were 32.6, 33.2, and 47.7 years with the last group being older statistically (p=0.01).

Additional surgical procedures in female-to-male patients included: oophorectomy/hysterectomy (92.1%) and phalloplasty (7.9%). Additional surgical procedures in male-to-female patients with male partner preference included facial hair electrolysis 62.5% and breast implantation (53.1%). Additional procedures in male-to-female patients with female partner preference included facial hair electrolysis (100%) and breast implantation (33.3%). The time between reassignment surgery and questionnaire completion did not differ by group.

Psychopathology as measured by the Global Severity Index of the SCL-90R was absent in all three patient groups. Interpretation did not differ by the sex of the normative cohort.

Of participants, 63.2% of female-to-male patients cohabitated with partners of their natal gender; 46.9% of male-to-female patients with male partner preference cohabitated with partners of their natal gender; and no male-to-female patients with female partner preference cohabitated with partners of their natal gender.

Of participants, 93.7% reported that they would definitely undergo reassignment surgery again. The remaining 6.3% (one female-to-male; one male-to-female with male partner preference; three male-to-female with female partner preference) indicated that they probably would undertake the surgery again. Post hoc analysis suggested that the more ambivalent responders had more recently undergone surgery. Of responders, 98.7% indicated that they preferred life in the reassigned gender. The one ambivalent subject was a skilled and well compensated tradesperson who was unable to return to work in her male dominated occupation.

Eldh J, Berg A, Gustafsson M. Long-term follow up after sex reassignment surgery. Scand J Plast Reconstr Surg Hand Surg. 1997 Mar;31(1):39-45.

Eldh et al. conducted a non-blinded, observational study using a prospective cross-sectional design with an investigator designed questionnaire and retrospective acquisition of pre-operative data. The investigators assessed economic circumstances, family status, satisfaction with surgical results, and sexual function in patients who had undergone gender reassignment surgery.

Of the 175 patients who underwent reassignment surgery in Sweden, 90 responded. Of this number, 50 were female-to-male and 40 were male-to-female (ratio: 1:0.8). Patients reportedly were generally satisfied with the appearance of the reconstructed genitalia (no numbers provided). Of the patients who had undergone surgery prior to 1986, seven (14%) were dissatisfied with shape or size of the neo-phallus; eight (16%) declined comment. There were 14 (35%), with 12 having surgery prior to 1986 and two between 1986 and 1995 inclusive, were moderately satisfied because of insufficient vaginal volume; 8 (20%) declined comment. A neo-clitoris was not constructed until the later surgical cohort. Three of 33 reported no sensation or no sexual sensation. Eight had difficulties

comprehending the question and did not respond.

A total of nine (18%) patients had doubts about their sexual orientation; 13 (26%) declined to answer the question. The study found that two female-to- male patients and two male-to-female patients regretted their reassignment surgery and continued to live as the natal gender, and two patients attempted suicide.

Hess J, Rossi Neto R, Panic L, Rübben H, Senf W. Satisfaction with male-to-female gender reassignment surgery. Dtsch Arztebl Int. 2014 Nov 21;111(47):795-801.

Hess at al. conducted a prospective, blinded, observational study using a cross-sectional design and a self-designed anonymous questionnaire. The investigators assessed post-operative satisfaction in male-to-female patients with gender dysphoria who were followed in a urology specialty clinic (Essen, Germany). Patients had met the ICD-10 diagnostic criteria, undergone gender reassignment surgeries including penile inversion vaginoplasty, and a Likert-style questionnaire with 11 elements. Descriptive statistics were provided.

There were 254 consecutive eligible patients who had undergone surgery between 2004 and 2010 identified and sent surveys, of whom 119 (46.9%) responded anonymously. Of the participants, 13 (10.9%) reported dissatisfaction with outward appearance and 16 (13.4%) did not respond; three (2.5%) reported dissatisfaction with surgical aesthetics and 25 (21.0%) did not respond; eight (6.7%) reported dissatisfaction with functional outcomes of the surgery and 26 (21.8%) did not respond; 16 (13.4%) reported they could not achieve orgasm and 28 (23.5%) did not respond; four (3.4%) reported feeling completely male/more male than female and 28 (23.5%) did not respond; six (5.0%) reported not feeling accepted as a woman, two (1.7%) did not understand the question, and 17 (14.3%) did not respond; and 16 (13.4%) reported that life was harder and 24 (20.2%) did not respond.

Lawrence A. Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. Arch Sex Behav. 2006 Dec;35(6):717-27. Epub 2006 Nov 16. (United States study)

Lawrence conducted a prospective, blinded observational study using a cross-sectional design and a partially self-designed quality of life tool using yes/no questions or Likert scales. The investigator assessed sexual function, urinary function, and other pre/post-operative complications in patients who underwent male-to-female gender reassignment surgery. Questions addressed core reassignment surgery (neo-vagina and sensate neo-clitoris) and related reassignment surgery (labiaplasty, urethral meatus revision, vaginal deepening/widening, and other procedures), use of electrolysis, and use of hormones.

Questionnaires were designed to be completed anonymously and mailed to 727 eligible patients. Of those eligible, 232 (32%) returned valid questionnaires. The age at the time reassignment surgery was 44±9 (range 18-70) years and mean duration after surgery was 3±1 (range 1-7) years.

Happiness with sexual function and the reassignment surgery was reported to be lower when permanent vaginal stenosis, clitoral necrosis, pain in the vagina or genitals, or other complications such as infection, bleeding, poor healing, other tissue loss, other tissue necrosis, urinary incontinence, and genital numbness were present. Quality of life was impaired when pain in the vagina or genitals was present.

Satisfaction with sexual function, gender reassignment surgery, and overall QOL was lower when genital sensation was impaired and when vaginal architecture and lubrication were perceived to be unsatisfactory. Intermittent regret regarding reassignment surgery was associated with vaginal hair and clitoral pain. Vaginal stenosis was associated with surgeries performed in the more distant past; whereas, more satisfaction with vaginal depth and width was present in more recent surgical treatment.

Salvador J, Massuda R, Andreazza T, Koff WJ, Silveira E, Kreische F, de Souza L, de Oliveira MH, Rosito T, Fernandes BS, Lobato MI. Minimum 2-year follow up of sex reassignment surgery in Brazilian male-to-female transsexuals. Psychiatry Clin Neurosci. 2012 Jun; 66(4):371-2. PMID: 22624747.

Salvador et al. conducted a single center (Port Alegre, Brazil) prospective, non-blinded, observational study using a cross-sectional design (albeit over an extended time interval) and a self-designed quality of life tool. The investigators assessed regret, sexual function, partnerships, and family relationships in patients who had undergone gender reassignment surgery at least 24 months prior.

Out of the 243 enrolled in the clinic over a 10 year interval, 82 underwent sex reassignment surgery. There were 69 participants with a minimum 2-year follow up, of whom 52 patients agreed to participate in the study. The age at follow-up was 36.3±8.9 (range 15-58) years with the time to follow-up being 3.8±1.7 (2-7) years. A total of 46 participants reported pleasurable neo-vaginal sex and post-surgical improvement in the quality of their sexual experience. The quality of sexual intercourse was rated as satisfactory to excellent, average, unsatisfactory, or not applicable in the absence of sexual contact by 84.6%, 9.6%, 1.9%, and 3.8% respectively. Of the participants, 78.8% reported greater ease in initiating and maintaining relationships; 65.4% reported having a partner; 67.3% reported increased frequency of intercourse; 36.8% reported improved familial relationships. No patient reported regret over reassignment surgery. The authors did not provide information about incomplete questionnaires.

Tsoi WF. Follow-up study of transsexuals after sex-reassignment surgery. Singapore Med J. 1993 Dec; 34(6):515-7.

Tsoi conducted a single-center (Singapore) prospective, non-blinded, observational study using a cross-sectional design and a self-designed quality of life tool. The investigator assessed overall life satisfaction, employment, partner status, and sexual function in gender-reassigned persons who had undergone gender reassignment surgery between 1972 and 1988 inclusive and who were approximately 2 to 5 years post-surgery. Acceptance criteria for surgery included good physical health, good mental health, absence of heterosexual tendencies, willingness to undergo hormonal therapy for ≥6 months, and willingness to function in the life of the desired gender for ≥6 months. Tsoi also undertook retrospective identification of variables that could predict outcomes.

The size of the pool of available patients was not identified. Of the 81 participants, 36 (44.4%) were female-to-male and 45 (55.6%) were male-to-female (ratio 1:1.25).

The mean ages at the time of the initial visit and operation were: female-to-male 25.4±4.4 (range 14-36) and 27.4 ±4.0; (range 14-36); male-to-female 22.9±4.6 (range 14-36) and 24.7±4.3 (14-36) years respectively. Of all participants, 14.8% were under age 20 at the time of the initial visit. All were at least 20 at the time of gender reassignment surgery. The reported age of onset was 8.6 years for female-to-male patients and 8.7 years for male-to-female patients.

All participants reported dressing without difficulty in the reassigned gender; 95% of patients reported good or satisfactory adjustment in employment and income status; 72% reported good or satisfactory adjustment in relationships with partners. Although the quality of life tool was self-designed, 81% reported good or satisfactory adjustment to their new gender, and 63% reported good or acceptable satisfaction with sexual activity. Of the female-to-male patients, 39% reported good or acceptable satisfaction with sex organ function in comparison to 91% of male-to-female patients ($p<0.001$). (The author reported that a fully functioning neo-phallus could not be constructed at the time.) The age of non-intercourse sexual activity was the only predictor of an improved outcome.

Weyers S, Elaut E, De Sutter P, Gerris J, T'Sjoen G, Heylens G, De Cuypere G, Verstraelen H. Long-term assessment of the physical, mental, and sexual health among transsexual women. J Sex Med. 2009 Mar;6(3):752-60. Epub 2008 Nov 17.

Weyers at al. (2009) conducted a prospective, non-blinded, observational study using a cross-sectional design and several measurement instruments including a non-specific quality of life tool and a semi-specific quality of life tool (using normative data) along with two self-designed tools.

The investigators assessed general quality of life, sexual function, and body image from the prior four weeks in Dutch-speaking male-to-female patients with gender dysphoria who attended a single-center (Ghent, Belgium), specialized, comprehensive care university clinic. Investigators used the Dutch version of the SF-36 and results were compared to normative data from Dutch women and U.S. women. The 19 items of the Dutch version of the Female Sexual Function Index (FSFI) were used to measure sexual desire, function, and satisfaction. A self-designed seven question visual analog scale (VAS) was used to measure satisfaction with gender related body traits and appearance perception by self and others. A self-designed survey measured a broad variety of questions regarding personal medical history, familial medical history, relationships, importance of sex, sexual orientation, gynecologic care, level of regret, and other health concerns. For this study, hormone levels were also obtained.

The study consisted of 50 (71.5% of the eligible recruits) participants. Analysis of the data revealed that the patient's average age was 43.1 ±10.4 years, and all of the patients had vaginoplasty. This same population also had undergone additional feminization surgical procedures (breast augmentation 96.0%, facial feminization 36.0%, vocal cord surgery 40.0%, and cricoid cartilage reduction 30.0%). A total of two (4.0%) participants reported "sometimes" regretting reassignment surgery and 23 (46.0%) were not in a relationship. For the cohort, estradiol, testosterone, and sex hormone binding globulin levels were in the expected range for the reassigned gender. The SF-36 survey revealed that the subscale scores of the participants did not differ substantively from those of Dutch and U.S. women. VAS scores of body image were highest for self-image, appearance to others, breasts, and vulva/vagina (approximately 7 to 8 of 10). Scores were lowest for body hair, facial hair, and voice characteristics (approximately 6 to 7 of 10).

The total FSFI score was 16.95±10.04 out of a maximal 36. The FSFI scores averaged 2.8 (6 point maximum): satisfaction 3.46±1.57, desire 3.12+1.47, arousal 2.95±2.17, lubrication 2.39±2.29, orgasm 2.82±2.29, and pain 2.21±2.46. Though these numbers were reported in the study, data on test population controls were not provided.

A post hoc exploration of the data suggested the following: perceived improvement in general health status was greater in the subset that had undergone reassignment surgery within the last year; sexual orientation impacted the likelihood of being in a relationship; SF-36 scores for vitality, social functioning, and mental health were nominally better for those in relationships, but that overall SF-36 scores did not differ by relationship status; sexual orientation and being in a relationship impacted FSFI scores; and reported sexual function was higher in those with higher satisfaction with regards to their appearance.

Wierckx K, Van Caenegem E, Elaut E, Dedecker D, Van de Peer F, Toye K, Weyers S, Hoebeke P, Monstrey S, De Cuypere G, T'Sjoen G. Quality of life and sexual health after sex reassignment surgery in transsexual men. J Sex Med. 2011 Dec;8 (12):3379-88. Epub 2011 Jun 23.

Wierckx at al. conducted a prospective, non-blinded, observational study using a cross-sectional design and several measurement instruments (a non-specific quality of life tool with reported normative data along with three self-designed tools). The investigators assessed general quality of life, sexual relationships, and surgical complications in Dutch-speaking female-to-male patients with gender dysphoria who attended a single-center, specialized, comprehensive care, university clinic (Ghent, Belgium). Investigators used the Dutch version of the SF-36 with 36 questions, eight subscales, and two domains evaluating physical and mental health. Results were compared to normative data from Dutch women and Dutch men. Self -designed questionnaires to evaluate aspects of medical history, sexual functioning (there were separate versions for those with and without partners), and surgical results were also used. The Likert-style format was used for many of the questions.

A total of 79 female-to-male patients with gender dysphoria had undergone reassignment surgery were recruited; ultimately, 47 (59.5%) chose to participate. Three additional patients were recruited by other patients. One of the 50 participants was later excluded for undergoing reassignment surgery within the one year window. The age of patients was: 30±8.2 years (range 16 to 49) at the time of reassignment surgery and 37.1 ±8.2 years (range 22 to 54) at the time of follow-up. The time since hysterectomy, oopherectomy, and mastectomy was 8 years (range 2 to 22). The patient population had undergone additional surgical procedures: metaidoiplasty (n=9; 18.4%), phalloplasty (n=8 after metaidoiplasty, 38 directly; 93.9% total), and implantation of erectile prosthetic device (n=32; 65.3%). All had started hormonal therapy at least two years prior to surgery and continued to use androgens.

The SF-36 survey was completed by 47 (95.9%) participants. The "Vitality" and the "Mental Health" scales were lower than the Dutch male population: 62.1±20.7 versus 71.9±18.3 and 72.6±19.2 versus 79.3±16.4 respectively. These subscale scores were equivalent to the mean scores of the Dutch women.

None of the participants were dissatisfied with their hysterectomy-oopherectomy procedures; 4.1% were dissatisfied with their mastectomies because of extensive scarring; and 2.2% were dissatisfied with their phalloplasties. Of the participants, 17.9% were dissatisfied with the implantation of an erectile prosthetic device; 25 (51.0%) reported at least one post-operative complication associated with phalloplasty (e.g., infection, urethrostenosis, or fistula formation); 16 (50.0% of the 32 with an erectile prosthetic device) reported at least one post-operative complication associated with implantation of an erectile prosthetic (e.g., infection, leakage, incorrect positioning, or lack of function).

A total of 18 (36.7%) participants were not in a relationship; 12.2% reported the inability to achieve orgasm with self-stimulation less than half the time; 12.2% did not respond to the question. Of those participants with partners, 28.5% reported the inability to achieve orgasm with intercourse less than half the time and 9.7% did not respond to this question. Also, 61.3% of those with partners reported (a) no sexual activities (19.4%) or (b) activities once or twice monthly (41.9%), and there were 12.9% who declined to answer.

c. Observational, surgical patients, cross-sectional, with controls

Ainsworth TA, Spiegel JH. Quality of life of individuals with and without facial feminization surgery or gender reassignment surgery. Qual Life Res. 2010 Sep;19(7):1019-24.

Ainsworth and Spiegel conducted a prospective, observational study using a cross-sectional design and a partially self-designed survey tool. The blind status is unknown. Treatment types served as the basis for controls.

The investigators, head and neck surgeons who provided facial feminization services, assessed perception of appearance and quality of life in male-to-female subjects with self-reported gender dysphoria. Patients could have received no therapeutic intervention, hormone therapy, reassignment surgery, and/or facial feminization surgery and an unrestricted length of transition. (Transition refers to the time when a transgender person begins to live as the gender with which they identify rather than the gender assigned at birth.) Criteria for the various types of interventions were not available because of the survey design of the study. Patients were recruited via website or at a 2007 health conference. Pre-specified controls to eliminate duplicate responders were not provided. The investigators employed a self-designed Likert-style facial feminization outcomes evaluation questionnaire and a "San Francisco 36" health questionnaire. No citations were provided for the latter. It appears to be the Short-form (SF) 36-version 2. Changes or differences considered to be biologically significant were not pre-specified. Power corrections for multiple comparisons were not provided.

The investigators reported that there were 247 participants. (The numbers of incomplete questionnaires was not reported.) Of the 247 participants, 25 (10.1%) received only primary sex trait reassignment surgery, 28 (11.3%)

received facial surgery without primary sex trait reassignment surgery, 47 (19.0%) received both facial and primary sex trait reassignment surgery, and 147 (59.5%) received neither facial nor reassignment surgery.

The mean age for each of these cohorts was: 50 years (no standard deviation [S.D.]) only reassignment surgery, 51 years (no S.D.) only facial surgery, 49 years (no S.D.) both types of surgery, and 46 years (no S.D.) (neither surgery). Of the surgical cohorts: 100% of those who had undergone primary sex trait reassignment surgery alone used hormone therapy, 86% of those who had undergone facial feminization used hormone therapy, and 98% of those who had undergone both primary sex trait reassignment surgery and facial feminization used hormone therapy. In contrast to the surgical cohorts, 66% of the "no surgery" cohort used hormonal therapy, and a large proportion (27%) had been in transition for less than one year.

The investigators reported higher scores on the facial outcomes evaluation in those who had undergone facial feminization. Scores of the surgical cohorts for the presumptive SF-36 comprehensive mental health domain did not differ from the general U.S. female population. Scores of the "no surgery" cohort for the comprehensive mental health domain were statistically lower than those of the general U.S. female population, but within one standard deviation of the normative mean. Mean scores of all the gender dysphoric cohorts for the comprehensive physical domain were statistically higher than those of the general female U.S. population, but were well within one standard deviation of the normative mean. Analyses of inter-cohort differences for the SF-36 results were not conducted. Although the investigators commented on the potential disproportionate impact of hormone therapy on outcomes and differences in the time in "transition", they did not conduct any statistical analyses to correct for putative confounding variables.

Kraemer B, Delsignore A, Schnyder U, Hepp U. Body image and transsexualism. Psychopathology. 2008;41(2):96-100. Epub 2007 Nov 23.

Kraemer et al. conducted a single center (Zurich, Switzerland) prospective, non-blinded, observational study using a cross-sectional design comparing pre-and post- surgical cohorts. Patients were required to meet DSM III or DSM IV criteria as applicable to the time of entry into the clinic. Post-surgical patients were from a long-term study group (Hepp et al., 2002). Pre-surgical patients were recent consecutive referrals. The assessment tool was the Fragebogen zur Beurteilung des eigenen Korpers (FBeK) which contained three domains.

There were 23 pre-operative patients: 7 (30.4%) female-to-male and 16 (69.6%) male-to-female (ratio 1:2.3). There were 22 post-operative patients: 8 (36.4 %) female-to-male and 14 (63.6%) male-to-female (ratio 1:1.8). The mean ages of the cohorts were as follows: pre-operative 33.0±11.3 years; post-operative 38.2±9.0 years. The mean duration after reassignment surgery was 51±25 months (range 5-96).

The pre-operative groups had statistically higher insecurity scores compared to normative data for the natal sex: female-to-male 9.0±3.8 versus 5.1±3.7; male-to-female 8.1±4.5 versus 4.7±3.1 as well as statistically lower self-confidence in one's attractiveness: female-to-male 3.1±2.9 versus 8.9±3.1; male-to-female 7.0±2.9 vs 9.5±2.6.

Mate-Kole C, Freschi M, Robin A. Aspects of psychiatric symptoms at different stages in the treatment of transsexualism. Br J Psychiatry. 1988 Apr;152: 550-3.

Mate-Kole at al. conducted a single site (London, United Kingdom) prospective non-blinded, observational study using a cross-sectional design and two psychological tests (one with some normative data). Concurrent controls were used in this study design. The investigators assessed neuroticism and sex role in natal males with gender dysphoria. Patients at various stages of management, (i.e., under evaluation, using cross-sex hormones, or post reassignment surgery [6 months to 2 years]) were matched by age of cross-dressing onset, childhood neuroticism, personal psychiatric history, and family psychiatric history. Both a psychologist and psychiatrist conducted assessments. The

instruments used were the Crown Crisp Experiential Index (CCEI) for psychoneurotic symptoms and the Bem Sex Role Inventory. ANOVA was used to identify differences between the three treatment cohorts.

For each cohort, investigators recruited 50 male-to-female patients from Charing Cross Hospital. The mean ages of the three cohorts were as follows: 34 years for patients undergoing evaluation; 35 years for wait-listed patients; and 37 years for post-operative patients. For the cohorts, 22% of those under evaluation, 24% of those on hormone treatment only, and 30% of those post-surgery had prior psychiatric histories, and 24%, 24%, while 14% in each cohort, respectively, had a history of attempted suicide. More than 30% of patients in each cohort had a first degree relative with a history of psychiatric disease.

The scores for the individual CCEI domains for depression and somatic anxiety were statistically higher (worse) for patients under evaluation than those on hormone treatment alone. The scores for all of the individual CCEI domains (free floating anxiety, phobic anxiety, somatic anxiety, depression, hysteria, and obsessionality) were statistically lower in the post-operative cohort than in the other two cohorts.

The Bem Sex Role Inventory masculinity score for the combined cohorts was lower than for North American norms for either men or women. The Bem Sex Role Inventory femininity score for the combined cohorts was higher than for North American norms for either men or women. Those who were undergoing evaluation had the most divergent scores from North American norms and from the other treatment cohorts. Absolute differences were small. All scores of gender dysphoric patients averaged between 3.95 and 5.33 on a 7 point scale while the normative scores averaged between 4.59 and 5.12.

Wolfradt U, Neumann K. Depersonalization, self-esteem and body image in male-to-female transsexuals compared to male and female controls. Arch Sex Behav. 2001 Jun;30(3):301-10.

Wolfradt and Neumann conducted a controlled, prospective, non-blinded, observational study using a cross-sectional design. The investigators assessed aspects of personality in male-to-female patients who had undergone vocal cord surgery for voice feminization and in healthy non-transgender volunteers from the region. The patients had undergone gender reassignment surgery 1 to 5 years prior to voice surgery. The volunteers were matched by age and occupation.

The primary hypothesis was that depersonalization, with the sense of being detached from one’s body or mental processes, would be more common in male-to- female patients with gender dysphoria. German versions of the Scale for Depersonalization Experiences (SDPE), the Body Image Questionnaire (BIQ), a Gender Identity Trait Scale (GIS), and the Self-Esteem Scale (SES) were used in addition to a question regarding global satisfaction. Three of the assessments used a 5 point scale (BIQ, GIS, and SDPE) for questions. One used a 4 point scale (SES). Another used a 7 point scale (global satisfaction). The study consisted of 30 male-to-female patients, 30 healthy female volunteers, and 30 healthy male volunteers. The mean age of study participants was 43 years (range 29- 67).

Results of the study revealed that there were no differences between the three groups for the mean scores of measures assessing depersonalization, global satisfaction, the integration of masculine traits, and body-image-rejected (subset). Also, the sense of femininity was equivalent for male-to-female patients and female controls and higher than that in male controls. The levels of self-esteem and body image-dynamic (subset) were equivalent for male-to-female patients and male controls and higher than that in female controls, and none of the numeric differences between means exceeded 0.61 units.

Kuhn A, Bodmer C, Stadlmayr W, Kuhn P, Mueller M, Birkhäuser M. Quality of life 15 years after sex reassignment surgery for transsexualism. Fertil Steril. 2009 Nov;92(5):1685-1689.e3. Epub 2008 Nov 6.

Kuhn et al. conducted a prospective, non-blinded, observational study using a cross-sectional design and semi-matched control cohort. The investigators assessed global satisfaction in patients who were from gynecology and endocrinology clinic (Bern, Switzerland), and who had undergone some aspect of gender reassignment surgery in the distant past, but were still receiving cross-sex hormones from the clinic. The quality of life assessment tools included a VAS and the King's Health Questionnaire (KHQ), which consists of eight domains with scores between zero and five or one and five, with lower scores indicating higher preference. The KHQ and the numerical change/difference required for clinical significance (≥5 points in a given domain, with higher scores being more pathologic) were included in the publication. Twenty healthy female controls from the medical staff who had previously undergone an abdominal or pelvic surgery were partially matched by age and body mass index (BMI), but not sex. No corroborative gynecologic or urologic evaluations were undertaken.

Of the 55 participants, three (5.4%) were female-to-male and 52 (94.5%) were male-to-female (ratio 1:17.3). Reassignment surgery had been conducted 8 to 23 years earlier (median 15 years). The median age of the patients at the time of this study was 51 years (range 39-62 years). The patients had undergone a median of nine surgical procedures in comparison to the two undergone by controls. Reassignment patients were less likely to be married (23.6% versus 65%; p=0.002); partnership status was unknown in five patients. The scores of VAS global satisfaction (maximal score eight) were lower for surgically reassigned patients (4.49±0.1 SEM) than controls (7.35±0.26 SEM) (p<0.0001).

The abstract stated that quality of life was lower in reassignment patients 15 years after surgery relative to controls. One table in the study, Table 2, delineated statistically and biologically significant differences for four of the eight KHQ domains between the patients and controls: physical limitation: 37.6±2.3 versus 20.9±1.9 (p<0.0001), personal limitation: 20.9±1.9 versus 11.6±0.4 (p<0.001), role limitation: 27.8+2.4 versus 34.6+1.7 (p=0.046), and general health: 31.7±2.2 versus 41.0±2.3 (p<0.02). There is a related paper by Kuhn et al. 2006.

Haraldsen IR, Dahl AA. Symptom profiles of gender dysphoric patients of transsexual type compared to patients with personality disorders and healthy adults. Acta Psychiatr Scand. 2000 Oct;102(4):276-81.

Haraldsen and Dahl conducted a single-center (Oslo, Norway) partially prospective, non-blinded, observational study using a cross-sectional design and a non-specific psychometric test. There was a control group, but it was not concurrent.

In the germane sub-study, the investigator assessed psychopathology in patients with gender dysphoria. Patients, who were independently evaluated by two senior psychiatrists, were required to meet DSM III-R or DSM IV diagnostic criteria and the Swedish criteria for reassignment surgery. The Norwegian version of the SCL-90 was used. The testing was conducted from 1987 to 1989 for those who had undergone reassignment surgery between 1963 and 1987 and from 1996 to 1998 for pre- surgical patients who had applied for reassignment surgery between 1996 and 1998. In addition, Axis I, Axis II, and Axis V (Global Functioning) was assessed.

Of 65 post–surgical and 34 pre-surgical patients, 59 post-surgical and 27 pre-surgical patients ultimately entered the study. The combined cohorts consisted of 35 (40.7%) female-to-male patients and 51 (59.3%) male-to-female patients (ratio 1:1.5). The ages were female-to-male 34±9.5 years and female-to-male 33.3±10.0 years. The other control group consisted of patients with personality disorder. Of these, 101 (27 men (33.9±7.3 years) and 74 women (31.6±8.2) were tested during a treatment program. One year later, 98% were evaluated. A total of 28 (32.5%) of the pre- and post- reassignment surgery patients had an Axis I diagnosis compared to 100 (99.0%) of those with personality disorders. Depression and anxiety were the most common diagnoses in both groups, but were approximately three to four times more common in the personality disorder cohort. Seventeen (19.8%) of the pre- and post-reassignment surgery patients had an Axis II diagnosis whereas the mean number of personality disorders in the personality disorder cohort was 1.7±1. The Global Assessment of Function was higher (better) in the gender

dysphoric groups (78.0±8.9) than in the personality disorder cohort (53.0±9.0).

Global Severity Indices (GSI) were highest for those with personality disorder regardless of gender and exceeded the cut-point score of 1.0. The GSI scores for females-to-males and males-to-females were 0.67±57 and 0.56±0.45. Although they were nominally higher than the healthy normative controls (males: 0.32±0.36 and females 0.41±0.43), they were well within the non- pathologic range. The same was true for the subscales.

SCL-90 GSI scores did not differ substantively between pre- and post-surgical patients, nor did the SCI subscale scores differ substantively between pre- and post-surgical patients. Any small non-significant differences tracked with the age and sex differences.

Beatrice J. A psychological comparison of heterosexuals, transvestites, preoperative transsexuals, and postoperative transsexuals. J Nerv Ment Dis. 1985 Jun;173(6):358-65. (United States study)

Beatrice conducted a prospective, non-blinded, observational study using a cross-sectional design and control cohorts in the U.S. The investigator assessed psychological adjustment and functioning (self-acceptance) in male-to-female patients with gender dysphoria (with and without GRS), transvestites from two university specialty clinics, and self-identified heterosexual males recruited from the same two universities. The criteria to qualify for the study included being known to the clinic for at least one year, cross-dressing for at least one year without arrest, attendance at 10 or more therapy sessions, emotionally self-supporting, and financially capable of payment for reassignment surgery, and all of these criteria were met by the pre-operative cohort as well as the post-operative cohort. The cohorts were matched to the post-operative cohort (age, educational level, income, ethnicity, and prior heterosexual object choice). The post-operative cohort was selected not on the basis of population representation, but on the basis of demographic feasibility for a small study. The instruments used were the Minnesota Multiphasic Personality Inventory (MMPI) and the Tennessee Self-Concept Scale (TSCS). Changes or differences considered to be biologically significant were not pre-specified.

Of the initial 54 recruits, ten subjects were left in each of the cohorts because of exclusions identified due to demographic factors. The mean age of each cohort were as follows: pre-operative gender dysphoric patients 32.5 (range 27-42) years, postoperative patients 35.1 (30-43) years old, transvestite 32.5 (29-37) years old, and heterosexual male 32.9 (28-38) years old. All were Caucasian. The mean age for cross-dressing in pre-operative patients (6.4 years) and post-operative patients (5.8 years) was significantly lower than for transvestites (11.8 years).

The scores for self-acceptance did not differ by diagnostic category or surgical status as measured by the TSCS instrument. As measured by the T-scored MMPI instrument (50±10), levels of paranoia and schizophrenia were higher for post-operative (GRS) patients (63.0 and 68.8) than transvestites (55.6 and 59.6) and heterosexual males (56.2 and 51.6). Levels of schizophrenia were higher for pre-operative patients (65.1) than heterosexual males (51.6). There were no differences between patients with gender dysphoria. Scores for the Masculine-Feminine domain were equivalent in those with transvestitism and gender dysphoria with or without surgery, but higher than in heterosexual males. The analysis revealed that despite the high level of socio-economic functioning in these highly selected subjects, the MMPI profiles based on the categories with the highest scores were notable for antisocial personality, emotionally unstable personality, and possible manic psychosis in the pre-operative GRS patients and for paranoid personality, paranoid schizophrenia, and schizoid personality in the post-operative GRS patients. By contrast, the same MMPI profiling in heterosexual males and transvestites was notable for the absence of psychological dysfunction.

d. Observational, surgical patients, longitudinal, with controls

Dhejne C, Lichtenstein P, Boman M, Johansson A, Långström N, Landén M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. PLoS One. 2011;6(2):e16885. Epub 2011 Feb 22.

Dhejne et al. conducted a retrospective, non-blinded, observational study of nation-wide mortality using a longitudinal and a population-based matched cohort. The investigators assessed conditions such as, but not limited to, mortality, suicide attempts, psychiatric hospitalization, and substance abuse in gender-reassigned persons and randomly selected unexposed controls matched by birth year and natal sex (1:10) as well as by birth year and the reassigned gender (1:10). Data were extracted from national databases including the Total Population Register (Statistics Sweden), the Medical Birth Register, the Cause of Death Register (Statistics Sweden), the Hospital Discharge Register (National Board of Health and Welfare), the Crime Register (National Council of Crime), and those from the Register of Education for highest educational level. The criteria required to obtain the initial certificate for reassignment surgery and change in legal status from the National Board of Health and Welfare were the 2002 WPATH criteria and included evaluation and treatment by one of six specialized teams, name change, a new national identity number indicative of gender, continued use of hormones, and sterilization/castration. Descriptive statistics with hazard ratios were provided.

Investigators identified 804 patients with gender identity disorder (or some other disorder) in Sweden during the period from 1973 to 2003 inclusive. Of these patients, 324 (40.3%) underwent gender-reassignment surgery (133 female-to-male [41.0%]; 191 male-to-female [59.0%]; ratio 1:1.4). The average follow-up time for all-cause mortality was 11.4 years (median 9.1). The average follow-up time for psychiatric hospitalization was 10.4 years (median 8.1).

The mean ages in female-to-male and male-to-female reassigned patients were: 33.3±8.7 (range 20–62) and 36.3± 10.1 (range 21–69) years, respectively. Immigrant status was two times higher in reassigned patients (n=70, 21.6%) than in either type of control (birth [natal] sex matched n=294 [9.1%] or reassigned gender matched n=264 [8.1%]). Educational attainment (10 or more years) was somewhat lower for reassigned patients (n=151 [57.8%]) than in either type of control (birth sex matched n=1,725 [61.5%] or reassigned gender matched n=1804 [64.3%]) (cohort data were incomplete). The biggest discordance in educational attainment was for female-to-male reassigned patients regardless of the control used. Prior psychiatric morbidity (which did not include hospitalization for gender dysphoria) was more than four times higher in reassigned patients (n=58, 17.9%) than in either type of control (birth sex matched n=123 [3.8%] or reassigned gender matched n=114 [3.5%]).

All-cause mortality was higher for patients who underwent gender reassignment surgery (n=27 [8.3%]) than in controls (hazard ratio 2.8 [CI 1.8-4.3]) even after adjustment for covariants (prior psychiatric morbidity and immigration status). Divergence in the survival curves began at 10 years. Survival rates at 20 year follow-up (as derived from figure 1) were: female control 97%, male controls 94%, female-to-male patients 88%, and male-to-female patients 82%. The major contributor to this mortality difference was completed suicide (n=10 [3.1%]; adjusted hazard ratio 19.1 [CI 5.8-62.9]). Mortality due to cardiovascular disease was modestly higher for reassigned patients (n=9 [2.8%]) than in controls (hazard ratio 2.5 [CI 1.2-5.3]).

Suicide attempts were more common in patients who underwent gender reassignment surgery (n= 29 [9.0%] than in controls (adjusted hazard ratio 4.9 [CI 2.9–8.5]). Male-to-female patients were at higher adjusted risk for attempted suicide than either control whereas female-to-male patients were at higher adjusted risk compared to only male controls and maintained the female pattern of higher attempted suicide risk. Hospitalizations for psychiatric conditions (not related to gender dysphoria) were more common in reassigned persons n= 64 [20.0%] than in controls (hazard ratio 2.8 [CI 2.0–3.9]) even after adjusting for prior psychiatric morbidity. Hospitalization for substance abuse was not greater than either type of control.

The nationwide mortality studies by Dhejne et al. (2011) includes much, if not all, of the Landén (1998) patient population and much of the Dhejne et al. (2014) population.

Dhejne C, Öberg K, Arver S, Landén M. An analysis of all applications for sex reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets. Arch Sex Behav. 2014 Nov;43(8):1535-45. Epub 2014 May 29 and Landén M, Wålinder J, Hambert G, Lundström B. Factors predictive of regret in sex reassignment. Acta Psychiatr Scand. 1998 Apr;97(4):284 (Dhejne et al., 2014; Landén et al., 1998) Sweden-All

Dhejne et al. conducted a non-blinded, observational study that was longitudinal for the capture of patients with "regret" in a national database. This same group (Landén et al., 1998) conducted a similar study along with retrospective acquisition of clinical data to explore the differences between the cohorts with and without regret. There were no external controls; only intra- group comparisons for this surgical series.

The investigators assessed the frequency of regret for gender reassignment surgery. Data were extracted from registries at the National Board of Health and Welfare to which patients seeking reassignment surgery or reversal of reassignment surgery make a formal application and which has maintained such records since a 1972 law regulating surgical and legal sex reassignment. The investigators reviewed application files from 1960 through 2010. The specific criteria to qualify for gender surgery were not delineated. Patients typically underwent diagnostic evaluation for at least one year. Diagnostic evaluation was typically followed by the initiation of gender confirmation treatment including hormonal therapy and real-life experience. After two years of evaluation and treatment, patients could make applications to the national board. Until recently sterilization or castration were the required minimal surgical procedures (Dhejne et al., 2011). Secular changes in this program included consolidation of care to limited sites, changes in accepted diagnostic criteria, and provision of non-genital surgery, e.g., mastectomy during the real- life experience phase, and family support.

There were 767 applicants for legal and surgical reassignment (289 [37.7%] female-to-male and 478 [62.3%] male-to-female; ratio 1:1.6). The number of applicants doubled each ten year interval starting in 1981.

Of the applicants, 88.8% or 681 (252 [37.0%] female-to-male and 429 [63.0%] male-to-female; ratio 1:1.7] had undergone surgery and changed legal status by June 30, 2011. This number included eight (four [50.0%] female-to-male and four [50.0%] male to female; ratio 1:1) people who underwent surgery prior to the 1972 law. This number appears to include 41 (two [4.9%] female-to-male and 39 [95.1%] male-to-female; ratio 1:19.5) people who underwent surgery abroad at their own expense (usually in Thailand or the U.S.). This cohort (6% of 681) includes one person who was denied reassignment surgery by Sweden.

Twenty-five (3.3%) of the applications were denied with the two most common reasons being an incomplete application or not meeting the diagnostic criteria. An additional 61(8.0%) withdrew their application, were wait-listed for surgery, postponed surgery (perhaps in hopes of the later revocation of the sterilization requirement), or were granted partial treatment.

The formal application for reversal of the legal gender status, the "regret rate", was 2.2%. No one who underwent sex- reassignment surgery outside of Sweden (36 of these 41 had surgery after 1991) has requested reversal. The authors noted, however, that this preliminary number may be low because the median time interval to reversal request was eight years-only three of which had elapsed by publication submission- and because it was the largest serial cohort. This number did not include other possible expressions of regret including suicide (Dhejne et al., 2011).

Dhejne et al. in 2014 reported that the female-to-male (n=5): male-to-female (n=10) ratio among those who made formal applications for reversal was 1:2. The investigators also reported that the female-to-male applicants for reversal were younger at the time of initial surgical application (median age 22 years) than the complete female-to-

male cohort at the time of surgical application (median age 27 years). By contrast the male-to-female applicants for reversal were older at the time of initial surgical application (median age 35 years) than the complete male-to-female cohort at the time of initial surgical application (median age 32 years). Other clinical data to explore the differences between the cohorts with and without regret were not presented in this update publication.

In their earlier publication, in addition to determining a regret rate (3.8%), Landén et al. extracted data from medical records and government verdicts. Pearson Chi-square testing with Yates' correction for small sample sizes was used to identify candidate variables predictive of regret. They observed that: (a) 25.0% of the cohort with regrets and 11.4% of the cohort without regrets were unemployed, (b) 16.7% of the cohort with regrets and 15.4% of the cohort without regrets were on "sick benefit", (c) 15.4% of the cohort with regrets and 13.9% of the cohort without regrets had problems with substance abuse, (d) 69.2% of the cohort with regrets and 34.6% of the cohort without regrets had undergone psychiatric treatment, (e) 15.4% of the cohort with regrets and 8.8% of the cohort without regrets had a mood disorder, and (f) 15.4% of the cohort with regrets and 1.5% of the cohort without regrets had a psychotic disorder.

The putative prognostic factors that were statistically different between the cohorts with and without regret included prior psychiatric treatment, a history of psychotic disorder, atypical features of gender identity, and poor family support. Factors that trended towards statistical difference included having an unstable personality, sexual orientation and transvestitism. Univariate regression analyses further clarified the most important variables. These variables were tested with logistic regression. Initial modeling included the variable "history of psychotic disorder". Although this variable was predictive, it was excluded from future analyses because it was already a contraindication to reassignment surgery. Additional multivariate regression analyses identified poor family support as the most predictive variable and atypical features of gender identity as the second most important variable. Presence of both variables had a more than additive effect.

The nationwide mortality studies by Dhejne et al. (2011) includes much, if not all, of the Landén (1998) patient population and most of the Dhejne (2014) population. There is a related paper by Landén et al. 1998b that included the criteria to qualify for surgical intervention at that time.

Heylens G, Verroken C, De Cock S, T'Sjoen G, De Cuypere G. Effects of different steps in gender reassignment therapy on psychopathology: a prospective study of persons with a gender identity disorder. J Sex Med. 2014 Jan;11(1):119-26. Epub 2013 Oct 28.

Heylens et al. conducted a prospective, non-blinded observational study using a longitudinal design in which patients served as their own controls. They used a non-specific psychiatric test with normative data along with two self-designed questionnaires. The investigators assessed psychosocial adjustment and psychopathology in patients with gender identity disorders. Patients were to be sequentially evaluated prior to institution of hormonal therapy, then 3 to 6 months after the start of cross-sex hormone treatment, and then again one to 12 months after reassignment surgery. The Dutch version of the SCL-90R with eight subscales (agoraphobia, anxiety, depression, hostility, interpersonal sensitivity, paranoid ideation/psychoticism, and sleeping problems) and a global score (psycho-neuroticism) was used serially. A seven parameter questionnaire was used serially to assess changes in social function. Another cross-sectional survey assessed emotional state. The cohorts at each time point consisted of patients who were in the treatment cohort at the time and who had submitted survey responses.

Ninety of the patients who applied for reassignment surgery between June 2005 and March 2009 were recruited. Fifty seven entered the study. Forty-six (51.1% of the recruited population) underwent reassignment surgery. Baseline questionnaire information was missing for 3 patients. Baseline SCL-90 scores were missing for 1 patient but included SCL-90 scores from some of the 11 recruits who had not yet undergone reassignment surgery. Time point 2 (after hormone therapy) SCL-90 information was missing for 10, but included SCL-90 scores from some of the 11

recruits who had not yet undergone reassignment surgery. At time point 3, 42 (91.3% of those who underwent reassignment surgery) patients completed some part of the SCL-90 survey and the psychosocial questionnaires. Some questionnaires were incomplete. The investigators reported response rates of 73.7% for the psychosocial questionnaires and 82.5% for the SCL-90.

Of those who responded at follow-up after surgery, 88.1% reported having good friends; 52.4% reported the absence of a relationship; 47.6% had no sexual contacts; 42.9% lived alone; 40.5% were unemployed, retired, students, or otherwise not working; 2.4% reported alcohol abuse; and 9.3% had attempted suicide. The frequency of these parameters reportedly did not change statistically during the study interval, but there was no adjustment for the inclusion of patients who did not undergo surgery.

In a cross-sectional, self-report mood survey, of the 42 study entrants who completed the entire treatment regimen including reassignment surgery and the final assessment (refers to the initial 57) reported improved body-related experience (97.6%), happiness (92.9%), mood (95.2%), and self-confidence (78.6%) and reduced anxiety (81.0%). Of participants, 16.7% reported thoughts of suicide. Patients also reported on the intervention phase that they believed was most helpful: hormone initiation (57.9%), reassignment surgery (31.6%), and diagnostic-psychotherapy phase (10.5%).

The global “psycho-neuroticism” SCL-90R score, along with scores of 7 of the 8 subscales, at baseline were statistically more pathologic than the general population. After hormone therapy, the score for global “psycho-neuroticism” normalized and remained normal after reassignment surgery. More specifically the range for the global score is 90 to 450 with higher scores being more pathologic. The score for the general population was 118.3±32.4. The respective scores for the various gender dysphoric cohorts were 157.7±49.8 at initial presentation, 119.7±32.1 after hormone therapy, and 127.9±37.2 after surgery. The scores for the general population and the scores after either hormone treatment or surgical treatment did not differ.

Kockott G, Fahrner EM. Transsexuals who have not undergone surgery: a follow-up study. Arch Sex Behav. 1987 Dec;16 (6):511-22.

Kockott and Fahrner conducted a single center (Munich, Germany) prospective, observational study using a longitudinal design. Treatment cohorts were used as controls, and patients served as their own controls. The investigators assessed psychosocial adjustment in patients with gender identity issues. Patients were to have met DSM III criteria. Trans-sexuality, transvestitism, and homosexuality were differentiated. The criteria required for patients to receive hormone therapy and/or reassignment surgery were not delineated. After receiving hormone therapy, patients were later classified by surgical reassignment status (pre-operative and post-operative) and desire for surgery (unchanged desire, hesitant, and no longer desired).

The first investigative tool was a semi-structured in-person interview consisting of 125 questions. The second investigative tool was a scale that organized the clinical material into nine domains which were then scored on a scale. The Psychological Integration of Trans-sexuals (PIT) instrument developed according to the scale used by Hunt and Hampson (1980) for assessment of 17 post-operative patients. There were 15 interviews and two separate interviewers. There were 80 patients identified, but 58 (72.5%) patients (26 pre-operative; 32 post-operative) were ultimately included in the analysis. The duration of follow-up was longer for post-operative patients (6.5 years) than for pre-operative patients (4.6 years) (including time for one patient subsequently excluded). The mean age of the post-operative patients was 35.5±13.1 years, and the age of the patients who maintained a continued desire for surgery was 31.7±10.2 years. The age of the patients who hesitated about surgery was somewhat older, 40.3±9.4 years. The age of the patients who were no longer interested in surgery was 31.8±6.5 years. All were employed or in school at baseline. Patients with hesitation were financially better-off, had longer-standing relationships even if unhappy, and had a statistical tendency to place less value on sex than those with an unchanged wish for surgery.

Post-operative patients more frequently reported contentment with the desired gender and the success of adaption to the gender role than the pre-operative patients with a persistent desire for surgery. Post-operative patients more frequently reported sexual satisfaction than pre-operative patients with a continuing desire for surgery. Post-operative patients also more frequently reported financial sufficiency and employment than pre-operative patients with a persistent desire for surgery. Suicide attempts were stated to be statistically less frequent in the post-surgical cohort.

Psychosocial adjustment scores were in the low end of the range with "distinct difficulties" (19-27) at the initial evaluation for the post-operative patients (19.7), the pre-operative patients with a persistent wish for surgery (20.2), and the hesitant patients (19.7). At initial evaluation, psychosocial adjustment scores for patients no longer wanting surgery were at the high end of the range with "few difficulties" (10-18). At the final evaluation, Psychosocial adjustment scores were at the high end of the range "few difficulties" (10-18) for the post-operative patients (13.2) and the patients no longer wanting surgery (16.5). Psychosocial adjustment scores at the final evaluation were in the borderline range between "few difficulties" (10-18) and "distinct difficulties" (19-27) for both the pre-operative patients with a persistent desire for surgery (18.7), and the hesitant patients (19.1).

The changes in the initial score and the final follow-up score within each group were tracked and reported to be statistically significant for the post-operative group, but not for the other groups. Statistical differences between groups were not presented. Moreover, the post-operative patients had an additional test immediately prior to surgery. The first baseline score (19.7) would have characterized the patients as having "distinct difficulties" in psychosocial adjustment while the second baseline score (16.7) would have categorized the patients as having "few difficulties" in psychosocial adjustment despite the absence of any intervention except the prospect of having imminent reassignment surgery. No statistics reporting on the change between scores of the initial test and the test immediately prior to surgery and the change between scores of the test immediately prior to surgery and the final follow-up were provided.

Meyer JK, Reter DJ. Sex reassignment. Follow-up. Arch Gen Psychiatry. 1979 Aug;36(9):1010-5. (United States study)

Meyer and Reter conducted a single-center (Baltimore, Maryland, U.S.) prospective, non-blinded, observational study using a longitudinal design and retrospective baseline data. Interview data were scored with a self-designed tool. There were treatment control cohorts, and patients served as their own controls. The investigators assessed patients with gender dysphoria. The 1971 criteria for surgery required documented cross-sex hormone use as well as living and working in the desired gender for at least one year in patients subsequently applying for surgery. Clinical data including initial interviews were used for baseline data. In follow-up, the investigators used extensive two to four hour interviews to collect information on (a) objective criteria of adaptation, (b) familial relationships and coping with life milestones, and (c) sexual activities and fantasies. The objective criteria, which were the subject of the publication, included employment status (Hollingshead job level), cohabitation patterns, and need for psychiatric intervention. The investigators designed a scoring mechanism for these criteria and used it to determine a global adjustment score. The score value or the change score that was considered to be biologically significant was not pre-specified in the methods.

The clinic opened with 100 patients, but when the follow-up was completed, 52 patients were interviewed and 50 gave consent for publication. Of these, 15 (four female-to-male, 11 male-to-female; ratio 1:2.8) were part of the initial operative cohort, 14 (one female-to-male; 13 male-to-female; ratio 1:13) later underwent reassignment surgery at the institution or elsewhere, and 21 (five female-to-male; 16 male-to-female; ratio 1:3.2) did not undergo surgery. The mean ages of these cohorts were 30.1, 30.9, and 26.7 years respectively. The mean follow-up time was 62 months (range 19-142) for those who underwent surgery and 25 months (range 15-48) for those who did not. Socioeconomic status was lowest in those who subsequently underwent reassignment surgery.

Of patients initially receiving surgery, 33% had some type of psychiatric contact prior to the initial clinic evaluation and 8% had psychiatric contact during the follow-up. Of the patients who had not under gone surgery or who had done so later, 72% had some type of psychiatric contact prior to the initial clinic evaluation and 28% had psychiatric contact during follow-up. There was a single female-to-male patient with multiple surgical complications who sought partial reassignment surgery reversal.

The adjustment scores improved over time with borderline statistical significance for the initial operative group and with statistical significance for the never operated group. The absolute score value at follow-up was the same for both groups (1.07+1.53 and 1.10+1.97 respectively). By contrast, the adjustment scores did not improve for those who were not in the cohort initially approved for surgery, but who subsequently underwent surgery later. This was particularly true if the surgery was performed elsewhere. The absolute score value at follow-up was 0.21+1.89.

Related papers include Meyer et al. (1971), Meyer et al. (1974a-d), and Derogatis et al. (1978) along with commentary response by Fleming et al. (1980).

Rakic Z, Starcevic V, Maric J, Kelin K. The outcome of sex reassignment surgery in Belgrade: 32 patients of both sexes. Arch Sex Behav. 1996 Oct;25(5):515-25.

Rakic et al. single-center (Belgrade, Yugoslavia) conducted a prospective, non-blinded, observational study using a cross-sectional design and an investigator- designed quality of life tool that asked longitudinal (pre- and post-treatment) questions. Patients served as their own controls. The authors state that the study was not designed to assess the predictors of poor outcomes.

The investigators assessed global satisfaction, body image, relationships, employment status, and sexual function in patients with gender dysphoria who underwent reassignment surgery between 1989 and 1993 and were at least six months post-operative. The criteria to qualify for gender surgery were delineated (1985 standards from the Harry Benjamin International Gender Dysphoria Association) and included cross-gender behavior for at least one year and sexual orientation to non-natal sex. The questionnaire consisted of 10 questions using yes/no answers or Likert-type scales. Findings were descriptive without statistical analysis. As such, changes or differences considered to be biologically significant were not pre-specified, and there were no adjustments for multiple comparisons.

Of the 38 patients who had undergone reassignment surgery, 34 were eligible for the study and 32 participated in the study (two were lost to follow-up and four were in the peri-operative period) - 10 (31.2%) female-to-male and 22 (68.8%) male-to-female (ratio 1:2.2). The duration of follow-up was 21.8 ±13.4 months (range 6 months to 4 years). The age was female-to-male 27.8±5.2 (range 23-37) and male-to-female 26.4±7.8 (range 19-47).

Using an investigator-designed quality of life tool, all patients reported satisfaction with having undergone the surgery. Of the total participants, four (12.5%) (all male-to-female) and eight (25%) (87.5% male-to-female) reported complete dissatisfaction or partial satisfaction with their appearance. Regarding relationships, 80% of female-to-male and 100% of male-to-female patients were dissatisfied with their relationships with others prior to surgery; whereas, no female-to-male patients and 18.1% of male-to-female patients were dissatisfied with relationships after surgery. Regarding sexual partners, 60% of female-to-male and 72.7% of male-to-female patients reported not having a sexual partner prior to surgery; whereas, 20% of female-to-male patients and 27.3% of male-to-female patients did not have a sexual partner after surgery. Of those with partners at each time interval, 100% of female-to-male and 50% of male-to-female patients reported not experiencing orgasm prior to surgery; whereas, 75% of female-to-male and 37.5% of male-to-female patients reported not experiencing orgasm after surgery.

Ruppin U, Pfäfflin F. Long-term follow-up of adults with gender identity disorder. Arch Sex Behav. 2015 Jul;44(5):1321-9. Epub 2015 Feb 18.

Ruppin and Pfafflin conducted a single-center (Ulm, Germany) partially prospective, non-blinded, observational study using a longitudinal design and non-specific psychometric tests and a self-designed interview tool and questionnaire. Patients served as their own controls.

The investigators assessed psychological symptoms, interpersonal difficulties, gender role stereotypes, personality characteristics, societal function, sexual function, and satisfaction with new gender role in patients with gender dysphoria. Patients were required to have met the ICD-10 criteria for trans-sexualism, been seen by the clinic by prior to 2001, and completed an official change in gender including name change prior to 2001. Assessment tools included German versions of standardized surveys with normative data: the SCL 90R, the Inventory of Interpersonal Problems (IIP), Bem Sex Role Inventory (BSRI), and the Freiburg Personality Inventory (FPI-R), along with semi-structured interviews with self-designed questionnaires. The prospective survey results were compared to retrospective survey results. Changes or inter-group differences considered to be biologically significant were not pre-specified. Diagnostic cut points were not provided. Statistical corrections for multiple comparisons were not included.

Overall, 140 patients received recruitment letters and then 71 (50.7%) agreed to participate. Of these participants, 36 (50.7%) were female-to-male; 35 (49.3%) were male-to-female (ratio 1:0.97). The ages of the patients were: 41.2±5.78 years (female-to-male) and 52.9±10.82 years (male-to-female). The intervals for follow-up were 14.1±1.97 years and 13.7±2.17 years, respectively.

All female-to-male patients had undergone mastectomy; 91.7% had undergone oopherectomy and/or hysterectomy; 61.1% had undergone radial forearm flap phalloplasty or metaoidioplasty. Of male-to-female patients, 94.3% had undergone vaginoplasty and perhaps an additional procedure (breast augmentation, larynx surgery, or vocal cord surgery). Two male-to-female patients had not undergone any reassignment surgery, but were still included in the analyses.

A total of 68 patients ranked their well-being as 4.35±0.86 out of five (three patients did not respond to this question). Of respondents, 40% reported not being in a steady relationship. Regular sexual relationships were reported by 57.1% of 35 female- to-male respondents and 39.4% of 33 male-to-female respondents (three patients did not respond to this question). A total of 11 patients reported receiving out-patient psychotherapy; 69 did not express a desire for gender role reversal (two did not respond to this question). The response rate was less than 100% for most of the self-designed survey questions.

Changes from the initial visit to the follow-up visit were assessed for the SCL-90R in 62 of 71 patients. The effect size was statistically significant and large only for the “Interpersonal Sensitivity” scale (one of 10 parameters). The absolute magnitude of mean change was small: from 0.70±0.67 to 0.26±0.34 (scale range 0-4). The duration of follow-up did not correlate with the magnitude of change on the various scales. Differences in baseline SCL-90R scores of 62 participants were compared with the score of 63 of the 69 eligible recruits who declined to enter the study and were notable for higher “Depression” scores for the latter.

Changes from the initial visit to the follow-up visit were assessed for the IIP in 55 of 71 patients. The effect size was statistically significant and large only for the “Overly Accommodating” scale (one of eight parameters). The absolute magnitude of mean change was small: from 11.64±5.99 to 7.04±4.73 (scale range 0-32). The duration of follow-up did not correlate with the magnitude of change on the various scales.

Changes from the initial visit to the follow-up visit were assessed for the FPI-R in 58 of 71 patients. The effect size was statistically significant and large only for the “Life Satisfaction” scale (one of 12 parameters). The absolute magnitude of mean change was substantive: from 4.43±2.99 to 8.31±2.63 (scale range 0-12). The duration of follow-up did not correlate with the magnitude of change on the various scales.

Changes from the initial visit to the follow-up visit were assessed for the BSRI in 16 of 36 female to male patients and 19 of 35 male to female patients. The "Social Desirability" score increased for the female-to-male respondents. At endpoint, both categories of respondents reported androgynous self-images.

This current report is an update of prior publications by Pfafflin including work with Junge which was published in a variety of formats and initially in German.

Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT. Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. Psychol Med. 2005 Jan;35(1):89-99.

Smith et al. conducted a single-center (Amsterdam, Netherlands) prospective, non-blinded, observational study using a longitudinal design and psychological function tools. Patients served as their own control prior to and after reassignment surgery. The investigators assessed gender dysphoria, body dissatisfaction, physical appearance, psychopathology, personality traits, and post-operative function in patients with gender dysphoria. Patients underwent some aspect of reassignment surgery. The test instruments included the Utrecht Gender Dysphoria Scale (12 items), the Body Image Scale adapted for a Dutch population (30 items), Appraisal of Appearance Inventory (3 observers, 14 items), the Dutch Short MMPI (83 items), the Dutch version of the Symptom Checklist (SCL)(90 items), and clinic-developed or modified questionnaires. Pre-treatment data was obtained shortly after the initial interview. Post- surgery data were acquired at least one year post reassignment surgery.

Three hundred twenty five consecutive adolescents and adults were screened for the study. One-hundred three (29 [28.2%] female-to-male patients and 74 [71.8%] male-to-female patients [ratio 1:2.6]) never started hormone therapy; 222 (76 [34.2%] female-to-male patients and 146 [65.8%] male-to-female patients [ratio 1:1.9]) initiated hormone therapy. Of the patients who started hormone therapy, 34 (5 [14.7%] female-to-male patients and 29 [85.3%] male-to-female patients [ratio 1:5.8]) discontinued hormone therapy.

Subsequently, the study analysis was limited to adults. One hundred sixty-two (58 [35.8%] female-to-male and 104 [64.2%] male-to-female [ratio 1:1.8]) were eligible and provided pre-surgical test data, and 126 (77.8% of eligible adults) (49 [38.9%] female-to-male and 77 [61.1%] male-to-female [ratio 1:1.6]) provided post-surgical data. For those patients who completed reassignment, the mean age at the time of surgical request was 30.9 years (range 17.7-68.1) and 35.2 years (range 21.3-71.9) years at the time of follow-up. The intervals between hormone treatment initiation and surgery and surgery and follow-up were 20.4 months (range 12 to 73) and 21.3 months (range 12 to 47) respectively.

Of the 126 adults who provided post-surgical data, 50 (40.0%) reported having a steady sexual partner, three (2.3%) were retired, and 58 (46.0%) were unemployed. Regarding regret, six patients expressed some regret regarding surgery, but did not want to resume their natal gender role, and one male-to-female had significant regret and would not make the same decision.

Post-surgery Utrecht dysphoria scores dropped substantially and approached reportedly normal values. The patients' appearance better matched their new gender. No one was dissatisfied with his/her overall appearance at follow-up. Satisfaction with primary sexual, secondary sexual, and non-sexual body traits improved over time. Male-to-female patients, however, were more dissatisfied with the appearance of primary sex traits than female-to-male patients. Regarding mastectomy, 27 of 38 (71.1%) female-to-male respondents (not including 11 non-respondents) reported incomplete satisfaction with their mastectomy procedure. For five of these patients, the incomplete satisfaction was because of scarring. Regarding vaginoplasty, 20 of 67 (29.8%) male-to-female respondents (not including 10 non-respondents) reported incomplete satisfaction with their vaginoplasty.

Most of the MMPI scales were already in the normal range at the time of initial testing and remained in the normal

range after surgery. SCL global scores for psycho- neuroticism were minimally elevated before surgery 143.0±40.7 (scoring range 90 to 450) and normalized after surgery 120.3±31.4. (An analysis using patient level data for only the completers was not conducted.)

Udeze B, Abdelmawla N, Khoosal D, Terry T. Psychological functions in male-to- female people before and after surgery. Sexual and Relationship Therapy. 2008 May; 23(2):141-5. (Not in PubMed) and Megeri D, Khoosal D. Anxiety and depression in males experiencing gender dysphoria. Sexual and Relationship Therapy. 2007 Feb; 22(1):77-81. (Not in PubMed)

Udeze et al. conducted a single-center (Leicester, United Kingdom) prospective, non-blinded, longitudinal study assessing a randomized subset of patients who had completed a non-specific psychological function tool prior to and after male-to-female reassignment surgery. Patients served as their own controls. The investigators used the WPATH criteria for patient selection. Psychiatric evaluations were routine. All patients selected for treatment were routinely asked to complete the self-administered SCL-90R voluntarily on admission to the program and post-operatively. A post-operative evaluations (psychiatric and SCL-90R assessment) were conducted within six months to minimize previously determined loss rates. The patient pool was domestic and international. There were 546 gender dysphoric patients from all over the United Kingdom and abroad, of whom 318 (58.2%) progressed to surgery. Of these, 127 were from the local Leicester area in the United Kingdom and 38 (29.9%) progressed to surgery. The mean age for the selected male-to-female patients at the time of study was 47.33±13.26 years (range 25 to 80) and reflected an average wait time for surgery of 14 months (range 2 months to 6 years). For this investigation, 40 male-to-female subjects were prospectively selected.

The raw SCL-90 global scores for psycho-neuroticism were unchanged over time: 48.33 prior to surgery and 49.15 after surgery. If the scale was consistent with T-scoring, the results were non-pathologic. No psychiatric disorders were otherwise identified prior to or after surgery.

Investigators from the same clinical group (Megeri, Khoosal, 2007) conducted additional testing to specifically address anxiety and depression with the Beck Depression Inventory, General Health Questionnaire (with 4 subscales), HADS, and Spielberger State and Trait Anxiety Questionnaire (STAI-X1 and STA-X2). The test population and study design appear to be the same. No absolute data were presented. Only changes in scores were presented. There were no statistically significant changes.

e. Randomized, surgical patients, longitudinal, with controls

Mate-Kole C, Freschi M, Robin A. A controlled study of psychological and social change after surgical gender reassignment in selected male transsexuals. Br J Psychiatry. 1990 Aug;157:261-4.

Mate-Kole at al. conducted a prospective, non-blinded, controlled, randomized, longitudinal study using investigator-designed patient self-report questionnaires and non-specific psychological tests with some normative data. The investigators assessed neuroticism and sex role in natal males with gender dysphoria who had qualified for male-to-female reassignment surgery at a single-center specialty clinic (London, United Kingdom). Forty sequential patients were alternately assigned to early reassignment surgery or to standard wait times for reassignment surgery. Patients were evaluated after acceptance and 2 years later. The criteria used to qualify for gender surgery were the 1985 standards from the Harry Benjamin International Gender Dysphoria Association. These included a ≥2 year desire to change gender, a ≥1 year demonstrable ability to live and be self-supporting in the chosen gender, and psychiatric assessment for diagnosis and reassessment at six months for diagnostic confirmation and exclusion of psychosis.

Reassignment surgery was defined as orchidectomy, penectomy, and construction of a neo-vagina. The instruments used were the CCEI for psychoneurotic symptoms and the Bem Sex Role Inventory along with an incompletely

described investigator- designed survey with questions about social life and sexual activity.

The mean age and range of the entire cohort was 32.5 years (21-53). Members of the early surgery cohort had a history of attempted suicide (one patient), psychiatric treatment for non-gender issues (six patients), and first degree relatives with psychiatric histories (four patients). Members of the standard surgery cohort were similar, with a history of attempted suicide (two patients), psychiatric treatment for non-gender issues (five patients), and first degree relatives with psychiatric histories (six patients). The early surgery group had surgery approximately 1.75 years prior to the follow-up evaluation. In both groups, cross-dressing began at about age 6.

At baseline, the Bem Sex Role Inventory femininity scores were slightly higher than masculinity scores for both cohorts and were similar to Bem North American female normative scores. The scores did not change in either group over time.

At baseline, the scores for the CCEI individual domains (free floating anxiety, phobic anxiety, somatic anxiety, depression, hysteria, and obsessionality) were similar for the cohorts. The total CCEI scores for the two cohorts were consistent with moderate symptoms (Birchnell et al. 1988). Over the two year interval, total CCEI scores increased for standard wait group and approached the relatively severe symptom category. During the same interval, scores dropped into the asymptomatic rage for the post-operative patients.

The investigator-designed survey assessed changes in social and sexual activity of the prior two years, but the authors only compared patients in a given cohort to themselves. Though the researchers did not conduct statistical studies to compare the differences between the two cohorts, they did report increased participation in some, but not all, types of social activities such as sports (solo or group), dancing, dining out, visiting pubs, and visiting others. Sexual interest also increased. By contrast, pre-operative patients did not increase their participation in these activities.

2. External Technology Assessments

a. CMS did not request an external technology assessment (TA) on this issue.

b. There were no AHRQ reviews on this topic.

c. There are no Blue Cross/Blue Shield Health Technology Assessments written on this topic within the last three years.

d. There were two publications in the COCHRANE database, and both were tangentially related. Both noted that there are gaps in the clinical evidence base for gender reassignment surgery.
Twenty Years of Public Health Research: Inclusion of Lesbian, Gay, Bisexual, and Transgender Populations Boehmer U. Am J Public Health. 2002; 92: 1125–30.

"Findings supported that LGBT issues have been neglected by public health research and that research unrelated to sexually transmitted diseases is lacking."

A systematic review of lesbian, gay, bisexual and transgender health in the West Midlands region of the UK compared to published UK research. West Midlands Health Technology Assessment Collaboration. Health Technology Assessment Database. Meads, et al., 2009. No.3.

"Further research is needed but must use more sophisticated designs with comparison groups. This systematic review demonstrated that there are so many gaps in knowledge around LGBT health that a wide variety of studies are needed."

e. There were no National Institute for Health and Care Excellence (NICE) reviews/guidance documents on this

topic.

f. There was a technology assessment commissioned by the New Zealand Ministry of Health and conducted by New Zealand Health Technology Assessment (NZHTA) (Christchurch School of Medicine and the University of Otago).

Tech Brief Series: Transgender Re-assignment Surgery Day P. NZHTA Report. February 2002;1(1). http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf

The research questions included the following:
1. Are there particular subgroups of people with transsexualism who have met eligibility criteria for gender reassignment surgery (GRS) where evidence of effectiveness of that surgery exists?

2. If there is evidence of effectiveness, what subgroups would benefit from GRS?"

The authors concluded that there was not enough evidence to answer either of the research questions.

3. Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) Meeting

CMS did not convene a MEDCAC meeting.

4. Evidence-Based Guidelines

a. American College of Obstetricians and Gynecologists (ACOG)

Though ACOG did not have any evidence-based guidelines on this topic, they did have the following document:
Health Care for Transgender Individuals: Committee Opinion
Committee on Health Care for Underserved Women; The American College of Obstetricians and Gynecologists. Dec 2011, No. 512. Obstet Gyncol. 2011;118:1454-8.

"Questions [on patient visit records] should be framed in ways that do not make assumptions about gender identity, sexual orientation, or behavior. It is more appropriate for clinicians to ask their patients which terms they prefer. Language should be inclusive, allowing the patient to decide when and what to disclose. The adoption and posting of a nondiscrimination policy can also signal health care providers and patients alike that all persons will be treated with dignity and respect. Assurance of confidentiality can allow for a more open discussion, and confidentiality must be ensured if a patient is being referred to a different health care provider. Training staff to increase their knowledge and sensitivity toward transgender patients will also help facilitate a positive experience for the patient."

b. American Psychiatric Association

Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder. Byne, W, Bradley SJ, Coleman E, Eyler AE, Green R, Menvielle EJ, Meyer-Bahlburg HFL, Richard R. Pleak RR, Tompkins DA. Arch Sex Behav. 2012; 41:759–96.

The American Psychiatric Association (APA) was unable to identify any Randomized Controlled Trials (RTCs) regarding mental health issues for transgender individuals.

"There are some level B studies examining satisfaction/regret following sex reassignment (longitudinal follow-up after an intervention, without a control group); however, many of these studies obtained data retrospectively and without a control group (APA level G). Overall, the evidence suggests that sex reassignment is associated with an

improved sense of well-being in the majority of cases, and also indicates correlates of satisfaction and regret. No studies have directly compared various levels of mental health screening prior to hormonal and surgical treatments on outcome variables; however, existing studies suggest that comprehensive mental health screening may be successful in identifying those individuals most likely to experience regrets."

Relevant Descriptions of APA Evidence Coding System/Levels:

[B] Clinical trial. A prospective study in which an intervention is made and the results of that intervention are tracked longitudinally. Does not meet standards for a randomized clinical trial."

[G] Other. Opinion-like essays, case reports, and other reports not categorized above."

c. Endocrine Society

Endocrine Treatment of Transsexual Persons: an Endocrine Society Clinical Practice Guideline.

Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, Tangpricha V, Montori VM; Endocrine Society. J Clin Endocrinol Metab. 2009; 94:3132-54.

This guideline primarily addressed hormone management and surveillance for complications of that management. A small section addressed surgery and found the quality of evidence to be low.

"This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe the strength of recommendations and the quality of evidence, which was low or very low."

d. World Professional Association for Transgender Health (WPATH)

Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People (Version 7). Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Kevan R. Wylie KR, Zucker K.
www.wpath.org/_files/140/files/Standards%20of%20Care,%20V7%20Full%20Book.pdf
Int J Transgend. 2011;13:165–232.

The WPATH is "an international, multidisciplinary, professional association whose mission is to promote evidence-based care, education, research, advocacy, public policy, and respect in transsexual and transgender health."

WPATH reported, "The standards of care are intended to be flexible in order to meet the diverse health care needs of transsexual, transgender, and gender-nonconforming people. While flexible, they offer standards for promoting optimal health care and guiding the treatment of people experiencing gender dysphoria—broadly defined as discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b)."

The WPATH standards of care (SOC) "acknowledge the role of making informed choices and the value of harm-

reduction approaches."

The SOC noted, "For individuals seeking care for gender dysphoria, a variety of therapeutic options can be considered. The number and type of interventions applied and the order in which these take place may differ from person to person (e.g., Bockting, Knudson, & Goldberg, 2006; Bolin, 1994; Rachlin, 1999; Rachlin, Green, & Lombardi, 2008; Rachlin, Hansbury, & Pardo, 2010). Treatment options include the following:

- Changes in gender expression and role (which may involve living part time or full time in another gender role, consistent with one's gender identity);
- Hormone therapy to feminize or masculinize the body;
- Surgery to change primary and/or secondary sex characteristics (e.g., breasts/chest, external and/or internal genitalia, facial features, body contouring);
- Psychotherapy (individual, couple, family, or group) for purposes such as exploring gender identity, role, and expression; addressing the negative impact of gender dysphoria and stigma on mental health; alleviating internalized transphobia; enhancing social and peer support; improving body image; or promoting resilience."

e. American Psychological Association

Suggested citation until formally published in the American Psychologist: American Psychological Association. (2015): *Guidelines for Psychological Practice with Transgender and Gender Nonconforming People Adopted by the Council of Representatives, August 5 & 7, 2015. www.apa.org/practice/guidelines/transgender.pdf*

"The purpose of the Guidelines for Psychological Practice with Transgender and Gender Nonconforming People (hereafter Guidelines) is to assist psychologists in the provision of culturally competent, developmentally appropriate, and trans-affirmative psychological practice with TGNC people."

"These Guidelines refer to psychological practice (e.g., clinical work, consultation, education, research, training) rather than treatment."

5. Other Reviews

a. Institute of Medicine (IOM)

The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. Robert Graham (Chair); Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities. (Study Sponsor: The National Institutes of Health). Issued March 31, 2011. http://www.nationalacademies.org/hmd/Reports/2011/The-Health-of-Lesbian-Gay-Bisexual-and- Transgender-People.aspx

"To advance understanding of the health needs of all LGBT individuals, researchers need more data about the demographics of these populations, improved methods for collecting and analyzing data, and an increased participation of sexual and gender minorities in research. Building a more solid evidence base for LGBT health concerns will not only benefit LGBT individuals, but also add to the repository of health information we have that pertains to all people."

"Best practices for research on the health status of LGBT populations include scientific rigor and respectful involvement of individuals who represent the target population. Scientific rigor includes incorporating and monitoring culturally competent study designs, such as the use of appropriate measures to identify participants and

implementation processes adapted to the unique characteristics of the target population. Respectful involvement refers to the involvement of LGBT individuals and those who represent the larger LGBT community in the research process, from design through data collection to dissemination."

b. National Institutes of Health (NIH)

National Institutes of Health Lesbian, Gay, Bisexual, and Transgender (LGBT) Research Coordinating Committee. Consideration of the Institute of Medicine (IOM) report on the health of lesbian, gay, bisexual, and transgender (LGBT) individuals. Bethesda, MD: National Institutes of Health; 2013. http://report.nih.gov/UploadDocs/LGBT%20Health%20Report_FINAL_2013-01-03-508%20compliant.pdf

In response to the IOM report, the NIH LBGT research Coordinating Committee noted that most of the health research for this set of populations is "focused in the areas of Behavioral and Social Sciences, HIV (human immunodeficiency virus)/AIDS, Mental Health, and Substance Abuse. Relatively little research has been done in several key health areas for LGBT populations including the impact of smoking on health, depression, suicide, cancer, aging, obesity, and alcoholism."

6. Pending Clinical Trials

ClinicalTrials.gov
There is one currently listed and recently active trial directed at assessment of the clinical outcomes pertaining to individuals who have had gender reassignment surgery. The study appears to be a continuation of work conducted by investigators cited in the internal technology assessment.

NCT01072825 (Ghent, Belgium sponsor) European Network for the Investigation of Gender Incongruence (ENIGI) is assessing the physical and psychological effects of the hormonal treatment of transgender subjects in two years prior to reassignment surgery and subsequent to surgery. This observational cohort study started in 2010 and is still in progress.

7. Consultation with Outside Experts

Consistent with the authority at 1862(l)(4) of the Act, CMS consulted with outside experts on the topic of treatment for gender dysphoria and gender reassignment surgery.

Given that the majority of the clinical research was conducted outside of the United States, and some studies either took place in or a suggested continuity-of-care and coordination-of-care were beneficial to health outcomes, we conducted expert interviews with centers across the U.S. that provided some form of specialty-focused or coordinated care for transgender patients. These interviews informed our knowledge about the current healthcare options for transgender people, the qualifications of the professionals involved, and the uniqueness of treatment options. We are very grateful to the organizations that made time to discuss treatment for gender dysphoria with us.

From our discussions with the all of the experts we spoke with, we noted the following practices in some centers: (1) specialized training for all staff about transgender healthcare and transgender cultural issues; (2) use of an intake assessment by either a social worker or health care provider that addressed physical health, mental health, and other life factors such as housing, relationship, and employment status; (3) offering primary care services for transgender people in addition to services related to gender-affirming therapy/treatments; (4) navigators who connected patients with name-change information or other legal needs related to gender; (5) counseling for individuals, groups, and families; (6) an informed-consent model whereby individuals were often referred to as

"clients" instead of "patients," and (7) an awareness of depression among transgender people (often measured with tools such as the Adult Outcomes Questionnaire and the Patient Health Questionnaire).

8. Public Comments

We appreciate the thoughtful public comments we received on the proposed decision memorandum. In CMS' experience, public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum. All comments that were submitted without personal health information may be viewed in their entirety by using the following link: https://www.cms.gov/medicare-coverage-database/details/nca-view-public-comments.aspx?NCAId=282&ExpandComments=n#Results

a. Initial Comment Period: December 3, 2015 – January 2, 2016

During the initial comment period, we received 103 comments. Of those, 78% supported coverage of gender reassignment surgery, 15% opposed, and 7% were neutral. The majority of comments supporting coverage were from individuals and advocacy groups.

b. Second Comment Period: June 2, 2016 – July 2, 2016

During the second 30-day public comment period, we received a total of 45 public comments, 7 of which were not posted on the web due to personal health information content. Overall, 82% supported coverage of gender reassignment surgery, 11% opposed, and 7% were neutral or silent in their comment whether they supported or opposed coverage. Half of the comments were submitted by individuals who expressed support for coverage of gender reassignment surgery (51%). We also received comments from physicians, providers, and other health professionals who specialize in healthcare for transgender individuals (17%). We received one comment from a municipality, the San Francisco Department of Public Health. Associations (American Medical Association, American College of Physicians, American Academy of Nursing, American Psychological Association, and LBGT PA Caucus) and advocates (Center for American Progress with many other signatories, Jamison Green & Associates) also submitted comments.

Below is a summary of the comments CMS received. In some instances, commenters identified typographical errors, context missed, and opportunities for CMS to clarify wording and classify articles for ease of reading in the memorandum. As noted earlier, when appropriate and to the extent possible, we updated the decision memorandum to reflect those corrections, improved the context, and clarified the language. In light of public comments, we re-evaluated the evidence and our summaries. We updated our summaries of the studies and clarified the language when appropriate.

1. Contractor Discretion and National Coverage Determination

Comment: Some commenters, including advocates, associations, and providers, supported CMS' decision for MAC contractor discretion/case-by-case determination for gender reassignment surgery. One stakeholder stated, "We agree with the conclusion that a NCD is not warranted at this time."

Response: We appreciate the support and understanding among stakeholders for our proposed decision to have the MACs determine coverage on a case-by-case basis. We have clarified in this final decision memorandum that

coverage is available for gender reassignment surgery when determined reasonable and necessary and not otherwise excluded by any other relevant statutory requirements by the MAC on a case-by-case basis. "The case-by-case model affords more flexibility to consider a particular individual's medical condition than is possible when the agency establishes a generally applicable rule." (78 Fed. Reg. 48165 (August 7, 2013)).

Comment: Some commenters cautioned that CMS' choice to not issue a NCD at this time must not be interpreted as a national non-coverage determination or used in any way to inappropriately restrict access to coverage for transgender Medicare beneficiaries or other transgender individuals. Multiple commenters indicated their disappointment that CMS did not propose a National Coverage Determination (NCD) and, instead, chose to continue to have local MACs make the coverage decisions on a case-by-case basis. Commenters stated this could result in variability in coverage.

Response: We appreciate the comments. We are not issuing a NCD at this time because the available evidence for gender reassignment surgery provides limited data on specific health outcomes and the characteristics of specific patient populations that might benefit from surgery. In the absence of a NCD, the MAC's use the same statutory authority as NCDs, section 1862(a)(1)(A) of the Social Security Act (the Act). Under section 1862(a)(1)(A) an item or service must be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. While CMS did not have enough evidence to issue a NCD, we believe the MACs will be able to make appropriate coverage decisions on a case-by-case basis taking into account individual characteristics of the Medicare beneficiary.

Comment: Some commenters sought a NCD that would establish guidelines for coverage and include elements such as a prescribed set of surgeries and a shared decision making element.

Response: For the reasons stated above, we are not issuing a NCD at this time and, therefore, are not establishing specific gender reassignment surgery coverage guidelines for the Medicare program. We generally agree that shared decision-making is a fundamental approach to patient-centered health care decisions and strongly encourage providers to use these types of evidence based decision aids. We have not found a shared decision aid on GRS and encourage the development of this necessary element to conduct formal shared-decision making.

Comment: Some commenters expressed concern that there is a misunderstanding of transgender individuals as having a disorder or being abnormal. Some commenters indicated a history of bias and discrimination within society as a whole that has occurred when transgender individuals have sought health care services from the medical community. Some commenters are concerned that the decision not to make a NCD will subject individuals seeking these services to corporate bias by Medicare contractors.

Response: We acknowledge the public comments and that there has been a transformation in the treatment of individuals with gender dysphoria over time. In this NCA, we acknowledge that gender dysphoria is a recognized Diagnostic and Statistical Manual of Mental Disorders (DSM) condition. With respect to the concern about potential bias by Medicare contractors, we have no reason to expect that the judgments made on specific claims will be influenced by an overriding bias, hostility to patients with gender dysphoria, or discrimination. Moreover, the Medicare statue and our regulations provide a mechanism to appeal an adverse initial decision if a claim is denied and those rights may include the opportunity for judicial review. We believe the Medicare appeals process would provide an opportunity to correct any adverse decision that was perceived to have been influenced by bias.

Comment: Commenters mentioned the cost of gender reassignment surgery could influence MAC decision making.

Response: The decisions on whether to cover gender reassignment surgery in a particular case are made on the basis of the statutory language in section 1862 of the Social Security Act that establish exclusions from coverage and

would not depend on the cost of the procedure.

2. Coverage with Evidence Development and Research

Comment: In our proposed decision memorandum, we specifically invited comments on whether a study could be developed that would support coverage with evidence development (CED). One organization commented, "We strongly caution against instituting a CED protocol." Commenters were opposed to coverage limited in clinical trials, suggesting that such coverage would restrict access to care. Several commenters provided suggested topics for clinical research studies for the transgender population. For example, one commenter suggested a study of non-surgical treatment for transgender children prior to puberty.

Response: While we appreciate the comments supporting further research, in general, for gender reassignment surgery, we agree that CED is not the appropriate coverage pathway at this time. While CED is an important mechanism to support research and has the potential to be used to help address gaps in the current evidence, we are not aware of any available, appropriate studies, ongoing or in development, on gender reassignment surgery for individuals with gender dysphoria that could be used to support a CED decision.

3. Gender Reassignment Surgery as Treatment

Comment: One group of commenters requested that CMS consider that, "The established medical consensus is that GRS is a safe, effective, and medically necessary treatment for many individuals with gender dysphoria, and for some individuals with severe dysphoria, it is the only effective treatment."

Response: We acknowledge that GRS may be a reasonable and necessary service for certain beneficiaries with gender dysphoria. The current scientific information is not complete for CMS to make a NCD that identifies the precise patient population for whom the service would be reasonable and necessary.

4. Physician Recommendations

Comment: Several commenters stated that gender reassignment surgery should be covered as long as it was determined to be necessary, or medically necessary by a beneficiary's physician.

Response: Physician recommendation is one of many potential factors that the local MAC may consider when determining whether the documentation is sufficient to pay a claim.

5. WPATH Standards of Care

Comment: Several commenters suggested that CMS should recommend the WPATH Standards of Care (WPATH) as the controlling guideline for gender reassignment surgery. They asserted it could satisfy Medicare's reasonable and necessary criteria for determining coverage on a case-by-case basis.

Response: Based on our review of the evidence and conversations with the experts and patient advocates, we are aware some providers consult the WPATH Standards of Care, while others have created their own criteria and requirements for surgery, which they think best suit the needs of their patients. As such, and given that WPATH acknowledges the guidelines should be flexible, we are not in the position to endorse exclusive use of WPATH for coverage. The MACs, Medicare Advantage plans, and Medicare providers can use clinical guidelines they determine useful to inform their determination of whether an item or service is reasonable and necessary. When making this

determination, local MACs may take into account physician's recommendations, the individual's clinical characteristics, and available clinical evidence relevant to that individual.

6. Scope of the NCA Request

Comment: One commenter stated that CMS did not address the full scope of the NCA request.

Response: The formal request for a NCD is publicly available on our tracking sheet. (https://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id282.pdf) The letter did not explicitly seek a national coverage determination related to counseling or hormone therapies, but focused on surgical remedies. CMS is aware that beneficiaries with gender dysphoria use a variety of therapies.

Comment: Other commenters stated the scope of the proposed decision is unnecessarily broad because it discussed therapies other than surgery. They suggested this discussion could lead to the unintended consequence of restricting access to those services for transgender Medicare beneficiaries and other transgender individuals.

Response: As we noted in our proposed decision, our decision focused only on gender reassignment surgery. In the course of reviewing studies related to those surgeries, occasionally authors discussed other therapies that were mentioned in our summaries of the evidence. To the extent possible, we have modified our decision to eliminate the discussion of other therapies which were not fully evaluated in this NCA.

7. NCA Question

Comment: Some commenters expressed concern about the phrasing of the question in this NCA.

Response: The phrasing of the research question is consistent with most NCAs and we believe it is appropriate.

8. Evidence Summary and Analysis

Comment: Several commenters disagreed with our summary of the clinical evidence and analysis. A few commenters contended that the overall tone of the review was not neutral and seemed biased or flawed. One commenter noted that the Barrett publication was available on the Internet.

Response: We appreciate the comments that identified technical errors, and we made the necessary revisions to this document. However, we disagree with the contention that our evidence review was not neutral and seemed biased or flawed. We believe that the summary and analysis of the clinical evidence are objective. As with previous NCAs, our review of the evidence was rigorous and methodical. Additionally, we reviewed the Barrett publication, but it did not meet our inclusion criteria to be included in the Evidence section.

9. Evidence Review with Transgender Experts

Comment: Several commenters requested that CMS re-review the clinical evidence discussed in the proposed decision memorandum with outside experts in the field of transgender health and transition/gender reassignment-related surgeries. Several offered the expertise within their organization to assist in this effort.

Response: We appreciate these comments and the transgender health community's willingness to participate. For

this NCA we discussed gender reassignment surgery protocols with experts, primarily in coordinated care settings. Additionally, the public comment periods provide opportunities for expert stakeholder input. According to our process for all NCAs, we do not jointly review evidence with external stakeholders but have carefully reviewed the very detailed comments submitted by a number of outside experts in transgender health care.

10. Previous Non-Coverage NCD

Comment: One commenter noted that they thought research studies for gender reassignment surgery could not take place when the old NCD that prohibited coverage for gender reassignment surgery was in effect.

Response: CMS does not directly conduct clinical studies or pay for research grants. Some medical services are non-covered by Medicare; however, national non-coverage does not preclude research via a number of avenues and other funding entities such as the National Institutes of Health. In this instance, the previous NCD did not preclude interested parties from funding research for gender reassignment surgery that could have been generalizable to the Medicare population.

11. How the Medicare Population Differs from the General Population

Comment: One commenter questioned how the Medicare population differed from the general population, and why any differences would be important in our decision-making.

Response: The Medicare population is different from the general population in age (65 years and older) and/or disability as defined by the Social Security Administration. Due to the biology of aging, older adults may respond to health care treatments differently than younger adults. These differences can be due to, for example, multiple health conditions or co-morbidities, longer duration needed for healing, metabolic variances, and impact of reduced mobility. All of these factors can impact health outcomes. The disabled Medicare population, who are younger than age 65, is different from the general population and typical study populations due to the presence of the causes of disability such as psychiatric disorders, musculoskeletal health issues, and cardiovascular issues.

12. Medicare Evidence Development & Coverage Advisory Committee (MEDCAC)

Comment: One commenter suggested CMS should have convened a MEDCAC for this topic.

Response: We appreciate the comment. Given the limited evidence, we did not believe a MEDCAC was warranted according to our guidance document entitled "Factors CMS Considers in Referring Topics to the Medicare Evidence Development & Coverage Advisory Committee" (https://www.cms.gov/Regulations-and-Guidance/Guidance/FACA/MEDCAC.html).

13. §1557 of the Affordable Care Act (ACA)

Comment: Some commenters asserted that by not explicitly covering gender reassignment surgery at the national level, CMS was discriminating against transgender beneficiaries in conflict with Section 1557 of the Accountable Care Act (ACA).

Response: This decision does not affect the independent obligation of covered entities, including the Medicare program and MACs, to comply with Section 1557 in making individual coverage decisions. In accordance with Section 1557, MACs will apply neutral nondiscriminatory criteria when making case-by-case coverage determinations related

to gender reassignment surgery.

14. Medicaid

Comment: Some commenters observed that some states cover gender reassignment surgery through Medicaid or require commercial insurers operating in the state to cover the surgery.

Response: We appreciate the information about Medicaid and state requirements; however, State decisions are separate from Medicare coverage determinations. We make evidence-based determinations based on our statutory standards and processes.

15. Commercial Insurers

Comment: In several instances, commenters told us that the healthcare industry looks to CMS coverage determinations to guide commercial policy coverage.

Response: CMS makes evidence-based national coverage determinations based on our statutory standards and processes as defined in the Social Security Act, which may not be the same standards that are used in commercial insurance policies or by other health care programs. In addition as noted above, the Medicare population is different (e.g., Medicare covers 95% of adults 65 and older) than the typical population under commercial insurers. We do not issue coverage decisions to drive policy for other health organizations' coverage in one way or the other.

16. Healthcare for Transgender Individuals

Comment: Numerous professional associations wrote to CMS to explain their support for access to healthcare for transgender individuals.

Response: CMS recognizes that transgender beneficiaries have specific healthcare needs. Many health care treatments are available. We encourage all beneficiaries to utilize their Medicare benefits to help them achieve their best health.

17. Intended Use of the Decision Memorandum

Comment: Several commenters expressed concern that the analysis provided in the proposed and final decision memorandums may be used by individuals, entities, or payers for purposes unrelated to Medicare such as denial of coverage for transgender-related surgeries.

Response: The purpose of the decision memoranda is to memorialize CMS' analysis of the evidence, provide responses to the public comments received, and to make available the clinical evidence and other data used in making our decision consistent with our obligations under the § 1862 of the Act. The NCD process is open and transparent and our decisions are publicly available. Congress requires that we provide a clear statement of the basis for our determinations. The decision memoranda are an important part of the record of the NCD. Our focus is the Medicare population which, as noted above, is different than the general population in a number of ways. Other entities may conduct separate evidence reviews and analyses that are suited for their specific populations.

18. Cost Barriers to Care and Effects

Comment: A few commenters stated that without Medicare coverage, surgery is difficult to afford and there may be a risk of negative consequences for the individual. One commenter suggested that CMS should consider prior-authorization for these surgeries.

Response: CMS is aware that paying out-of-pocket for medical care is a strain on a beneficiary's finances. We are also aware of beneficiaries' hesitancy to undergo surgery prior to knowing whether or not Medicare will pay the claim. Gender reassignment surgeries are not the only procedures whereby payment is not determined until after the provider submits the claim to Medicare. Importantly, documentation for the claims need to be explicit about what procedures were performed and include the appropriate information in the documentation to justify using the code or codes for surgery. Of note, CMS has claims data that indicate Medicare has paid for gender reassignment surgeries in the recent past. Determining which services are designated for prior-authorization is outside of the scope of the NCA process.

19. Surgical Risks and Benefits

Comment: A number of commenters conveyed the benefits of gender reassignment surgery, while other commenters expressed concern that gender reassignment surgery was harmful.

Response: We appreciate these comments.

20. Expenditure of Federal Funds

Comment: Some commenters opposed spending Medicare program funds on gender reassignment surgery for a variety of reasons. For example, some commenters believe it is an "elective" procedure. Other commenters suggested that funds should first be spent on other priorities such as durable medical equipment (DME) or mobility items such as power chairs; increasing reimbursement to providers; or that spending should be limited to the proportion to the transgender adult population in the Medicare program.

Response: The purpose of this NCA is to determine whether or not CMS should issue a NCD to cover surgery for patients who have gender dysphoria. NCAs do not establish payment amounts or spending priorities and, therefore, these comments are outside the scope of this consideration.

VIII. CMS Analysis

National coverage determinations are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under § 1862(l)(6) of the Act. In general, in order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B and must not be otherwise excluded from coverage.

Moreover, in most circumstances, the item or service must be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member (§1862(a)(1)(A)). The Supreme Court has recognized that "[t]he Secretary's decision as to whether a particular medical service is 'reasonable and necessary' and the means by which she implements her decision, whether by promulgating a generally applicable rule or by allowing individual adjudication, are clearly discretionary decisions." Heckler v. Ringer, 466 U.S. 602, 617 (1984). See also, 78 Fed. Reg. 48,164, 48,165 (August 7, 2013)

When making national coverage determinations, we consider whether the evidence is relevant to the Medicare

beneficiary population. In considering the generalizability of the results of the body of evidence to the Medicare population, we carefully consider the demographic characteristics and comorbidities of study participants as well as the provider training and experience. This section provides an analysis of the evidence, which included the published medical literature and guidelines pertaining to gender dysphoria, that we considered during our review to answer the question:

Is there sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria?

CMS carefully considered all the studies listed in this decision memorandum to determine whether they answered the question posed in this NCA. While there appears to be many publications regarding gender reassignment surgery, it became clear that many of the publications did not meet our inclusion/exclusion criteria as explained earlier in the decision memorandum.

Thirty-three papers were eligible based on our inclusion/exclusion criteria for the subsequent review (Figure 1). All studies reviewed had potential methodological flaws which we describe below.

A. Quality of the Studies Reviewed

Overall, the quality and strength of evidence were low due to mostly observational study designs with no comparison groups, subjective endpoints, potential confounding (a situation where the association between the intervention and outcome is influenced by another factor such as a co-intervention), small sample sizes, lack of validated assessment tools, and considerable lost to follow-up (Appendices C and F). The impact of a specific therapeutic intervention can be difficult to determine when there are multiple serial treatments such as psychotherapy, hormone treatment and surgery. To reduce confounding, outcome assessment just prior to and after surgery such as in a longitudinal study would be helpful. The objective endpoints included psychiatric treatment, attempted suicide, requests for surgical reversal, morbidity (direct and indirect adverse events), and mortality (Appendix F). CMS agrees with the utility of these objective endpoints. Quality of life, while important, is more difficult to measure objectively (Appendix E).

Of the 33 studies reviewed, published results were conflicting – some were positive; others were negative. Collectively, the evidence is inconclusive for the Medicare population. The majority of studies were non-longitudinal, exploratory type studies (i.e., in a preliminary state of investigation or hypothesis generating), or did not include concurrent controls or testing prior to and after surgery. Several reported positive results but the potential issues noted above reduced strength and confidence. After careful assessment, we identified six studies that could provide useful information (Figure 1). Of these, the four best designed and conducted studies that assessed quality of life before and after surgery using validated (albeit non-specific) psychometric studies did not demonstrate clinically significant changes or differences in psychometric test results after GRS. (Heylens et al., 2014; Ruppin, Pfafflin, 2015; Smith et al., 2005; Udeze et al., 2008) (Appendix C Panel A and Appendix G.)

Two studies (three articles) assessed functional endpoints (request for surgical reassignment reversal and morbidity/mortality) (Dhejne et al., 2011; Dhejne et al., 2014 along with Landén et al., 1998) (Figure 1 and Appendix C, Panel A and Appendix G). Although the data are observational, they are robust because the Swedish national database is comprehensive (including all patients for which the government had paid for surgical services) and is notable for uniform criteria to qualify for treatment and financial coverage by the government. Dhejne et al. (2014) and Landén et al. (1998) reported cumulative rates of requests for surgical reassignment reversal or change in legal status of 3.3% while Dhejne et al. (2014) reported 2.2%. The authors indicated that the later updated calculation had the potential to be an underestimate because the most recent surgical cohorts were larger in size and had shorter periods of follow-up.

Dhejne et al., (2011) tracked all patients who had undergone reassignment surgery (mean age 35.1 years) over a 30 year interval and compared them to 6,480 matched controls. The study identified increased mortality and psychiatric hospitalization compared to the matched controls. The mortality was primarily due to completed suicides (19.1-fold greater than in control Swedes), but death due to neoplasm and cardiovascular disease was increased 2 to 2.5 times as well. We note, mortality from this patient population did not become apparent until after 10 years. The risk for psychiatric hospitalization was 2.8 times greater than in controls even after adjustment for prior psychiatric disease (18%). The risk for attempted suicide was greater in male-to-female patients regardless of the gender of the control. Further, we cannot exclude therapeutic interventions as a cause of the observed excess morbidity and mortality. The study, however, was not constructed to assess the impact of gender reassignment surgery *per se.*

We believe at minimum study designs should have a pre-test/post-test longitudinal design accompanied by characterization of all patients lost to follow-up over the entire treatment series as well as those patients who did not complete questionnaires, and the use of psychometric quality-of-life tools which are well validated with linkage to "hard" (objective) patient outcomes in this particular patient population (Trentacosti 2007, PRO 2009) (Appendices C and D).

Patient Care

Clinical evidentiary questions regarding the care of patients with gender dysphoria remain. Many of the publications focused on aspects of surgical technique as opposed to long-term patient outcomes. The specific type(s) of gender/sex reassignment surgery (e.g., genital, non-genital) that could improve health outcomes in adults remain(s) uncertain because most studies included patients who had undertaken one or more of a spectrum of surgical procedures or did not define the specific types of surgical procedures under study. Furthermore, surgical techniques have changed significantly over the last 60 years and may not reflect current practice (Bjerrome Ahlin et al., 2014; Doornaert, 2011; Green, 1998; Pauly, 1968; Selvaggi et al., 2007; Selvaggi, Bellringer, 2011; Tugnet et al., 2007; Doornaert, 2011).

The WPATH care recommendations present a general framework and guidance on the care of the transgender individual. The standards of care are often cited by entities that perform gender reassignment surgery. WPATH notes, "More studies are needed that focus on the outcomes of current assessment and treatment approaches for gender dysphoria." Appendix D in the WPATH Standards of Care briefly describes their evidence base and acknowledges the historical problems with evidentiary standards, the preponderance of retrospective data, and the confounding impact of multiple interventions, specifically distinguishing the impact of hormone therapy from surgical intervention.

Additionally, CMS met with several stakeholders and conducted several interviews with centers that focus on healthcare for transgender individuals in the U.S. Primary care rather than gender reassignment surgery was often the main focus. Few of the U.S.-based reassignment surgeons we could identify work as part of an integrated practice, and few provide the most complex procedures.

Psychometric Tools

CMS reviewed psychometric endpoints because gender dysphoria (inclusive of prior nomenclature) describes an incongruence between the gender assigned at birth and the gender(s) with which the person identifies.

The psychometric tools used to assess outcomes have limitations. Most instruments that were specific for gender dysphoria were designed by the investigators themselves or by other investigators within the field using limited populations and lacked well documented test characterization. (Appendices E and F) By contrast, test instruments with validation in large populations were non-specific and lacked validation in the gender dysphoric patient populations. (Appendices E and F). In addition, the presentation of psychometric results must be accompanied by

enough information about the test itself to permit adequate interpretation of test results. The relevant diagnostic cut-points for scores and changes in scores that are clinically significant should also be scientifically delineated for interpretation.

Generalizability

It is difficult to generalize these study results to the current Medicare population. Many of the studies are old given they were conducted more than 10 years ago. Most of these studies were conducted outside of the U.S. in very different medical systems for treatment and follow-up. Many of the programs were single-site centers without replication elsewhere. The study populations were young and without significant physical or psychiatric co-morbidity (Appendix D). As noted earlier, psychiatric co-morbidity may portend poor outcomes (Asscheman et al., 2011; Landén et al., 1998).

Knowledge Gaps

This patient population faces complex and unique challenges. The medical science in this area is evolving. This review has identified gaps in the evidentiary base as well as recommendations for good study designs. The Institute of Medicine, the National Institutes of Health, and others also identified many of the gaps in the data. (Boehmer, 2002; HHS-HP, 2011; IOM, 2011; Kreukels-ENIGI, 2012; Lancet, 2011; Murad et al., 2010; NIH-LGBT, 2013) The current or completed studies listed in ClinicalTrials.gov are not structured to assess these gaps. These gaps have been delineated as they represent areas in which patient care can be optimized and are opportunities for much needed research.

B. Health Disparities

Four studies included information on racial or ethnic background. The participants in the three U.S. based studies were predominantly Caucasian (Beatrice, 1985; Meyer, Reter, 1979; Newfield et al., 2006). All of the participants in the single Asian study were Chinese (Tsoi, 1993). Additional research is needed in this area.

C. Summary

Based on an extensive assessment of the clinical evidence as described above, there is not enough high quality evidence to determine whether gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria and whether patients most likely to benefit from these types of surgical intervention can be identified prospectively.

The knowledge on gender reassignment surgery for individuals with gender dysphoria is evolving. Much of the available research has been conducted in highly vetted patients at select care programs integrating psychotherapy, endocrinology, and various surgical disciplines. Additional research of contemporary practice is needed. To assess long-term quality of life and other psychometric outcomes, it will be necessary to develop and validate standardized psychometric tools in patients with gender dysphoria. Further, patient preference is an important aspect of any treatment. As study designs are completed, it is important to include patient-centered outcomes.

Because CMS is mindful of the unique and complex needs of this patient population and because CMS seeks sound data to guide proper care of the Medicare subset of this patient population, CMS strongly encourages robust clinical studies with adequate patient protections that will fill the evidence gaps delineated in this decision memorandum. As the Institute of Medicine (IOM, 2011) importantly noted: "Best practices for research on the health status of LGBT populations include scientific rigor and respectful involvement of individuals who represent the target population.

Scientific rigor includes incorporating and monitoring culturally competent study designs, such as the use of appropriate measures to identify participants and implementation processes adapted to the unique characteristics of the target population. Respectful involvement refers to the involvement of LGBT individuals and those who represent the larger LGBT community in the research process, from design through data collection to dissemination."

IX. Decision

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on a case-by-case basis. We have a received a complete, formal request to make a national coverage determination on surgical remedies for gender identity disorder (GID), now known as gender dysphoria. The Centers for Medicare & Medicaid Services (CMS) is not issuing a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria because the clinical evidence is inconclusive for the Medicare population.

In the absence of a NCD, coverage determinations for gender reassignment surgery, under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements, will continue to be made by the local MACs on a case-by-case basis. To clarify further, the result of this decision is not national non-coverage rather it is that no national policy will be put in place for the Medicare program. In the absence of a national policy, MACs will make the determination on whether or not to cover gender reassignment surgery based on whether gender reassignment surgery is reasonable and necessary for the individual beneficiary after considering the individual's specific circumstances. For Medicare beneficiaries enrolled in Medicare Advantage (MA) plans, the initial determination of whether or not surgery would be reasonable and necessary will be made by the MA plans.

Consistent with the request CMS received, the focus of this National Coverage Analysis (NCA) was gender reassignment surgery. Specific types of surgeries were not individually assessed. We did not analyze the clinical evidence for counseling or hormone therapy treatments for gender dysphoria. As requested by several public commenters, we have modified our final decision memorandum to remove language that was beyond the scope of the specific request. We are not making a national coverage determination relating to counseling, hormone therapy treatments, or any other potential treatment for gender dysphoria.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

A. Appendix A

Diagnostic & Statistical Manual of Mental Disorders (DSM) Criteria for Disorders of Gender Identity since 1980

DSM Version	Condition Name	Criteria	Criteria	Comments
DSM III 1980 *Chapter: Psychosexual Disorders*	**Trans-sexualism** *302.5x [Gender Identity Disorder of*	Required A (cross-gender identification) and B (aversion to one's natal	Sense of discomfort and inappropriateness about one's anatomic sex. Wish to be rid of one's own genitals and to live as a member of the other sex. The	Further characterization by sexual orientation Distinguished from Atypical Gender

	Child-hood (302.6)]	gender) criteria Dx excluded by physical intersex condition Dx excluded by another mental disorder, e.g., schizophrenia	disturbance has been continuous (not limited to periods of stress) for at least 2 years.	Identity Disorder 302.85
DSM III-Revised 1987 *TS classified as an Axis II dx (personality disorders and mental retardation) in a different chapter. GID included under Disorders Usually First Evident in Infancy, Childhood, Adolescence*	**Trans-sexualism** *(TS) (302.50) [GID of C]*	Required A and B criteria	Persistent discomfort and sense of inappropriateness about one's assigned sex. Persistent preoccupation for at least 2 years with getting rid of one's 1^{o} and 2^{o} sex characteristics and acquiring the sex characteristics of the other sex. Has reached puberty	Further characterization by sexual orientation Distinguished from Gender Identity Disorder of Adolescence or Adulthood, Non-trans-sexual Type • e.g., cross-dressing not for the purposes of sexual excitement Gender Identity Disorder Not Otherwise Specified 302.6 • e.g., intersex conditions Gender Identity Disorder Not Otherwise Specified 302.85 • e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex
	GID of adulthood, non-trans-sexual type, added			
DSM IV 1994 *Chapter: Sexual & Gender Identity Disorders*	**Gender Identity Disorder** in Adolescents and Adults (302.85) (Separate criteria & code for children, but	Required A and B criteria Dx excluded by physical intersex condition	Cross-gender identification • e.g., Stated desire to be another sex • e.g., Desire to live or be treated as a member of the other sex • e.g., conviction that he/she has the typical feelings and reactions of the other sex	Further characterization by sexual orientation Distinguished from Gender Identity Disorder Not Otherwise Specified 302.6 • e.g., intersex

	same name)		• e.g., frequent passing as the other sex Persistent discomfort with his/her sex or sense of inappropriateness in the gender role of that sex. • e.g., belief the he/she was born the wrong sex • e.g., preoccupation with getting rid of 1^{o} and 2^{o} sex characteristics &/or acquiring sexual traits of the other sex • Clinically significant distress or impairment in social, occupational, or other important areas of functioning	conditions • e.g., stress related cross-dressing • e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex
DSM IV-Revised 2000 *Chapter: Sexual & Gender Identity Disorders*	**Gender Identity Disorder** (Term trans-sexual-ism eliminated)	Required A & B criteria Dx excluded by physical intersex condition	Cross-gender identification • e.g., stated desire to be the other sex • e.g., desire to live or be treated as the other sex • e.g., conviction that he/she has the typical feelings & reactions of the other sex • e.g., frequent passing as the other sex Persistent discomfort with his or her sex OR sense of inappropriateness in the gender role of that sex • e.g., belief the he/she was born the wrong sex • e.g., preoccupation with getting rid of 1^{o} and 2^{o} sex characteristics &/or acquiring sexual traits of the other sex Clinically significant distress or impairment in social, occupational, or other important areas of functioning	Outcome may depend on time of onset Further characterization by sexual orientation Distinguished from Gender Identity Disorder Not Otherwise Specified 302.6 • e.g., intersex conditions • e.g., stress related cross-dressing • e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex
DSM V 2013 *Separate Chapter from Sexual Dysfunctions & Paraphilic Disorders*	**Gender Dysphoria** *(302.85)*	Gender nonconformity itself not considered to be a mental disorder The dysphoria associated with the gender incongruence is Eliminates A & B criteria	• Marked discordance between natal 1^{o} and 2^{o} sex characteristics* and experienced/expressed gender • Conviction that he/she has the typical feelings & reactions of the other sex (or some alternative gender) • Marked desire to be the other sex (or some alternative gender) • Marked desire to desire be treated as the other sex (or some alternative gender)	Includes diagnosis for post transition state to permit continued treatment access Includes disorders of sexual development such as congenital hyperplasia and androgen insensitivity

		Considers gender incongruence to be a spectrum Considers intersex/ "disorders of sex development" to be a subsidiary and not exclusionary to dx of GD	• Marked desire to be rid of natal 1^{O} and 2^{O} sex characteristics** • Marked desire to acquire 1^{O} and 2^{O} sex characteristics of the other sex (or some alternative gender) Clinically significant distress or impairment in social, occupational, or other important areas of functioning * or in young adolescents, the anticipated 2^{O} sex characteristics ** or in young adolescents, prevent the development of the anticipated 2^{O} sex characteristics ≥ 6 month marked discordance between natal gender & experienced/expressed gender as demonstrated by ≥ 6 criteria: • Strong desire to be of the other gender or an insistence that one is of another gender. • Strong preference for cross-gender roles in make-believe play. • Strong preference for the toys, games, or activities of the other gender. • Strong preference for playmates of the other gender. • In boys, strong preference for cross-dressing; in girls, strong preference for wearing masculine clothing • In boys, rejection of masculine toys, games, activities, avoidance of rough and tumble play; in girls, rejection of feminine toys, games, and activities.	syndromes
	Unspecified Gender Dysphoria (302.6) (F64.9)		This category applies to presentations in which sx c/w gender dysphoria that cause clinically significant distress or impairment, but do not meet the full criteria for gender dysphoria & the reason for not meeting the criteria is not provided.	
	Specified Gender Dysphoria 302.6 (F64.8)		If the reason that the presentation does not meet the full criteria is provided then this dx should be used	

C/W=consistent with Dx=diagnosis GD=gender dysphoria Sx=symptoms TS=transsexual 1^{O}=primary 2^{O}=secondary

B. Appendix B

1. General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).

- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well-designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

Randomized controlled trials
Non-randomized controlled trials
Prospective cohort studies
Retrospective case control studies
Cross-sectional studies
Surveillance studies (e.g., using registries or surveys)
Consecutive case series
Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

Appendix C

Patient Population: Enrolled & Treated with Sex Reassignment Surgery Loss of Patients & Missing Data

Panel A (Controlled Studies)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Dhejne 2011	Longitudinal Controlled	804 w GD	324	324 (100%)	-
Dhejne 2014 Landén	Longitudinal for test variable Controlled	767 applied for SRS 25 applications denied. 61 not granted full legal status	681	681 (100%)	NA: Clinical data extracted retrospectively in earlier paper

		15 formal applications for surgical reversal			
Heylens	Longitudinal Controlled	90 applicants for SRS 33 excluded 11 later excluded had not yet received SRS by study close.	57 (→46)	46 (80.7%) Only those w SRS evaluated	Psycho-social survey missing data for 3 at baseline & 4 after SRS. SCL90 not completed by 1 at baseline, 10 after hormone tx, & 4 after SRS →missing data for another 1.1% to 11.1%.
Kockott	Longitudinal Controlled	80 applicants for SRS 21 excluded	59	32 (54.2%) went to surgery	1 preoperative patient was later excluded b/c lived completely in aspired gender w/o SRS. Questions on financial sufficiency not answered by 1 surgical pt. Questions on sexual satisfaction & gender contentment not answered by 1 & 2 patients awaiting surgery respectively.
Mate-Kole 1990	Longitudinal Controlled	40 sequential patients of accepted patients. The number in the available patient pool was not specified.	40	20 (50%) went to surgery	-
Meyer	Longitudinal Controlled	Recruitment pool: 100 50 were excluded.	50	15 (30%) had undergone surgery 14 (28%) underwent surgery later	The assessments of all were complete
Rakic	Longitudinal Controlled	92 were evaluated 54 were excluded from surgery 2 post SRS were lost to follow-up 2 post SRS were excluded for being in the peri-operative period	32	32 (100%)	Questionnaire completed by all.
Ruppin	Longitudinal Controlled	The number in the available patient pool was not specified. 140 received recruitment letters. 69 were excluded	71	69 (97.2%)	The SCL-90, BSRI, FPI-R, & IPP tests were not completed by 9, 34, 13, &16 respectively. Questions about romantic relationships, sexual relationships, friendships, & family relationships were not answered by 1, 3, 2, & 23 respectively.

					Questions regarding gender security & regret & were not answered by 1& 2 respectively.
Smith	Longitudinal Controlled	The number in the available adult patient pool was not specified. 325 adult & adolescent applicants for SRS were recruited. 103 were excluded from additional tx	162	162 (100%)	36 to 61 (22.2%-37.6% of those adults w pre-SRS data) did not complete various post-SRS tests.
Udeze Megeri	Longitudinal Controlled	International patient w GD 546 & post SRS 318. 40 M to F subjects were prospectively selected.	40	40 (100%)	-
Ainsworth	Internet/convention Survey Cross-sectional Controlled	Number of incomplete questionnaires not reported	247	72 (29.1%) 75 (30.6%) facial 147 (59.5%) had received neither facial nor reassignment surgery	-
Beatrice	Cross-sectional Controlled	14 excluded for demographic matching reasons	40	10 (25%)	The assessments were completed by all
Haraldsen	Cross-sectional Controlled	Recruitment pool: 99	86	59 (68.6%)	-
Kraemer	Cross-sectional Controlled	The number in the available patient pool was not specified.	45	22 (48.9%)	-
Kuhn	Cross-sectional Controlled	The number in the available patient pool was not specified.	75	55 (73.3%)	-
Mate-Kole 1988	Cross-sectional Controlled	150 in 3 cohorts. Matched on select traits. The number in the available patient pool was not specified.	150	50 (66.7%)	-
Wolfradt	Cross-sectional Controlled	The number in the available patient pool was not specified.	90	30 (33.3%)	-

Panel B (Surgical Series: No Concurrent Controls)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Blanchard	Cross-sectional	294 clinic patients w GD	79	79(100%)	-

et al.	Control: Normative test data	had completed study questionnaire 116 authorized for GRS. 103 completed GRS & 1 yr post-operative. 24 excluded			
Weyers et al.	Cross-sectional Control: Normative test data	>300 M to F patients had undergone GRS 70 eligible patients recruited 20 excluded	50	50 (100%)	SF-26 not completed by 1
Wierckx et al.	Cross-sectional except for recall questions Control: Normative test data	79 F to M patients had undergone GRS & were recruited. 3 additional non-clinic patients were recruited by other patients. 32 excluded initially; 1 later.	49	49 (100%)	SF-36 test not completed by 2. Questions regarding sexual re-lationship, sex function, & surgical satisfaction were answered by as few as 27, 28, 32 respectively.
Eldh et al.	Cross-sectional except for 1 variable Control: Self for 1 variable-employ-ment	136 were identified. 46 excluded	90	90 (100%)	Questions regarding gender iden-tity, sex life, acceptance, & overall satisfaction were not answered by 13, 14, 14 & 16 respectively. Employment data missing for 11.
Hess et al.	Cross-sectional No control	254 consecutive eligible patients post GRS identified & sent surveys. 135 excluded.	119	119 (100%)	Questions regarding the esthetics, functional, and social outcomes of GRS were not answered by 16 to 28 patients.
Lawrence	Cross-sectional No control	727 eligible patients were recruited. 495 were excluded	232	232 (100%)	-
Salvador et al.	Cross-sectional No control	243 had enrolled in the clinic 82 completed GRS 69 eligible patients were identified. 17 excluded.	52	52 (100%)	-
Tsoi	Cross-sectional No control	The number in the available patient pool was not specified.	81	81 (100%)	-

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Gómez-Gil et al. 2012	Cross-sectional No direct control: Analysis of variance	200 consecutive patients were recruited.	187	79 (42.2%)	See prior box.

		13 declined participation or were excluded for incomplete questionnaires.			
Hepp et al.	Cross-sectional No direct control: Analysis of variance	The number in the available patient pool was not specified.	31	7 (22.6%)	HADS test not completed by 1
Motmans et al.	Cross-sectional No direct control: Analysis of variance & regression	255 with GD were identified. 77 were excluded.	148 (→140)	Not clearly stated. At least 103 underwent some form of GRS.	8 later excluded for incomplete SF-36 tests. 37 w recent GRS or hormone initiation were excluded from analysis of SF-36 results→103.
Newfield et al.	Internet survey Cross-sectional No direct control: Analysis of variance	Number of incomplete questionnaires not reported 446 respondents; 384 U.S respondents 62 non-U.S. respondents excluded from SF-36 test results 8 U.S. respondents excluded	376 (U.S.)	139 to 150 (37.0-39.9%) in U.S.	-
Gomez-Gil et al. 2014	Cross-sectional No direct control: Analysis w regression	The number in the available patient pool was not specified. 277 were recruited. 25 excluded	252(→193)	80 (41.4%) non-genital surgery	59 were excluded for incomplete questionnaires. See prior box.
Asscherman	Longitudinal No analysis by tx status	The number in the available patient pool was not specified.	1331	1177 (88.4%)	-
Johansson et al.	Cross-sectional except for 1 variable No analysis by tx status except for 1 question	60 eligible patients 18 excluded.	42	32 (76.2% of enrolled & 53.3% of eligible) (genital surgery)	-
Leinung et al.	Cross-sectional No analysis by tx status	242 total clinic patients	242	91 (37.6%)	Employment status data missing for 81 of all patients

*Data obtained via a survey on a website and distributed at a conference
B/C=because
BSRI=Bem Sex Role Inventory
F=Female
FP-R=Freiberg Personality Inventory
GD=Gender dysphoria
GID=Gender identity disorder
HADS=Hospital Anxiety & Depression Scale

IPP=Inventory of Interpersonal Problems
M=Male
NA=Not applicable
SCL-90=Symptom Checklist-90
SF-36=Short Form 36
GRS=Sex reassignment surgery
Tx=Treatment
W/o=without

Appendix D

Demographic Features of Study Populations

Panel A (Controlled Studies)

Author	Age (years; mean, S.D., range)	Gender	Race
Ainsworth	Only reassignment surgery:50 (no S.D.) Only facial surgery: 51 (no S.D.) Both types of surgery: 49 (no S.D.) Neither surgery: 46 (no S.D.)	247 M to F	-
Beatrice	Pre-SRS M to F: 32.5 (27-42), Post-SRS: 35.1 (30-43)	20 M to F plus 20 M controls	100% Caucasian
Dehjne 2011	Post-SRS: all 35.1±9.7 (20-69), F to M 33.3+8.7 (20–62), M to F 36.3+ 10.1(21–69)	133 (41.0%) F to M, 191 (59.0%) M to F; ratio 1:1.4	-
Dhejne 2014 Landén	F to M SRS cohort: median age 27 M to F SRS cohort: median age 32 F to M applicants for reversal: median age 22 M to F applicants for reversal: median age 35	767 applicants for legal/surgical reassignment 289 (37.7%) F to M, 478 (62.3%) M to F; ratio 1:1.6 681 post SRS & legal change 252 (37.0%) F to M, 429 (63.0%) M to F; ratio 1:1.7 15 applicants for reversal 5 (33.3%) F to M, 10 (66.7%) M to F; ratio 1:2	-
Haraldsen	Pre-SRS & Post-SRS: F to M 34±9.5, F to M 33.3±10.0 Post-SRS cohort reportedly older. No direct data provided.	Pre & Post SRS 35 (40.7%) F to M, 51 (59.3%) M to F; ratio 1:1.5	-
Heylens	-	11 (19.3% of 57) F to M, 46 (80.7%); ratio 1:4.2 (80.7% underwent surgery)	-
Kockott	Pre-SRS (continued wish for surgery): 31.7±10.2 Post-SRS: 35.5±13.1	Pre-SRS (continued wish for surgery) 3 (25%) F to M, 9 (75%) M to F; ratio 1:3 Post SRS: 14 (43.8%) F to M, 18 (56.2%) M to F; ratio 1:1.3	-
Kraemer	Pre-SRS: 33.0±11.3, Post-SRS: 38.2±9.0	Pre-SRS 7 F to M (30.4%), 16 M to F (69.6%); ratio 1:2.3 Post-SRS 8 F to M (36.4%), 14 M to F	-

		(63.6%); ratio 1:1.8	
Kuhn	All post SRS: median (range): 51 (39-62) (long-term follow-up)	3 (5.4%) F to M, 52 (94.5%) M to F; ratio 1:17.3.	-
Mate-Kole 1988	Initial evaluation: 34, Pre-SRS: 35, Post-SRS: 37	150 M to F	-
Mate-Kole 1990	Early & Usual wait SRS: 32.5 years (21-53)	40 M to F	-
Meyer	Pre-SRS: 26.7 Delayed, but completed SRS: 30.9 Post-SRS: 30.1	Pre-SRS: 5 (23.8%) F to M, 16 (76.2%) M to F; ratio 1:3.2 Delayed, but completed SRS: 1 (7.1%) F to M, 13 (92.9%) M to F; ratio 1:13 Post-SRS: 4 (26.7%) F to M, 11 (73.3%) M to F; ratio 1:2.8	86% Caucasian
Rakic	All: 26.8±6.9 (median 25.5, range 19-47), F to M: 27.8±5.2 (median 27, range 23-37), M to F: 26.4±7.8 (median 24, range 19-47).	10 (31.2%) F to M, 22 (68.8%) M to F; ratio 1:2.2	-
Ruppin	All: 47.0±10.42 (but 2 w/o SRS) (13.8±2.8 yrs post legal name change) (long-term follow-up) F to M: 41.2±5.78, M to F 52.9±10.82	36 (50.7%) F to M, 35 (49.3%) M to F; ratio 1:0.97	-
Smith	Time of surgical request for post-SRS: 30.9 (range 17.7-68.1) Time of follow-up for post-SRS: 35.2 (range 21.3-71.9)	Pre-SRS: 162: 58 (35.8%) F to M, 104 [64.2%] M to F; ratio 1:1.8 Post-SRS: 126: 49 (38.9%) F to M, 77 (61.1%) M to F; ratio 1:1.6	-
Udeze Megeri	M to F: 47.33±13.26 (range 25-80).	40 M to F	-
Wolfradt	Patients & controls: 43 (range 29-67).	30 M to F plus 30 F controls plus 30 M controls.	-

*Data obtained via a survey on a website and distributed at a conference SD=Standard deviation

Panel B (Surgical Series: No Concurrent Controls)

Author	Age (years; mean, S.D., range)	Gender	Caucasian
Blanchard et al.	F to M: 32.6, M to F w M partner preference: 33.2, F to M w F partner preference: 47.7 years	Post-GRS: 47 (45.6%) F to M, 56 (54.4%) M to F; ratio 1:1.19. In study: 38 (48.1%) F to M, 32 (40.5%) M to F w M partner preference, 9 (11.4%) M to F w F partner preference; ratio 1:0.8: 0.2	-
Weyers et al.	Post-GRS M to F: 43.1 ±10.4 (long-term follow-up)	50 M to F	-
Wierckx et al.	Time of GRS: 30±8.2 years (range 16 to 49) Time of follow-up: 37.1 ±8.2.4 years (range 22 to 54)	49 M to F	-
Eldh et al.	-	50 (55.6%) F to M, 40 (44.4%) M to F; ratio 1:0.8 There is 1 inconsistency in the text	-

		suggesting that these should be reversed.	
Hess et al.	-	119 M to F	-
Lawrence	Time of GRS: 44±9 (range 18-70)	232 M to F	-
Salvador et al.	Time of follow-up for post-GRS: 36.28±8.94 (range 18-58) (Duration of follow-up: 3.8±1.7 [2-7])	52 M to F	-
Tsoi	Time of initial visit: All: 24.0±4.5, F to M: 25.4±4.4 (14-36), M to F: 22.9±4.6 (14-36). Time of GRS: All: 25.9±4.14, F to M: 27.4±4.0 (20-36), M to F: 24.7+4.3 (20-36).	36 (44.4%) F to M, 45 (55.6%) M to F; ratio 1:1.25	0% 100% Asian

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	Age (years; mean, S.D., range)	Gender	Caucasian
Gómez-Gil et al. 2012	W & W/O GRS: All: 29.87±9.15 (range 15-61), W/O hormone tx: 25.9±7.5, W current hormone tx: 33.6±9.1. (At hormone initiation: 24.6±8.1).	W/O hormone tx: 38 (56.7%) F to M, 29 (43.3%) M to F; ratio 1:0.8. W hormone tx: 36 (30.0%) F to M, 84 (70.0%) M to F; ratio 1:2.3. Post-GRS: 29 (36.7%) F to M, 50 (63.3%) M to F; ratio 1:1.7.	-
Hepp et al.	W & W/O GRS: 32.2±10.3	W & W/O GRS: 11 (35.5%) F to M; 20 (64.5%) M to F; ratio 1:1.8.	-
Motmans et al.	W & W/O GRS: All (n=140) : 39.9±10.2, F to M: 37.0±8.5, M to F: 42.3±10.4	W & W/O GRS: N=140 63(45.0%) F to M, 77 (55.0%) M to F; ratio 1:1.2 N=103 49 (47.6%) F to M; 54 (52.4%) M toF; ratio 1:1.1	-
Newfield et al.	W & W/O GRS: U.S.+ non-U.S. : 32.8±11.2, U.S. 32.6±10.8	W & W/O GRS: U.S.+ non-U.S.: F to M, 438, U.S.: F to M: 376	89% of 336 respondents Caucasian
Gomez-Gil, et al. 2014	W & W/O Non-genital GRS: 31.2±9.9 (range 16-67).	W & W/O Non-genital GRS: 74 (38.3%) F to M, 119 (61.7%) M to F; ratio1:1.6.	-
Asscherman	Time of hormone tx: F to M: 26.1±7.6 (16–56), M to F: 31.4±11.4 (16–76)	Met hormone tx requirements: 365 (27.4%) F to M, 966 (72.6%) M to F; ratio 1:2.6. Post-GRS: 343 (29.1%) F to M, 834 (70.9%) M to F; ratio 1:2.4.	-
Johanssen	Time of initial evaluation: F toM: 27.8 (18-46), M to F 37.3 (21-60). Time of GRS: F to M: 31.4 (22-49), M to F 38.2 (22-57). Time of follow-up for post-GRS: F to M: 38.9 (28-53), M to F 46.0 (25-69) (Long-term follow-up)	Approved for GRS: 21 (35%) F to M, 39 (65%) M to F; ratio 1:1.9) Post GRS: 14 (43.8%) F to M; 18 (56.2%) M to F; ratio 1:1.3)	-
Leinung et al.	Time of hormone initiation : F to M: 27.5, M to F 35.5	W & W/O GRS: 50 (20.7%) F to M, 192 M to F (79.3%); ratio 1:3.8. Post-GRS: 32 F to M (35.2%); 59 (64.8%) M to F; ratio 1:1.8.	-

Appendix E

Psychometric and Satisfaction Survey Instruments

Instrument Name and Developer	Development and Validation Information
APGAR Family Adaptability, Partner-ship Growth, Affection, and Resolve *Smilkstein*	Published in 1978 Initial data: 152 families in the U.S. A "friends" component was added in 1983. Utility has challenged by many including Gardner 2001
Beck Depression Inventory *Beck, Ward, Mendelson, Mock, & Erbaugh*	Published initially in 1961 with subsequent revisions It was initially evaluated in psychiatric patients in the U.S.A. Salkind (1969) evaluated its use in 80 general outpatients in the UK. Itis copyrighted and requires a fee for use
Bem Sex Role Inventory *Bem*	Published 1974 Initial data: 100 Stanford Undergraduates 1973 update: male 444; female 279 1978 update: 470; female 340
Body Image Questionnaire *Clement & Lowe*	Validity study published 1996 (German) Population: 405 psychosomatic patients, 141 medical students, 208 sports students
Body Image Scale *Lindgren & Pauly (Kuiper, Dutch adaptation 1991)*	1975 Initial data: 16 male and 16 female transsexual patients in Oregon
Crown Crisp Experiential Index (formerly Middlesex Hospital Questionnaire) *Crown & Crisp*	Developed circa 1966 Manual published 1970 Initial data: 52 nursing students while in class in the UK
(2nd) European Quality of Life Survey *Anderson, Mikuliç, Vermeylen, Lyly-Yrjanainen, & Zigante,*	Published in 2007 The pilot survey was tested in the UK and Holland with 200 interviews. The survey was revised especially for non-response questions. Another version was tested in 25 persons of each of the 31 countries to be surveyed. Sampling methods were devised. 35,634 Europeans were ultimately surveyed. Additional updates
Female Sexual Function Index *Rosen, Brown, Heiman, Leiblum, Meston, Shabsigh, Ferguson, D'Agostino Wiegel, Meston, & Rosen*	Published in 2000 Initial data: 131 normal controls & 128 age-matched subjects with female sexual arousal disorder from 5 U.S. research centers. Updated 2005: the addition of those with hypoactive sexual desire disorder, female sexual orgasm disorder, dyspareunia/vaginismus, & multiple sexual dysfunctions (n=568), plus more controls (n=261).

Fragebogen zur Beurteilung des eigenen Korpers *Strauss*	Published 1996 (German)
Freiberg Personality Inventory *Fahrenberg, Hampel, & Selg*	7th edition published 2001, 8th edition in 2009 (Not in PubMed) German equivalent of MMPI
"gender identity disorder in childhood" *Smith, van Goozen, Kuiper, & Cohen-Kettenis*	11 items derived from the Biographical Questionnaire for Trans-sexuals (Verschoor Poortinga 1988) (Modified by authors of the Smith study)
Gender Identity Trait Scale *Altstotter-Gleich*	Published 1989 (German)
General Health Questionnaire *Goldberg & Blackwell (initial study)* *Goldberg & Williams (manual)*	Initial publication 1970 Manual published ?1978, 1988 (Not in PubMed) Initial data: 553 consecutive adult patients in a single UK primary care practice were assessed. Sample of 200 underwent standardized psychiatric interview. Developed to screen for hidden psychological morbidity. Proprietary test. Now 4 versions.
Hospital Anxiety & Depression Scale *Zigmond & Snaith*	Published in 1983 Initial data: Patients between 16 & 65 in outpatient clinics in the UK >100 patients; 2 refusals. 1st 50 compared to 2nd 50.
Inventory of Interpersonal Problems *Horowitz*	Published 1988 Initial data: 103 patients about to undergo psychotherapy; some patients post psycho-therapy (Kaiser Permanente-San Francisco) Proprietary test
King's Health Questionnaire *Kelleher, Cardozo, Khullar, & Salvatore*	1997 Initial data: 293 consecutive women referred for urinary incontinence evaluation in London Comparison to SF-36
Minnesota Multi-phasic Personality Inventory *Hathaway & McKinley* *Butcher, Dahlstrom, Graham, & Tellegen*	Published in 1941 Updated in 1989 with new, larger, more diverse sample. MMPI-2: 1,138 men & 462 women from diverse communities & several geographic regions in the U.S.A. The test is copyrighted.
Modified Androphia-Gynephilia Index	Neither the underlying version or the Blanchard modified version could be located in PubMed (Designed by the author of the Blanchard et al. study)
"post-operative functioning 13 items" *Doorn, Kuiper, Verschoor, Cohen-Kettenis*	Published 1996 (Dutch) (Not in PubMed) (Designed by 1 of the authors of the Smith study)
"post-operative functioning 21 items" *Doorn, Kuiper, Verschoor,*	Published 1996 (Dutch) (Not in PubMed) (Designed by 1 of the authors of the Smith study)

Cohen-Kettenis	
Scale for Depersonalization Experiences *Wolfradt*	Unpublished manuscript 1998 (University of Halle) (Designed by 1 of the authors of the Wolfradt study)
"sex trait function" *Cohen-Kettenis & van Goozen*	Published 1997 Assessed in 22 adolescents (Designed by 1 of the authors of the Smith Study)
Self-Esteem Scale *Rosenberg*	Published 1965 (Not in PubMed) Initial data: 5,024 high-school juniors & seniors from 10 randomly selected New York schools
Short-Form 36 *RAND* *Ware & Sherbourne1992* *McHorney, Ware, & Raczek 1993*	Originally derived from the Rand Medical Outcomes Study (n=2471 in version 1; 6742 in version 2 1989). The earliest test version is free. Alternative scoring has been developed. There is a commercial version with a manual.
Social Anxiety & Distress Scale *Watson & Friend*	Initial publication in1969 Requires permission for use
Social Support Scale *Van Tilburg 1988*	Published 1988 (Dutch) (Not in PubMed)
Spielberger State & Trait Anxiety Questionnaire *Spielberger, Gorsuch, Lushene, Vagg, & Jacobs*	Current format published in 1983 Proprietary test
Symptom Checklist-90 *Derogatis, Lipman, Covi Derogatis & Cleary*	Published in 1973 & 1977 Reportedly with normative data for psychiatric patients (in- & out-patient) & normal subjects in the U.S. Has undergone a revision Requires qualification for use
Tennessee Self-Concept Scale *Fitts & Warren*	In use prior to 1988 publication. Initial data: 131 psychiatric day care patients. Updated manual published 1996. Update population >3000 with age stratification. No other innformation available. Requires qualification for use
Utrecht Gender Dysphoria Scale *Cohen-Kettenis & van Goozen*	Published in 1997 Initial population: 22 transgender adolescents who underwent reassignment surgery. (Designed by 1 of the authors of the Smith study)
WHO-Quality of Life (abbreviated version) *Harper for WHO group*	Field trial version released 1996 Tested in multiple countries. The Seattle site consisted of 192 of the 8294 subjects tested). Population not otherwise described. The minimal clinically important difference has not been determined. Permission required

Althof et al., 1983; Greenberg, Frank, 1965; Gurtman, 1996; Lang, Vernon, 1977; Paap et al., 2012; Salkind et al., 1969; Vacchiano, Strauss, 1968.

Appendix F

Endpoint Data Types and Sources

Panel A (Controlled Studies)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substan-tive &/or Accessible Normative Data	Investigator-designed	Other	Other
Dhejne 2011	Yes	-	-	-	-	Mortality (Suicide, Cardiovascular Disease [possible adverse events from Hormone Tx], Cancer), Psych hx & hospitalization, Suicide attempts
Dhejne Landén	Yes	-	-	-	Includes demographics*	Education, Employment, Formal application for reversal of status, Psych dx & tx, Substance abuse** More elements in earlier paper
Beatrice	-	MMPI form R, TSCS	-	-	Demographic	Education, Income, Relationships
Haraldsen	-	SCL-90/90R	-	-	Demographic	DSM Axis 1, II, V (GAF), Substance abuse
Heylens	-	SCL-90	-	Yes-2	Demographic	Employment, Relationships, Substance abuse, Suicide attempts
Ainsworth	-	Likely SF-36v2*	-	Yes-1	Demographic	-
Ruppin	-	SCL-90R	BSRI, FPI-R, IIP	Yes-2	Demographic	Adverse events from surgery, Employment, Psych tx, Relationships, Substance abuse
Smith	-	MMPI-short, SCL-90?R	BIS, UGDS, ? Cohen-Kettenis', Doorn's x2, (Gid-c, SSS)	Yes-1 or 2	Demographic	Adverse events from surgery, Employment, Relationships
Udeze Megeri	-	SCL-90R	BDI, GHQ, HADS,STAI-X1, STAI-X2	-	-	Psych eval & ICD-10 dx
Kuhn	-	-	KHQ	Yes-1	Demographic	Relationships

Mate-Kole 1990	-	-	BSRI, CCEI	Yes-1	Demographic	Employment (relative change), Psych hx, Suicide hx
Wolfradt	-	-	BIQ, GITS, SDE, SES	Yes-1	-	-
Kraemer	-	-	FBeK	-	Demographic	-
Mate-Kole 1988	-	-	BSRI, CCEI	-	Demographic	Employment, Psych hx, Suicide hx,
Kockott	-	-	-	Yes-1	Demographic	Employment, Income, Relationships, Suicide attempts
Meyer	-	-	-	Yes-1	Demographic	Education, Employment, Income, Psych tx, Phallus removal request
Rakic	-	-	-	Yes-1	Demographic	Employment, Relationships

Panel B (Surgical Series: No Concurrent Controls)

Author	**National Data**	**Instrument w Substantive Normative Data**	**Instrument w/o Substantive &/or Accessible Normative Data**	**Investigator-designed**	**Other**	**Other**
Weyers	-	SF-36	FSFI	Yes-2	Demographic	Hormone levels, Adverse events from surgery, Relationships
Blanchard	-	SCL-90R	(AG)	Yes-1	Demographic	Education, Employment, Income, Relationships, Suicide (Incidental finding)
Wierckx	-	SF-36	-	Yes-3	Demographic	Hormone levels, Adverse events from surgery, Relationships
Eldh	-	-	-	Yes-1	-	Adverse events from surgery, Employment, Relationships, Suicide attempts

Hess	-	-	-	Yes-1	-	-
Lawrence	-	-	-	Yes-4	Demographic	Adverse events from surgery
Salvador	-	-	-	Yes-1	Demographic	Relationships
Tsoi	-	-	-	Yes-1	Demographic	Education, Employment, Relationships (relative change)

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	**National Data**	**Instrument w Substantive Normative Data**	**Instrument w/o Sub-stantive &/or Accessible Normative Data**	**Investigator-designed**	**Other**	**Other**
Asscheman et al.	Yes	-	-	-	Demographic	Mortality (HIV, Possible adverse events from Hormone Tx, Substance abuse, Suicide)
Motmans et al.	-	SF36 EQOLS (2nd)	-	-	Demographic	Education, Employment, Income, Relationships
Newfield et al.	-	SF-36v2	-	-	Demographic	Income
Gómez-Gil et al. 2014	-	WHOQOL-BREF	APGAR	Yes-1	Demographic	Education, Employment, Relationships
Gómez-Gil et al. 2012	-	-	HADS, SADS	-	Demographic	Education, Employment, Living arrangements
Hepp et al.	-	-	HADS	-	Demographic	DSM Axis 1& II Psych dx
Johansson et al.	-	-	-	Yes-1	Demographic	Axis V change (Pt & Clinician) Employment (relative change) Relationship (relative change)
Leinung et al.	-	-	-	-	Demographic	Employment, Disability, DVT, HIV status, Psych dx

*Listed as San Francisco-36 in manuscript

** From medical charts & verdicts ?=Possibly self-designed

AG=Androphilia-Gynephilia Index (investigator designed 1985) (used more for classification)

APGAR=Family Adaptability, Partnership growth, Affection, and Resolve

BDI=Beck Depression Inventory

BIQ=Body Image Questionnaire
BIS=Body Image Scale
BSRI=Bem Sex Role Inventory
CCEI=Crown Crisp Experiential Index
Cohen-Kettenis'= Sex trait function (An author helped design)
Dorn's x2= Post-operative functioning 13 items (An author helped design)
Post-operative functioning 21 items (An author helped design)
EQOLS (2nd)=2nd European Quality of Life Survey
FBeK=Fragebogen zur Beurteilung des eigenen Korpers
FPI-R=A version of the Freiberg Personality Inventory
FSFI+Female Sexual Function Index
GHQ=General Health Questionnaire
Gid-c=Gender identity disorder in childhood (used more for predictors) (An author helped design)
GITS=Gender Identity Trait Scale
HADS=Hospital Anxiety Depression Scale
IIP=Inventory of Interpersonal Problems
KHQ=King's Health Questionnaire
MMPI=Minnesota Multi-phasic Personality Inventory
SADS=Social Anxiety & Distress Scale
SCL-90 (±R)=A version of the Symptom Checklist 90
SDE=Scale for Depersonalized Experiences (An author designed)
SES=Self-Esteem Scale
SF-36 (v2)=Short Form-36(version2)
SSS=Social Support Scale (used more for predictors)
STAI-X1, STAI-X2=Spielberger State and Trait Anxiety Questionnaire
TSCS=Tennessee Self-Concept Scale
UGDS=Utrecht Gender Dysphoria Scale (An author helped design)
WHOQOL-BREF=World Health Organization-Quality of Life (abbreviated version)

Appendix G.

Longitudinal Studies Which Used Patients as Their Own Controls and Which Used Psychometric Tests with Extensive Normative Data or Longitudinal Studies Which Used National Data Sets

Author		Test	Patient and Data Loss	Results
		Psychometric Test		
Heylens et al. Belgium 2014		SCL-90R	90 applicants for SRS were recruited. • 8 (8.9%) declined participation. • 12 (13.3%) excluded b/c GID-NOS dx. • 12 (13.3%) did not complete the treatment sequence b/c of psychiatric/physical co-morbidity, personal decision for no tx, or personal decision for only	At t=0, the mean global "psychoneuroticism" SCL-90R score, along with scores of 7 of 8 subscales, were statistically more pathologic than the general population. After hormone tx, the mean score for global "psychoneuroticism" normalized & remained normal after reassignment surgery.

			hormone tx. • 1 (1.1%) committed suicide during follow-up. 57 (63.3% of recruited) entered the study. • 1 (12.2% of initial recruits) had not yet received SRS by study close. →**46 (51.1% of recruited) underwent serial evaluation** • The test was not completed by 1 at t=0, 10 at t=1 (after hormone tx), & 4 at t=2 (after SRS) →**missing data for another 1.1% to 11.1%.**	
Ruppin,Pfafflin, Germany 2015		SCL-90R	The number in the available patient pool was not specified. 140 received recruitment letters. • 2 (1.4% of those with recruitment letters) had died. • 1 (0.7%) was institutionalized. • 5 (3.6%) were ill. • 8 (5.7%) did not have time. • 8 (5.7%) stated that GD was no longer an issue. • 8 (5.7%) provided no reason. • 28 (20.0%) declined further contact. • 9 (6.4%) were lost to follow-up. →**71 (50.7%) agreed to participate.** • **2 (1.4%) had not undergone SRS** • The test was not completed by 9. →**missing data for another 6.4%.**	At t=0, the "global severity index "SCL-90R score was 0.53±0.49. At post-SRS follow-up the score had decreased to 0.28±0.36. The scores were statistically different from one another, but are of limited biologic significance given the range of the score for this scale: 0-4. In the same way, all of the subscale scores were statistically different, but the effect size was reported as large only for "interpersonal sensitivity": 0.70±0.67 at t=0 and 0.26±0.34 post-SRS.
Smith et al. Holland		MMPI SCL-90	The number in the available adult patient	Most of the MMPI scales were already in the normal range at

2005			pool was not specified. 325 adult & adolescent applicants for SRS were recruited. • 103 (31.7%) were not eligible to start hormone tx & real-life experience. • 34 (10.7%) discontinued hormone tx 162 (an unknown percentage of the initial recruitment) provided pre-SRS test data. • **36 to 61 (22.2%-37.6% of those adults w pre-SRS data) did not complete post-SRS testing.**	the time of initial testing. At t=0, the global "psychoneuroticism" SCL-90 score, which included the drop-outs, was 143.0±40.7. At post SRS-follow-up, the score had decreased to 120.3±31.4. The scores were statistically different from one another, but are of limited biologic significance given the range of the score for this scale: 90 to 450, with higher scores consistent with more psychological instability.
Udeze, et al. 2008 Megeri, Khoosal 2007 UK		SCL-90R	The number in the available patient pool was not specified. 40 subjects were prospectively selected. • Post-operative testing was conducted within 6 months to minimize previously determined loss rates.	At t=0, the mean raw global score was 48.33. At post-SRS follow-up, the mean score was 49.15. There were no statistically significant changes in the global score or for any of the subscales.
	National Databases			
Dehjne Sweden 2011		Swedish National Records	804 with GID in Sweden 1973 to 2003 were identified. • 480 (59.7%) did not apply or were not approved for SRS 324 (40.3%) underwent SRS. • All were followed. 3240 controls of the natal sex and 3240 controls of the reassigned gender were randomly selected from national records	All cause mortality was higher (n=27[8%]) than in controls (H.R 2.8 [1.8-4.3]) even after adjustment for covariants. Divergence in survival curves was observed after 10 years. The major contributor was completed suicide (n=10 [3%]; adjusted H.R. 19.1 [5.8-62.9]). Suicide attempts were more common (n= 29 [9%]) than in controls (adjusted H.R. 4.9 [2.9–8.5]). Hospitalizations for psychiatric conditions (not related to gender dysphoria) were more common n= 64 [20%] than in controls (H.R. 2.8 [2.0–3.9]) even after adjusting for prior

			psychiatric morbidity.
Dhejne et al. 2014 Landén et al. 1998 Sweden	Swedish National Registry	767 applied for SRS/legal status (1960-2010) • 25 (3.3%) applications denied. • 61 (8.0%) not granted full legal status 681 (88.7%) underwent SRS. • All were followed.	15 formal applications for reversal to natal/original gender (2.2% of the SRS population) were identified thus far (preliminary number). (Does not reflect other manifestations of regret such as suicide.)

GID-NOS=Gender Identity Disorder-Not Otherwise Specified HR=Hazard Ratio SRS=Sex reassignment surgery Tx=Treatment

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DEFENDANT'S EXHIBIT 17

DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS

FIFTH EDITION

DSM-5™

American Psychiatric Publishing
A Division of American Psychiatric Association

Washington, DC
London, England

Manufactured in the United States of America on acid-free paper.

ISBN 978-0-89042-554-1 (Hardcover)

ISBN 978-0-89042-555-8 (Paperback)

American Psychiatric Association
1000 Wilson Boulevard
Arlington, VA 22209-3901
www.psych.org

The correct citation for this book is American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013.

Library of Congress Cataloging-in-Publication Data
Diagnostic and statistical manual of mental disorders : DSM-5. — 5th ed.
p. ; cm.
DSM-5
DSM-V
Includes index.
ISBN 978-0-89042-554-1 (hardcover : alk. paper) — ISBN 978-0-89042-555-8 (pbk. : alk. paper)
I. American Psychiatric Association. II. American Psychiatric Association. DSM-5 Task Force. III. Title: DSM-5. IV. Title: DSM-V.
[DNLM: 1. Diagnostic and statistical manual of mental disorders. 5th ed. 2. Mental Disorders—classification. 3. Mental Disorders—diagnosis. WM 15]
RC455.2.C4
616.89'075—dc23

2013011061

British Library Cataloguing in Publication Data
A CIP record is available from the British Library.

Text Design—Tammy J. Cordova

Manufacturing—Edwards Brothers Malloy

Gender Dysphoria

In this chapter, there is one overarching diagnosis of gender dysphoria, with separate developmentally appropriate criteria sets for children and for adolescents and adults. The area of sex and gender is highly controversial and has led to a proliferation of terms whose meanings vary over time and within and between disciplines. An additional source of confusion is that in English "sex" connotes both male/female and sexuality. This chapter employs constructs and terms as they are widely used by clinicians from various disciplines with specialization in this area. In this chapter, *sex* and *sexual* refer to the biological indicators of male and female (understood in the context of reproductive capacity), such as in sex chromosomes, gonads, sex hormones, and nonambiguous internal and external genitalia. Disorders of sex development denote conditions of inborn somatic deviations of the reproductive tract from the norm and/or discrepancies among the biological indicators of male and female. *Cross-sex* hormone treatment denotes the use of feminizing hormones in an individual assigned male at birth based on traditional biological indicators or the use of masculinizing hormones in an individual assigned female at birth.

The need to introduce the term *gender* arose with the realization that for individuals with conflicting or ambiguous biological indicators of sex (i.e., "intersex"), the lived role in society and/or the identification as male or female could not be uniformly associated with or predicted from the biological indicators and, later, that some individuals develop an identity as female or male at variance with their uniform set of classical biological indicators. Thus, *gender* is used to denote the public (and usually legally recognized) lived role as boy or girl, man or woman, but, in contrast to certain social constructionist theories, biological factors are seen as contributing, in interaction with social and psychological factors, to gender development. *Gender assignment* refers to the initial assignment as male or female. This occurs usually at birth and, thereby, yields the "natal gender." *Gender-atypical* refers to somatic features or behaviors that are not typical (in a statistical sense) of individuals with the same assigned gender in a given society and historical era; for behavior, *gender-nonconforming* is an alternative descriptive term. *Gender reassignment* denotes an official (and usually legal) change of gender. *Gender identity* is a category of social identity and refers to an individual's identification as male, female, or, occasionally, some category other than male or female. *Gender dysphoria* as a general descriptive term refers to an individual's affective/cognitive discontent with the assigned gender but is more specifically defined when used as a diagnostic category. *Transgender* refers to the broad spectrum of individuals who transiently or persistently identify with a gender different from their natal gender. *Transsexual* denotes an individual who seeks, or has undergone, a social transition from male to female or female to male, which in many, but not all, cases also involves a somatic transition by cross-sex hormone treatment and genital surgery (*sex reassignment surgery*).

Gender dysphoria refers to the distress that may accompany the incongruence between one's experienced or expressed gender and one's assigned gender. Although not all individuals will experience distress as a result of such incongruence, many are distressed if the desired physical interventions by means of hormones and/or surgery are not available. The current term is more descriptive than the previous DSM-IV term *gender identity disorder* and focuses on dysphoria as the clinical problem, not identity per se.

Gender Dysphoria

Diagnostic Criteria

Gender Dysphoria in Children 302.6 (F64.2)

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least six of the following (one of which must be Criterion A1):

1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender).
2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire; or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing.
3. A strong preference for cross-gender roles in make-believe play or fantasy play.
4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender.
5. A strong preference for playmates of the other gender.
6. In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities.
7. A strong dislike of one's sexual anatomy.
8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender.

B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning.

Specify if:

With a disorder of sex development (e.g., a congenital adrenogenital disorder such as 255.2 [E25.0] congenital adrenal hyperplasia or 259.50 [E34.50] androgen insensitivity syndrome).

Coding note: Code the disorder of sex development as well as gender dysphoria.

Gender Dysphoria in Adolescents and Adults 302.85 (F64.1)

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least two of the following:

1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics).
2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).
3. A strong desire for the primary and/or secondary sex characteristics of the other gender.
4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender).
5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender).
6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).

B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

With a disorder of sex development (e.g., a congenital adrenogenital disorder such as 255.2 [E25.0] congenital adrenal hyperplasia or 259.50 [E34.50] androgen insensitivity syndrome).

Coding note: Code the disorder of sex development as well as gender dysphoria.

Specify if:

Posttransition: The individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one cross-sex medical procedure or treatment regimen—namely, regular cross-sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in a natal male; mastectomy or phalloplasty in a natal female).

Specifiers

The posttransition specifier may be used in the context of continuing treatment procedures that serve to support the new gender assignment.

Diagnostic Features

Individuals with gender dysphoria have a marked incongruence between the gender they have been assigned to (usually at birth, referred to as *natal gender*) and their experienced/expressed gender. This discrepancy is the core component of the diagnosis. There must also be evidence of distress about this incongruence. Experienced gender may include alternative gender identities beyond binary stereotypes. Consequently, the distress is not limited to a desire to simply be of the other gender, but may include a desire to be of an alternative gender, provided that it differs from the individual's assigned gender.

Gender dysphoria manifests itself differently in different age groups. Prepubertal natal girls with gender dysphoria may express the wish to be a boy, assert they are a boy, or assert they will grow up to be a man. They prefer boys' clothing and hairstyles, are often perceived by strangers as boys, and may ask to be called by a boy's name. Usually, they display intense negative reactions to parental attempts to have them wear dresses or other feminine attire. Some may refuse to attend school or social events where such clothes are required. These girls may demonstrate marked cross-gender identification in role-playing, dreams, and fantasies. Contact sports, rough-and-tumble play, traditional boyhood games, and boys as playmates are most often preferred. They show little interest in stereotypically feminine toys (e.g., dolls) or activities (e.g., feminine dress-up or role-play). Occasionally, they refuse to urinate in a sitting position. Some natal girls may express a desire to have a penis or claim to have a penis or that they will grow one when older. They may also state that they do not want to develop breasts or menstruate.

Prepubertal natal boys with gender dysphoria may express the wish to be a girl or assert they are a girl or that they will grow up to be a woman. They have a preference for dressing in girls' or women's clothes or may improvise clothing from available materials (e.g., using towels, aprons, and scarves for long hair or skirts). These children may role-play female figures (e.g., playing "mother") and often are intensely interested in female fantasy figures. Traditional feminine activities, stereotypical games, and pastimes (e.g., "playing house"; drawing feminine pictures; watching television or videos of favorite female characters) are most often preferred. Stereotypical female-type dolls (e.g., Barbie) are often favorite toys, and girls are their preferred playmates. They avoid rough-and-tumble play and competitive sports and have little interest in stereotypically masculine toys (e.g., cars, trucks). Some may pretend not to have a penis and insist on sitting to urinate. More

rarely, they may state that they find their penis or testes disgusting, that they wish them removed, or that they have, or wish to have, a vagina.

In young adolescents with gender dysphoria, clinical features may resemble those of children or adults with the condition, depending on developmental level. As secondary sex characteristics of young adolescents are not yet fully developed, these individuals may not state dislike of them, but they are concerned about imminent physical changes.

In adults with gender dysphoria, the discrepancy between experienced gender and physical sex characteristics is often, but not always, accompanied by a desire to be rid of primary and/or secondary sex characteristics and/or a strong desire to acquire some primary and/or secondary sex characteristics of the other gender. To varying degrees, adults with gender dysphoria may adopt the behavior, clothing, and mannerisms of the experienced gender. They feel uncomfortable being regarded by others, or functioning in society, as members of their assigned gender. Some adults may have a strong desire to be of a different gender and treated as such, and they may have an inner certainty to feel and respond as the experienced gender without seeking medical treatment to alter body characteristics. They may find other ways to resolve the incongruence between experienced/expressed and assigned gender by partially living in the desired role or by adopting a gender role neither conventionally male nor conventionally female.

Associated Features Supporting Diagnosis

When visible signs of puberty develop, natal boys may shave their legs at the first signs of hair growth. They sometimes bind their genitals to make erections less visible. Girls may bind their breasts, walk with a stoop, or use loose sweaters to make breasts less visible. Increasingly, adolescents request, or may obtain without medical prescription and supervision, hormonal suppressors ("blockers") of gonadal steroids (e.g., gonadotropin-releasing hormone [GnRH] analog, spironolactone). Clinically referred adolescents often want hormone treatment and many also wish for gender reassignment surgery. Adolescents living in an accepting environment may openly express the desire to be and be treated as the experienced gender and dress partly or completely as the experienced gender, have a hairstyle typical of the experienced gender, preferentially seek friendships with peers of the other gender, and/or adopt a new first name consistent with the experienced gender. Older adolescents, when sexually active, usually do not show or allow partners to touch their sexual organs. For adults with an aversion toward their genitals, sexual activity is constrained by the preference that their genitals not be seen or touched by their partners. Some adults may seek hormone treatment (sometimes without medical prescription and supervision) and gender reassignment surgery. Others are satisfied with either hormone treatment or surgery alone.

Adolescents and adults with gender dysphoria before gender reassignment are at increased risk for suicidal ideation, suicide attempts, and suicides. After gender reassignment, adjustment may vary, and suicide risk may persist.

Prevalence

For natal adult males, prevalence ranges from 0.005% to 0.014%, and for natal females, from 0.002% to 0.003%. Since not all adults seeking hormone treatment and surgical reassignment attend specialty clinics, these rates are likely modest underestimates. Sex differences in rate of referrals to specialty clinics vary by age group. In children, sex ratios of natal boys to girls range from 2:1 to 4.5:1. In adolescents, the sex ratio is close to parity; in adults, the sex ratio favors natal males, with ratios ranging from 1:1 to 6.1:1. In two countries, the sex ratio appears to favor natal females (Japan: 2.2:1; Poland: 3.4:1).

Development and Course

Because expression of gender dysphoria varies with age, there are separate criteria sets for children versus adolescents and adults. Criteria for children are defined in a more con-

crete, behavioral manner than those for adolescents and adults. Many of the core criteria draw on well-documented behavioral gender differences between typically developing boys and girls. Young children are less likely than older children, adolescents, and adults to express extreme and persistent anatomic dysphoria. In adolescents and adults, incongruence between experienced gender and somatic sex is a central feature of the diagnosis. Factors related to distress and impairment also vary with age. A very young child may show signs of distress (e.g., intense crying) only when parents tell the child that he or she is "really" not a member of the other gender but only "desires" to be. Distress may not be manifest in social environments supportive of the child's desire to live in the role of the other gender and may emerge only if the desire is interfered with. In adolescents and adults, distress may manifest because of strong incongruence between experienced gender and somatic sex. Such distress may, however, be mitigated by supportive environments and knowledge that biomedical treatments exist to reduce incongruence. Impairment (e.g., school refusal, development of depression, anxiety, and substance abuse) may be a consequence of gender dysphoria.

Gender dysphoria without a disorder of sex development. For clinic-referred children, onset of cross-gender behaviors is usually between ages 2 and 4 years. This corresponds to the developmental time period in which most typically developing children begin expressing gendered behaviors and interests. For some preschool-age children, both pervasive cross-gender behaviors and the expressed desire to be the other gender may be present, or, more rarely, labeling oneself as a member of the other gender may occur. In some cases, the expressed desire to be the other gender appears later, usually at entry into elementary school. A small minority of children express discomfort with their sexual anatomy or will state the desire to have a sexual anatomy corresponding to the experienced gender ("anatomic dysphoria"). Expressions of anatomic dysphoria become more common as children with gender dysphoria approach and anticipate puberty.

Rates of persistence of gender dysphoria from childhood into adolescence or adulthood vary. In natal males, persistence has ranged from 2.2% to 30%. In natal females, persistence has ranged from 12% to 50%. Persistence of gender dysphoria is modestly correlated with dimensional measures of severity ascertained at the time of a childhood baseline assessment. In one sample of natal males, lower socioeconomic background was also modestly correlated with persistence. It is unclear if particular therapeutic approaches to gender dysphoria in children are related to rates of long-term persistence. Extant follow-up samples consisted of children receiving no formal therapeutic intervention or receiving therapeutic interventions of various types, ranging from active efforts to reduce gender dysphoria to a more neutral, "watchful waiting" approach. It is unclear if children "encouraged" or supported to live socially in the desired gender will show higher rates of persistence, since such children have not yet been followed longitudinally in a systematic manner. For both natal male and female children showing persistence, almost all are sexually attracted to individuals of their natal sex. For natal male children whose gender dysphoria does not persist, the majority are *androphilic* (sexually attracted to males) and often self-identify as gay or homosexual (ranging from 63% to 100%). In natal female children whose gender dysphoria does not persist, the percentage who are *gynephilic* (sexually attracted to females) and self-identify as lesbian is lower (ranging from 32% to 50%).

In both adolescent and adult natal males, there are two broad trajectories for development of gender dysphoria: early onset and late onset. *Early-onset gender dysphoria* starts in childhood and continues into adolescence and adulthood; or, there is an intermittent period in which the gender dysphoria desists and these individuals self-identify as gay or homosexual, followed by recurrence of gender dysphoria. *Late-onset gender dysphoria* occurs around puberty or much later in life. Some of these individuals report having had a desire to be of the other gender in childhood that was not expressed verbally to others. Others do not recall any signs of childhood gender dysphoria. For adolescent males with late-onset gender dysphoria, parents often report surprise because they did not see signs of gender

dysphoria during childhood. Expressions of anatomic dysphoria are more common and salient in adolescents and adults once secondary sex characteristics have developed.

Adolescent and adult natal males with early-onset gender dysphoria are almost always sexually attracted to men (androphilic). Adolescents and adults with late-onset gender dysphoria frequently engage in transvestic behavior with sexual excitement. The majority of these individuals are gynephilic or sexually attracted to other posttransition natal males with late-onset gender dysphoria. A substantial percentage of adult males with late-onset gender dysphoria cohabit with or are married to natal females. After gender transition, many self-identify as lesbian. Among adult natal males with gender dysphoria, the early-onset group seeks out clinical care for hormone treatment and reassignment surgery at an earlier age than does the late-onset group. The late-onset group may have more fluctuations in the degree of gender dysphoria and be more ambivalent about and less likely satisfied after gender reassignment surgery.

In both adolescent and adult natal females, the most common course is the early-onset form of gender dysphoria. The late-onset form is much less common in natal females compared with natal males. As in natal males with gender dysphoria, there may have been a period in which the gender dysphoria desisted and these individuals self-identified as lesbian; however, with recurrence of gender dysphoria, clinical consultation is sought, often with the desire for hormone treatment and reassignment surgery. Parents of natal adolescent females with the late-onset form also report surprise, as no signs of childhood gender dysphoria were evident. Expressions of anatomic dysphoria are much more common and salient in adolescents and adults than in children.

Adolescent and adult natal females with early-onset gender dysphoria are almost always gynephilic. Adolescents and adults with the late-onset form of gender dysphoria are usually androphilic and after gender transition self-identify as gay men. Natal females with the late-onset form do not have co-occurring transvestic behavior with sexual excitement.

Gender dysphoria in association with a disorder of sex development. Most individuals with a disorder of sex development who develop gender dysphoria have already come to medical attention at an early age. For many, starting at birth, issues of gender assignment were raised by physicians and parents. Moreover, as infertility is quite common for this group, physicians are more willing to perform cross-sex hormone treatments and genital surgery before adulthood.

Disorders of sex development in general are frequently associated with gender-atypical behavior starting in early childhood. However, in the majority of cases, this does not lead to gender dysphoria. As individuals with a disorder of sex development become aware of their medical history and condition, many experience uncertainty about their gender, as opposed to developing a firm conviction that they are another gender. However, most do not progress to gender transition. Gender dysphoria and gender transition may vary considerably as a function of a disorder of sex development, its severity, and assigned gender.

Risk and Prognostic Factors

Temperamental. For individuals with gender dysphoria without a disorder of sex development, atypical gender behavior among individuals with early-onset gender dysphoria develops in early preschool age, and it is possible that a high degree of atypicality makes the development of gender dysphoria and its persistence into adolescence and adulthood more likely.

Environmental. Among individuals with gender dysphoria without a disorder of sex development, males with gender dysphoria (in both childhood and adolescence) more commonly have older brothers than do males without the condition. Additional predisposing

factors under consideration, especially in individuals with late-onset gender dysphoria (adolescence, adulthood), include habitual fetishistic transvestism developing into autogynephilia (i.e., sexual arousal associated with the thought or image of oneself as a woman) and other forms of more general social, psychological, or developmental problems.

Genetic and physiological. For individuals with gender dysphoria without a disorder of sex development, some genetic contribution is suggested by evidence for (weak) familiality of transsexualism among nontwin siblings, increased concordance for transsexualism in monozygotic compared with dizygotic same-sex twins, and some degree of heritability of gender dysphoria. As to endocrine findings, no endogenous systemic abnormalities in sex-hormone levels have been found in 46,XY individuals, whereas there appear to be increased androgen levels (in the range found in hirsute women but far below normal male levels) in 46,XX individuals. Overall, current evidence is insufficient to label gender dysphoria without a disorder of sex development as a form of intersexuality limited to the central nervous system.

In gender dysphoria associated with a disorder of sex development, the likelihood of later gender dysphoria is increased if prenatal production and utilization (via receptor sensitivity) of androgens are grossly atypical relative to what is usually seen in individuals with the same assigned gender. Examples include 46,XY individuals with a history of normal male prenatal hormone milieu but inborn nonhormonal genital defects (as in cloacal bladder exstrophy or penile agenesis) and who have been assigned to the female gender. The likelihood of gender dysphoria is further enhanced by additional, prolonged, highly gender-atypical postnatal androgen exposure with somatic virilization as may occur in female-raised and noncastrated 46,XY individuals with 5-alpha reductase-2 deficiency or 17-beta-hydroxysteroid dehydrogenase-3 deficiency or in female-raised 46,XX individuals with classical congenital adrenal hyperplasia with prolonged periods of non-adherence to glucocorticoid replacement therapy. However, the prenatal androgen milieu is more closely related to gendered behavior than to gender identity. Many individuals with disorders of sex development and markedly gender-atypical behavior do not develop gender dysphoria. Thus, gender-atypical behavior by itself should not be interpreted as an indicator of current or future gender dysphoria. There appears to be a higher rate of gender dysphoria and patient-initiated gender change from assigned female to male than from assigned male to female in 46,XY individuals with a disorder of sex development.

Culture-Related Diagnostic Issues

Individuals with gender dysphoria have been reported across many countries and cultures. The equivalent of gender dysphoria has also been reported in individuals living in cultures with institutionalized gender categories other than male or female. It is unclear whether with these individuals the diagnostic criteria for gender dysphoria would be met.

Diagnostic Markers

Individuals with a somatic disorder of sex development show some correlation of final gender identity outcome with the degree of prenatal androgen production and utilization. However, the correlation is not robust enough for the biological factor, where ascertainable, to replace a detailed and comprehensive diagnostic interview evaluation for gender dysphoria.

Functional Consequences of Gender Dysphoria

Preoccupation with cross-gender wishes may develop at all ages after the first 2–3 years of childhood and often interfere with daily activities. In older children, failure to develop age-typical same-sex peer relationships and skills may lead to isolation from peer groups and to distress. Some children may refuse to attend school because of teasing and harass-

ment or pressure to dress in attire associated with their assigned sex. Also in adolescents and adults, preoccupation with cross-gender wishes often interferes with daily activities. Relationship difficulties, including sexual relationship problems, are common, and functioning at school or at work may be impaired. Gender dysphoria, along with atypical gender expression, is associated with high levels of stigmatization, discrimination, and victimization, leading to negative self-concept, increased rates of mental disorder comorbidity, school dropout, and economic marginalization, including unemployment, with attendant social and mental health risks, especially in individuals from resource-poor family backgrounds. In addition, these individuals' access to health services and mental health services may be impeded by structural barriers, such as institutional discomfort or inexperience in working with this patient population.

Differential Diagnosis

Nonconformity to gender roles. Gender dysphoria should be distinguished from simple nonconformity to stereotypical gender role behavior by the strong desire to be of another gender than the assigned one and by the extent and pervasiveness of gender-variant activities and interests. The diagnosis is not meant to merely describe nonconformity to stereotypical gender role behavior (e.g., "tomboyism" in girls, "girly-boy" behavior in boys, occasional cross-dressing in adult men). Given the increased openness of atypical gender expressions by individuals across the entire range of the transgender spectrum, it is important that the clinical diagnosis be limited to those individuals whose distress and impairment meet the specified criteria.

Transvestic disorder. Transvestic disorder occurs in heterosexual (or bisexual) adolescent and adult males (rarely in females) for whom cross-dressing behavior generates sexual excitement and causes distress and/or impairment without drawing their primary gender into qūestion. It is occasionally accompanied by gender dysphoria. An individual with transvestic disorder who also has clinically significant gender dysphoria can be given both diagnoses. In many cases of late-onset gender dysphoria in gynephilic natal males, transvestic behavior with sexual excitement is a precursor.

Body dysmorphic disorder. An individual with body dysmorphic disorder focuses on the alteration or removal of a specific body part because it is perceived as abnormally formed, not because it represents a repudiated assigned gender. When an individual's presentation meets criteria for both gender dysphoria and body dysmorphic disorder, both diagnoses can be given. Individuals wishing to have a healthy limb amputated (termed by some *body integrity identity disorder*) because it makes them feel more "complete" usually do not wish to change gender, but rather desire to live as an amputee or a disabled person.

Schizophrenia and other psychotic disorders. In schizophrenia, there may rarely be delusions of belonging to some other gender. In the absence of psychotic symptoms, insistence by an individual with gender dysphoria that he or she is of some other gender is not considered a delusion. Schizophrenia (or other psychotic disorders) and gender dysphoria may co-occur.

Other clinical presentations. Some individuals with an emasculinization desire who develop an alternative, nonmale/nonfemale gender identity do have a presentation that meets criteria for gender dysphoria. However, some males seek castration and/or penectomy for aesthetic reasons or to remove psychological effects of androgens without changing male identity; in these cases, the criteria for gender dysphoria are not met.

Comorbidity

Clinically referred children with gender dysphoria show elevated levels of emotional and behavioral problems—most commonly, anxiety, disruptive and impulse-control, and de-

pressive disorders. In prepubertal children, increasing age is associated with having more behavioral or emotional problems; this is related to the increasing non-acceptance of gender-variant behavior by others. In older children, gender-variant behavior often leads to peer ostracism, which may lead to more behavioral problems. The prevalence of mental health problems differs among cultures; these differences may also be related to differences in attitudes toward gender variance in children. However, also in some non-Western cultures, anxiety has been found to be relatively common in individuals with gender dysphoria, even in cultures with accepting attitudes toward gender-variant behavior. Autism spectrum disorder is more prevalent in clinically referred children with gender dysphoria than in the general population. Clinically referred adolescents with gender dysphoria appear to have comorbid mental disorders, with anxiety and depressive disorders being the most common. As in children, autism spectrum disorder is more prevalent in clinically referred adolescents with gender dysphoria than in the general population. Clinically referred adults with gender dysphoria may have coexisting mental health problems, most commonly anxiety and depressive disorders.

Other Specified Gender Dysphoria

302.6 (F64.8)

This category applies to presentations in which symptoms characteristic of gender dysphoria that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for gender dysphoria. The other specified gender dysphoria category is used in situations in which the clinician chooses to communicate the specific reason that the presentation does not meet the criteria for gender dysphoria. This is done by recording "other specified gender dysphoria" followed by the specific reason (e.g., "brief gender dysphoria").

An example of a presentation that can be specified using the "other specified" designation is the following:

The current disturbance meets symptom criteria for gender dysphoria, but the duration is less than 6 months.

Unspecified Gender Dysphoria

302.6 (F64.9)

This category applies to presentations in which symptoms characteristic of gender dysphoria that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for gender dysphoria. The unspecified gender dysphoria category is used in situations in which the clinician chooses *not* to specify the reason that the criteria are not met for gender dysphoria, and includes presentations in which there is insufficient information to make a more specific diagnosis.

WPATH WORLD PROFESSIONAL ASSOCIATION for TRANSGENDER HEALTH

Standards of Care

for the Health of Transsexual, Transgender, and Gender-Nonconforming People

The World Professional Association for Transgender Health

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7th Version[1] | www.wpath.org

ISBN: X-XXX-XXXXX-XX

1 This is the seventh version of the *Standards of Care* since the original 1979 document. Previous revisions were in 1980, 1981, 1990, 1998, and 2001. Version seven was published in the International Journal of Transgenderism, 13(4), 165–232. doi:10.1080/15532739.2011.700873

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Purpose and Use of the *Standards of Care*

The World Professional Association for Transgender Health (WPATH)[I] is an international, multidisciplinary, professional association whose mission is to promote evidence-based care, education, research, advocacy, public policy, and respect in transsexual and transgender health. The vision of WPATH is a world wherein transsexual, transgender, and gender-nonconforming people benefit from access to evidence-based health care, social services, justice, and equality.

One of the main functions of WPATH is to promote the highest standards of health care for individuals through the articulation of *Standards of Care (SOC) for the Health of Transsexual, Transgender, and Gender Nonconforming People*. The *SOC* are based on the best available science and expert professional consensus.[II] Most of the research and experience in this field comes from a North American and Western European perspective; thus, adaptations of the *SOC* to other parts of the world are necessary. Suggestions for ways of thinking about cultural relativity and cultural competence are included in this version of the *SOC*.

The overall goal of the *SOC* is to provide clinical guidance for health professionals to assist transsexual, transgender, and gender-nonconforming people with safe and effective pathways to achieving lasting personal comfort with their gendered selves, in order to maximize their overall health, psychological well-being, and self-fulfillment. This assistance may include primary care, gynecologic and urologic care, reproductive options, voice and communication therapy, mental health services (e.g., assessment, counseling, psychotherapy), and hormonal and surgical treatments. While this is primarily a document for health professionals, the *SOC* may also be used by individuals, their families, and social institutions to understand how they can assist with promoting optimal health for members of this diverse population.

WPATH recognizes that health is dependent upon not only good clinical care but also social and political climates that provide and ensure social tolerance, equality, and the full rights of citizenship. Health is promoted through public policies and legal reforms that promote tolerance and equity

I Formerly the Harry Benjamin International Gender Dysphoria Association

II The *Standards of Care (SOC), Version 7,* represents a significant departure from previous versions. Changes in this version are based upon significant cultural shifts, advances in clinical knowledge, and appreciation of the many health care issues that can arise for transsexual, transgender, and gender-nonconforming people beyond hormone therapy and surgery (Coleman, 2009a, b, c, d).

for gender and sexual diversity and that eliminate prejudice, discrimination, and stigma. WPATH is committed to advocacy for these changes in public policies and legal reforms.

The *Standards of Care* Are Flexible Clinical Guidelines

The *SOC* are intended to be flexible in order to meet the diverse health care needs of transsexual, transgender, and gender-nonconforming people. While flexible, they offer standards for promoting optimal health care and guiding the treatment of people experiencing gender dysphoria—broadly defined as discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b).

As in all previous versions of the *SOC*, the criteria put forth in this document for hormone therapy and surgical treatments for gender dysphoria are clinical guidelines; individual health professionals and programs may modify them. Clinical departures from the *SOC* may come about because of a patient's unique anatomic, social, or psychological situation; an experienced health professional's evolving method of handling a common situation; a research protocol; lack of resources in various parts of the world; or the need for specific harm-reduction strategies. These departures should be recognized as such, explained to the patient, and documented through informed consent for quality patient care and legal protection. This documentation is also valuable for the accumulation of new data, which can be retrospectively examined to allow for health care—and the *SOC*—to evolve.

The *SOC* articulate standards of care but also acknowledge the role of making informed choices and the value of harm-reduction approaches. In addition, this version of the *SOC* recognizes and validates various expressions of gender that may not necessitate psychological, hormonal, or surgical treatments. Some patients who present for care will have made significant self-directed progress towards gender role changes, transition, or other resolutions regarding their gender identity or gender dysphoria. Other patients will require more intensive services. Health professionals can use the *SOC* to help patients consider the full range of health services open to them, in accordance with their clinical needs and goals for gender expression.

Global Applicability of the *Standards of Care*

While the *SOC* are intended for worldwide use, WPATH acknowledges that much of the recorded clinical experience and knowledge in this area of health care is derived from North American and Western European sources. From place to place, both across and within nations, there are differences in all of the following: social attitudes towards transsexual, transgender, and gender-nonconforming people; constructions of gender roles and identities; language used to describe different gender identities; epidemiology of gender dysphoria; access to and cost of treatment; therapies offered; number and type of professionals who provide care; and legal and policy issues related to this area of health care (Winter, 2009).

It is impossible for the *SOC* to reflect all of these differences. In applying these standards to other cultural contexts, health professionals must be sensitive to these differences and adapt the *SOC* according to local realities. For example, in a number of cultures, gender-nonconforming people are found in such numbers and living in such ways as to make them highly socially visible (Peletz, 2006). In settings such as these, it is common for people to initiate a change in their gender expression and physical characteristics while in their teens or even earlier. Many grow up and live in a social, cultural, and even linguistic context quite unlike that of Western cultures. Yet almost all experience prejudice (Peletz, 2006; Winter, 2009). In many cultures, social stigma towards gender nonconformity is widespread and gender roles are highly prescriptive (Winter et al., 2009). Gender-nonconforming people in these settings are forced to be hidden and, therefore, may lack opportunities for adequate health care (Winter, 2009).

The *SOC* are not intended to limit efforts to provide the best available care to all individuals. Health professionals throughout the world—even in areas with limited resources and training opportunities—can apply the many core principles that undergird the *SOC*. These principles include the following: Exhibit respect for patients with nonconforming gender identities (do not pathologize differences in gender identity or expression); provide care (or refer to knowledgeable colleagues) that affirms patients' gender identities and reduces the distress of gender dysphoria, when present; become knowledgeable about the health care needs of transsexual, transgender, and gender-nonconforming people, including the benefits and risks of treatment options for gender dysphoria; match the treatment approach to the specific needs of patients, particularly their goals for gender expression and need for relief from gender dysphoria; facilitate access to appropriate care; seek patients' informed consent before providing treatment; offer continuity of care; and be prepared to support and advocate for patients within their families and communities (schools, workplaces, and other settings).

Terminology is culture- and time-dependent and is rapidly evolving. It is important to use respectful language in different places and times, and among different people. As the *SOC* are translated into other languages, great care must be taken to ensure that the meanings of terms are accurately translated. Terminology in English may not be easily translated into other languages, and vice versa. Some languages do not have equivalent words to describe the various terms within this document; hence, translators should be cognizant of the underlying goals of treatment and articulate culturally applicable guidance for reaching those goals.

The Difference Between Gender Nonconformity and Gender Dysphoria

Being Transsexual, Transgender, or Gender-Nonconforming Is a Matter of Diversity, Not Pathology

WPATH released a statement in May 2010 urging the de-psychopathologization of gender nonconformity worldwide (WPATH Board of Directors, 2010). This statement noted that "the expression of gender characteristics, including identities, that are not stereotypically associated with one's assigned sex at birth is a common and culturally diverse human phenomenon [that] should not be judged as inherently pathological or negative."

Unfortunately, there is stigma attached to gender nonconformity in many societies around the world. Such stigma can lead to prejudice and discrimination, resulting in "minority stress" (I. H. Meyer, 2003). Minority stress is unique (additive to general stressors experienced by all people), socially based, and chronic, and may make transsexual, transgender, and gender-nonconforming individuals more vulnerable to developing mental health concerns such as anxiety and depression (Institute of Medicine, 2011). In addition to prejudice and discrimination in society at large, stigma can contribute to abuse and neglect in one's relationships with peers and family members, which in turn can lead to psychological distress. However, these symptoms are socially induced and are not inherent to being transsexual, transgender, or gender-nonconforming.

Gender Nonconformity Is Not the Same as Gender Dysphoria

Gender nonconformity refers to the extent to which a person's gender identity, role, or expression differs from the cultural norms prescribed for people of a particular sex (Institute of Medicine, 2011). *Gender dysphoria* refers to discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b). Only *some* gender-nonconforming people experience gender dysphoria at *some* point in their lives.

Treatment is available to assist people with such distress to explore their gender identity and find a gender role that is comfortable for them (Bockting & Goldberg, 2006). Treatment is individualized: What helps one person alleviate gender dysphoria might be very different from what helps another person. This process may or may not involve a change in gender expression or body modifications. Medical treatment options include, for example, feminization or masculinization of the body through hormone therapy and/or surgery, which are effective in alleviating gender dysphoria and are medically necessary for many people. Gender identities and expressions are diverse, and hormones and surgery are just two of many options available to assist people with achieving comfort with self and identity.

Gender dysphoria can in large part be alleviated through treatment (Murad et al., 2010). Hence, while transsexual, transgender, and gender-nonconforming people may experience gender dysphoria at some points in their lives, many individuals who receive treatment will find a gender role and expression that is comfortable for them, even if these differ from those associated with their sex assigned at birth, or from prevailing gender norms and expectations.

Diagnoses Related to Gender Dysphoria

Some people experience gender dysphoria at such a level that the distress meets criteria for a formal diagnosis that might be classified as a mental disorder. Such a diagnosis is not a license for stigmatization or for the deprivation of civil and human rights. Existing classification systems such as the *Diagnostic Statistical Manual of Mental Disorders (DSM)* (American Psychiatric Association, 2000) and the *International Classification of Diseases* (*ICD*) (World Health Organization, 2007) define hundreds of mental disorders that vary in onset, duration, pathogenesis, functional disability, and treatability. All of these systems attempt to classify clusters of symptoms and conditions, not the individuals themselves. A disorder is a description of something with which a person might struggle, not a description of the person or the person's identity.

Thus, transsexual, transgender, and gender-nonconforming individuals are not inherently disordered. Rather, the distress of gender dysphoria, when present, is the concern that might be diagnosable and for which various treatment options are available. The existence of a diagnosis for such dysphoria often facilitates access to health care and can guide further research into effective treatments.

Research is leading to new diagnostic nomenclatures, and terms are changing in both the *DSM* (Cohen-Kettenis & Pfäfflin, 2010; Knudson, De Cuypere, & Bockting, 2010b; Meyer-Bahlburg, 2010; Zucker, 2010) and the *ICD*. For this reason, familiar terms are employed in the *SOC* and definitions are provided for terms that may be emerging. Health professionals should refer to the most current diagnostic criteria and appropriate codes to apply in their practice areas.

IV
Epidemiologic Considerations

Formal epidemiologic studies on the incidence[III] and prevalence[IV] of transsexualism specifically or transgender and gender-nonconforming identities in general have not been conducted, and efforts to achieve realistic estimates are fraught with enormous difficulties (Institute of Medicine, 2011; Zucker & Lawrence, 2009). Even if epidemiologic studies established that a similar proportion of transsexual, transgender, or gender-nonconforming people existed all over the world, it is likely that cultural differences from one country to another would alter both the behavioral expressions of different gender identities and the extent to which gender dysphoria—distinct from one's gender identity—is actually occurring in a population. While in most countries, crossing normative gender boundaries generates moral censure rather than compassion, there are examples in certain cultures of gender-nonconforming behaviors (e.g., in spiritual leaders) that are less stigmatized and even revered (Besnier, 1994; Bolin, 1988; Chiñas, 1995; Coleman, Colgan, & Gooren, 1992; Costa & Matzner, 2007; Jackson & Sullivan, 1999; Nanda, 1998; Taywaditep, Coleman, & Dumronggittigule, 1997).

For various reasons, researchers who have studied incidence and prevalence have tended to focus on the most easily counted subgroup of gender-nonconforming individuals: transsexual individuals who experience gender dysphoria and who present for gender-transition-related care at specialist gender clinics (Zucker & Lawrence, 2009). Most studies have been conducted in European countries such as Sweden (Wålinder, 1968, 1971), the United Kingdom (Hoenig & Kenna, 1974),

III **incidence**—the number of new cases arising in a given period (e.g., a year)
IV **prevalence**—the number of individuals having a condition, divided by the number of people in the general population

the Netherlands (Bakker, Van Kesteren, Gooren, & Bezemer, 1993; Eklund, Gooren, & Bezemer, 1988; van Kesteren, Gooren, & Megens, 1996), Germany (Weitze & Osburg, 1996), and Belgium (De Cuypere et al., 2007). One was conducted in Singapore (Tsoi, 1988).

De Cuypere and colleagues (2007) reviewed such studies, as well as conducted their own. Together, those studies span 39 years. Leaving aside two outlier findings from Pauly in 1965 and Tsoi in 1988, ten studies involving eight countries remain. The prevalence figures reported in these ten studies range from 1:11,900 to 1:45,000 for male-to-female individuals (MtF) and 1:30,400 to 1:200,000 for female-to-male (FtM) individuals. Some scholars have suggested that the prevalence is much higher, depending on the methodology used in the research (e.g., Olyslager & Conway, 2007).

Direct comparisons across studies are impossible, as each differed in their data collection methods and in their criteria for documenting a person as transsexual (e.g., whether or not a person had undergone genital reconstruction, versus had initiated hormone therapy, versus had come to the clinic seeking medically supervised transition services). The trend appears to be towards higher prevalence rates in the more recent studies, possibly indicating increasing numbers of people seeking clinical care. Support for this interpretation comes from research by Reed and colleagues (2009), who reported a doubling of the numbers of people accessing care at gender clinics in the United Kingdom every five or six years. Similarly, Zucker and colleagues (2008) reported a four- to five-fold increase in child and adolescent referrals to their Toronto, Canada clinic over a 30-year period.

The numbers yielded by studies such as these can be considered minimum estimates at best. The published figures are mostly derived from clinics where patients met criteria for severe gender dysphoria and had access to health care at those clinics. These estimates do not take into account that treatments offered in a particular clinic setting might not be perceived as affordable, useful, or acceptable by all self-identified gender dysphoric individuals in a given area. By counting only those people who present at clinics for a specific type of treatment, an unspecified number of gender dysphoric individuals are overlooked.

Other clinical observations (not yet firmly supported by systematic study) support the likelihood of a higher prevalence of gender dysphoria: (i) Previously unrecognized gender dysphoria is occasionally diagnosed when patients are seen with anxiety, depression, conduct disorder, substance abuse, dissociative identity disorders, borderline personality disorder, sexual disorders, and disorders of sex development (Cole, O'Boyle, Emory, & Meyer III, 1997). (ii) Some crossdressers, drag queens/kings or female/male impersonators, and gay and lesbian individuals may be experiencing gender dysphoria (Bullough & Bullough, 1993). (iii) The intensity of some people's gender dysphoria fluctuates below and above a clinical threshold (Docter, 1988). (iv) Gender nonconformity among FtM individuals tends to be relatively invisible in many cultures, particularly to Western health

professionals and researchers who have conducted most of the studies on which the current estimates of prevalence and incidence are based (Winter, 2009).

Overall, the existing data should be considered a starting point, and health care would benefit from more rigorous epidemiologic study in different locations worldwide.

V

Overview of Therapeutic Approaches for Gender Dysphoria

Advancements in the Knowledge and Treatment of Gender Dysphoria

In the second half of the 20th century, awareness of the phenomenon of gender dysphoria increased when health professionals began to provide assistance to alleviate gender dysphoria by supporting changes in primary and secondary sex characteristics through hormone therapy and surgery, along with a change in gender role. Although Harry Benjamin already acknowledged a spectrum of gender nonconformity (Benjamin, 1966), the initial clinical approach largely focused on identifying who was an appropriate candidate for sex reassignment to facilitate a physical change from male to female or female to male as completely as possible (e.g., Green & Fleming, 1990; Hastings, 1974). This approach was extensively evaluated and proved to be highly effective. Satisfaction rates across studies ranged from 87% of MtF patients to 97% of FtM patients (Green & Fleming, 1990), and regrets were extremely rare (1–1.5% of MtF patients and <1% of FtM patients; Pfäfflin, 1993). Indeed, hormone therapy and surgery have been found to be medically necessary to alleviate gender dysphoria in many people (American Medical Association, 2008; Anton, 2009; World Professional Association for Transgender Health, 2008).

As the field matured, health professionals recognized that while many individuals need both hormone therapy and surgery to alleviate their gender dysphoria, others need only one of these treatment options and some need neither (Bockting & Goldberg, 2006; Bockting, 2008; Lev, 2004). Often with the help of psychotherapy, some individuals integrate their trans- or cross-gender feelings into the gender role they were assigned at birth and do not feel the need to feminize or masculinize their body. For others, changes in gender role and expression are sufficient to alleviate

gender dysphoria. Some patients may need hormones, a possible change in gender role, but not surgery; others may need a change in gender role along with surgery, but not hormones. In other words, treatment for gender dysphoria has become more individualized.

As a generation of transsexual, transgender, and gender-nonconforming individuals has come of age—many of whom have benefitted from different therapeutic approaches—they have become more visible as a community and demonstrated considerable diversity in their gender identities, roles, and expressions. Some individuals describe themselves not as gender-nonconforming but as unambiguously cross-sexed (i.e., as a member of the other sex; Bockting, 2008). Other individuals affirm their unique gender identity and no longer consider themselves to be either male or female (Bornstein, 1994; Kimberly, 1997; Stone, 1991; Warren, 1993). Instead, they may describe their gender identity in specific terms such as transgender, bigender, or genderqueer, affirming their unique experiences that may transcend a male/female binary understanding of gender (Bockting, 2008; Ekins & King, 2006; Nestle, Wilchins, & Howell, 2002). They may not experience their process of identity affirmation as a "transition," because they never fully embraced the gender role they were assigned at birth or because they actualize their gender identity, role, and expression in a way that does not involve a change from one gender role to another. For example, some youth identifying as genderqueer have always experienced their gender identity and role as such (genderqueer). Greater public visibility and awareness of gender diversity (Feinberg, 1996) has further expanded options for people with gender dysphoria to actualize an identity and find a gender role and expression that are comfortable for them.

Health professionals can assist gender dysphoric individuals with affirming their gender identity, exploring different options for expression of that identity, and making decisions about medical treatment options for alleviating gender dysphoria.

Options for Psychological and Medical Treatment of Gender Dysphoria

For individuals seeking care for gender dysphoria, a variety of therapeutic options can be considered. The number and type of interventions applied and the order in which these take place may differ from person to person (e.g., Bockting, Knudson, & Goldberg, 2006; Bolin, 1994; Rachlin, 1999; Rachlin, Green, & Lombardi, 2008; Rachlin, Hansbury, & Pardo, 2010). Treatment options include the following:

- Changes in gender expression and role (which may involve living part time or full time in another gender role, consistent with one's gender identity);
- Hormone therapy to feminize or masculinize the body;

- Surgery to change primary and/or secondary sex characteristics (e.g., breasts/chest, external and/or internal genitalia, facial features, body contouring);
- Psychotherapy (individual, couple, family, or group) for purposes such as exploring gender identity, role, and expression; addressing the negative impact of gender dysphoria and stigma on mental health; alleviating internalized transphobia; enhancing social and peer support; improving body image; or promoting resilience.

Options for Social Support and Changes in Gender Expression

In addition (or as an alternative) to the psychological- and medical-treatment options described above, other options can be considered to help alleviate gender dysphoria, for example:

- In-person and online peer support resources, groups, or community organizations that provide avenues for social support and advocacy;
- In-person and online support resources for families and friends;
- Voice and communication therapy to help individuals develop verbal and non-verbal communication skills that facilitate comfort with their gender identity;
- Hair removal through electrolysis, laser treatment, or waxing;
- Breast binding or padding, genital tucking or penile prostheses, padding of hips or buttocks;
- Changes in name and gender marker on identity documents.

VI

Assessment and Treatment of Children and Adolescents With Gender Dysphoria

There are a number of differences in the phenomenology, developmental course, and treatment approaches for gender dysphoria in children, adolescents, and adults. In children and adolescents, a rapid and dramatic developmental process (physical, psychological, and sexual) is involved and

there is greater fluidity and variability in outcomes, particularly in prepubertal children. Accordingly, this section of the *SOC* offers specific clinical guidelines for the assessment and treatment of gender dysphoric children and adolescents.

Differences Between Children and Adolescents with Gender Dysphoria

An important difference between gender dysphoric children and adolescents is in the proportion for whom dysphoria persists into adulthood. Gender dysphoria during childhood does not inevitably continue into adulthood.[V] Rather, in follow-up studies of prepubertal children (mainly boys) who were referred to clinics for assessment of gender dysphoria, the dysphoria persisted into adulthood for only 6–23% of children (Cohen-Kettenis, 2001; Zucker & Bradley, 1995). Boys in these studies were more likely to identify as gay in adulthood than as transgender (Green, 1987; Money & Russo, 1979; Zucker & Bradley, 1995; Zuger, 1984). Newer studies, also including girls, showed a 12–27% persistence rate of gender dysphoria into adulthood (Drummond, Bradley, Peterson-Badali, & Zucker, 2008; Wallien & Cohen-Kettenis, 2008).

In contrast, the persistence of gender dysphoria into adulthood appears to be much higher for adolescents. No formal prospective studies exist. However, in a follow-up study of 70 adolescents who were diagnosed with gender dysphoria and given puberty-suppressing hormones, all continued with actual sex reassignment, beginning with feminizing/masculinizing hormone therapy (de Vries, Steensma, Doreleijers, & Cohen-Kettenis, 2010).

Another difference between gender dysphoric children and adolescents is in the sex ratios for each age group. In clinically referred, gender dysphoric children under age 12, the male/female ratio ranges from 6:1 to 3:1 (Zucker, 2004). In clinically referred, gender dysphoric adolescents older than age 12, the male/female ratio is close to 1:1 (Cohen-Kettenis & Pfäfflin, 2003).

As discussed in section IV and by Zucker and Lawrence (2009), formal epidemiologic studies on gender dysphoria—in children, adolescents, and adults—are lacking. Additional research is needed to refine estimates of its prevalence and persistence in different populations worldwide.

V Gender-nonconforming behaviors in children may continue into adulthood, but such behaviors are not necessarily indicative of gender dysphoria and a need for treatment. As described in section III, gender dysphoria is not synonymous with diversity in gender expression.

Phenomenology in Children

Children as young as age two may show features that could indicate gender dysphoria. They may express a wish to be of the other sex and be unhappy about their physical sex characteristics and functions. In addition, they may prefer clothes, toys, and games that are commonly associated with the other sex and prefer playing with other-sex peers. There appears to be heterogeneity in these features: Some children demonstrate extremely gender-nonconforming behavior and wishes, accompanied by persistent and severe discomfort with their primary sex characteristics. In other children, these characteristics are less intense or only partially present (Cohen-Kettenis et al., 2006; Knudson, De Cuypere, & Bockting, 2010a).

It is relatively common for gender dysphoric children to have coexisting internalizing disorders such as anxiety and depression (Cohen-Kettenis, Owen, Kaijser, Bradley, & Zucker, 2003; Wallien, Swaab, & Cohen-Kettenis, 2007; Zucker, Owen, Bradley, & Ameeriar, 2002). The prevalence of autism spectrum disorders seems to be higher in clinically referred, gender dysphoric children than in the general population (de Vries, Noens, Cohen-Kettenis, van Berckelaer-Onnes, & Doreleijers, 2010).

Phenomenology in Adolescents

In most children, gender dysphoria will disappear before, or early in, puberty. However, in some children these feelings will intensify and body aversion will develop or increase as they become adolescents and their secondary sex characteristics develop (Cohen-Kettenis, 2001; Cohen-Kettenis & Pfäfflin, 2003; Drummond et al., 2008; Wallien & Cohen-Kettenis, 2008; Zucker & Bradley, 1995). Data from one study suggest that more extreme gender nonconformity in childhood is associated with persistence of gender dysphoria into late adolescence and early adulthood (Wallien & Cohen-Kettenis, 2008). Yet many adolescents and adults presenting with gender dysphoria do not report a history of childhood gender-nonconforming behaviors (Docter, 1988; Landén, Wålinder, & Lundström, 1998). Therefore, it may come as a surprise to others (parents, other family members, friends, and community members) when a youth's gender dysphoria first becomes evident in adolescence.

Adolescents who experience their primary and/or secondary sex characteristics and their sex assigned at birth as inconsistent with their gender identity may be intensely distressed about it. Many, but not all, gender dysphoric adolescents have a strong wish for hormones and surgery. Increasing numbers of adolescents have already started living in their desired gender role upon entering high school (Cohen-Kettenis & Pfäfflin, 2003).

Among adolescents who are referred to gender identity clinics, the number considered eligible for early medical treatment—starting with GnRH analogues to suppress puberty in the first Tanner stages—differs among countries and centers. Not all clinics offer puberty suppression. If such treatment is offered, the pubertal stage at which adolescents are allowed to start varies from Tanner stage 2 to stage 4 (Delemarre-van de Waal & Cohen-Kettenis, 2006; Zucker et al., 2012). The percentages of treated adolescents are likely influenced by the organization of health care, insurance aspects, cultural differences, opinions of health professionals, and diagnostic procedures offered in different settings.

Inexperienced clinicians may mistake indications of gender dysphoria for delusions. Phenomenologically, there is a qualitative difference between the presentation of gender dysphoria and the presentation of delusions or other psychotic symptoms. The vast majority of children and adolescents with gender dysphoria are not suffering from underlying severe psychiatric illness such as psychotic disorders (Steensma, Biemond, de Boer, & Cohen-Kettenis, published online ahead of print January 7, 2011).

It is more common for adolescents with gender dysphoria to have coexisting internalizing disorders such as anxiety and depression, and/or externalizing disorders such as oppositional defiant disorder (de Vries et al., 2010). As in children, there seems to be a higher prevalence of autistic spectrum disorders in clinically referred, gender dysphoric adolescents than in the general adolescent population (de Vries et al., 2010).

Competency of Mental Health Professionals Working with Children or Adolescents with Gender Dysphoria

The following are recommended minimum credentials for mental health professionals who assess, refer, and offer therapy to children and adolescents presenting with gender dysphoria:

1. Meet the competency requirements for mental health professionals working with adults, as outlined in section VII;

2. Trained in childhood and adolescent developmental psychopathology;

3. Competent in diagnosing and treating the ordinary problems of children and adolescents.

Roles of Mental Health Professionals Working with Children and Adolescents with Gender Dysphoria

The roles of mental health professionals working with gender dysphoric children and adolescents may include the following:

1. Directly assess gender dysphoria in children and adolescents (see general guidelines for assessment, below).

2. Provide family counseling and supportive psychotherapy to assist children and adolescents with exploring their gender identity, alleviating distress related to their gender dysphoria, and ameliorating any other psychosocial difficulties.

3. Assess and treat any coexisting mental health concerns of children or adolescents (or refer to another mental health professional for treatment). Such concerns should be addressed as part of the overall treatment plan.

4. Refer adolescents for additional physical interventions (such as puberty-suppressing hormones) to alleviate gender dysphoria. The referral should include documentation of an assessment of gender dysphoria and mental health, the adolescent's eligibility for physical interventions (outlined below), the mental health professional's relevant expertise, and any other information pertinent to the youth's health and referral for specific treatments.

5. Educate and advocate on behalf of gender dysphoric children, adolescents, and their families in their community (e.g., day care centers, schools, camps, other organizations). This is particularly important in light of evidence that children and adolescents who do not conform to socially prescribed gender norms may experience harassment in school (Grossman, D'Augelli, & Salter, 2006; Grossman, D'Augelli, Howell, & Hubbard, 2006; Sausa, 2005), putting them at risk for social isolation, depression, and other negative sequelae (Nuttbrock et al., 2010).

6. Provide children, youth, and their families with information and referral for peer support, such as support groups for parents of gender-nonconforming and transgender children (Gold & MacNish, 2011; Pleak, 1999; Rosenberg, 2002).

Assessment and psychosocial interventions for children and adolescents are often provided within a multidisciplinary gender identity specialty service. If such a multidisciplinary service is not available, a mental health professional should provide consultation and liaison arrangements with a pediatric endocrinologist for the purpose of assessment, education, and involvement in any decisions about physical interventions.

Psychological Assessment of Children and Adolescents

When assessing children and adolescents who present with gender dysphoria, mental health professionals should broadly conform to the following guidelines:

1. Mental health professionals should not dismiss or express a negative attitude towards nonconforming gender identities or indications of gender dysphoria. Rather, they should acknowledge the presenting concerns of children, adolescents, and their families; offer a thorough assessment for gender dysphoria and any coexisting mental health concerns; and educate clients and their families about therapeutic options, if needed. Acceptance, and alleviation of secrecy, can bring considerable relief to gender dysphoric children/adolescents and their families.

2. Assessment of gender dysphoria and mental health should explore the nature and characteristics of a child's or adolescent's gender identity. A psychodiagnostic and psychiatric assessment—covering the areas of emotional functioning, peer and other social relationships, and intellectual functioning/school achievement—should be performed. Assessment should include an evaluation of the strengths and weaknesses of family functioning. Emotional and behavioral problems are relatively common, and unresolved issues in a child's or youth's environment may be present (de Vries, Doreleijers, Steensma, & Cohen-Kettenis, 2011; Di Ceglie & Thümmel, 2006; Wallien et al., 2007).

3. For adolescents, the assessment phase should also be used to inform youth and their families about the possibilities and limitations of different treatments. This is necessary for informed consent, but also important for assessment. The way that adolescents respond to information about the reality of sex reassignment can be diagnostically informative. Correct information may alter a youth's desire for certain treatment, if the desire was based on unrealistic expectations of its possibilities.

Psychological and Social Interventions for Children and Adolescents

When supporting and treating children and adolescents with gender dysphoria, health professionals should broadly conform to the following guidelines:

1. Mental health professionals should help families to have an accepting and nurturing response to the concerns of their gender dysphoric child or adolescent. Families play an important role in the psychological health and well-being of youth (Brill & Pepper, 2008; Lev, 2004). This also applies to peers and mentors from the community, who can be another source of social support.

2. Psychotherapy should focus on reducing a child's or adolescent's distress related to the gender dysphoria and on ameliorating any other psychosocial difficulties. For youth pursuing sex reassignment, psychotherapy may focus on supporting them before, during, and after reassignment. Formal evaluations of different psychotherapeutic approaches for this situation have not been published, but several counseling methods have been described (Cohen-Kettenis, 2006; de Vries, Cohen-Kettenis, & Delemarre-van de Waal, 2006; Di Ceglie & Thümmel, 2006; Hill, Menvielle, Sica, & Johnson, 2010; Malpas, in press; Menvielle & Tuerk, 2002; Rosenberg, 2002; Vanderburgh, 2009; Zucker, 2006).

   Treatment aimed at trying to change a person's gender identity and expression to become more congruent with sex assigned at birth has been attempted in the past without success (Gelder & Marks, 1969; Greenson, 1964), particularly in the long term (Cohen-Kettenis & Kuiper, 1984; Pauly, 1965). Such treatment is no longer considered ethical.

3. Families should be supported in managing uncertainty and anxiety about their child's or adolescent's psychosexual outcomes and in helping youth to develop a positive self-concept.

4. Mental health professionals should not impose a binary view of gender. They should give ample room for clients to explore different options for gender expression. Hormonal or surgical interventions are appropriate for some adolescents, but not for others.

5. Clients and their families should be supported in making difficult decisions regarding the extent to which clients are allowed to express a gender role that is consistent with their gender identity, as well as the timing of changes in gender role and possible social transition. For example, a client might attend school while undergoing social transition only partly (e.g., by wearing clothing and having a hairstyle that reflects gender identity) or completely (e.g., by also using a name and pronouns congruent with gender identity). Difficult issues include whether and when to inform other people of the client's situation, and how others in their lives might respond.

6. Health professionals should support clients and their families as educators and advocates in their interactions with community members and authorities such as teachers, school boards, and courts.

7. Mental health professionals should strive to maintain a therapeutic relationship with gender-nonconforming children/adolescents and their families throughout any subsequent social changes or physical interventions. This ensures that decisions about gender expression and the treatment of gender dysphoria are thoughtfully and recurrently considered. The same reasoning applies if a child or adolescent has already socially changed gender role prior to being seen by a mental health professional.

Social Transition in Early Childhood

Some children state that they want to make a social transition to a different gender role long before puberty. For some children, this may reflect an expression of their gender identity. For others, this could be motivated by other forces. Families vary in the extent to which they allow their young children to make a social transition to another gender role. Social transitions in early childhood do occur within some families with early success. This is a controversial issue, and divergent views are held by health professionals. The current evidence base is insufficient to predict the long-term outcomes of completing a gender role transition during early childhood. Outcomes research with children who completed early social transitions would greatly inform future clinical recommendations.

Mental health professionals can help families to make decisions regarding the timing and process of any gender role changes for their young children. They should provide information and help parents to weigh the potential benefits and challenges of particular choices. Relevant in this respect are the previously described relatively low persistence rates of childhood gender dysphoria (Drummond et al., 2008; Wallien & Cohen-Kettenis, 2008). A change back to the original gender role can be highly distressing and even result in postponement of this second social transition on the child's part (Steensma & Cohen-Kettenis, 2011). For reasons such as these, parents may want to present this role change as an exploration of living in another gender role rather than an irreversible situation. Mental health professionals can assist parents in identifying potential in-between solutions or compromises (e.g., only when on vacation). It is also important that parents explicitly let the child know that there is a way back.

Regardless of a family's decisions regarding transition (timing, extent), professionals should counsel and support them as they work through the options and implications. If parents do not allow their young child to make a gender-role transition, they may need counseling to assist them with meeting their child's needs in a sensitive and nurturing way, ensuring that the child has ample possibilities to explore gender feelings and behavior in a safe environment. If parents do allow their young child to make a gender role transition, they may need counseling to facilitate a positive experience for their child. For example, they may need support in using correct pronouns, maintaining a safe and supportive environment for their transitioning child (e.g., in school, peer group settings), and communicating with other people in their child's life. In either case, as a child nears puberty, further assessment may be needed as options for physical interventions become relevant.

Physical Interventions for Adolescents

Before any physical interventions are considered for adolescents, extensive exploration of psychological, family, and social issues should be undertaken, as outlined above. The duration of this exploration may vary considerably depending on the complexity of the situation.

Physical interventions should be addressed in the context of adolescent development. Some identity beliefs in adolescents may become firmly held and strongly expressed, giving a false impression of irreversibility. An adolescent's shift towards gender conformity can occur primarily to please the parents and may not persist or reflect a permanent change in gender dysphoria (Hembree et al., 2009; Steensma et al., published online ahead of print January 7, 2011).

Physical interventions for adolescents fall into three categories or stages (Hembree et al., 2009):

1. *Fully reversible interventions*. These involve the use of GnRH analogues to suppress estrogen or testosterone production and consequently delay the physical changes of puberty. Alternative treatment options include progestins (most commonly medroxyprogesterone) or other medications (such as spironolactone) that decrease the effects of androgens secreted by the testicles of adolescents who are not receiving GnRH analogues. Continuous oral contraceptives (or depot medroxyprogesterone) may be used to suppress menses.

2. *Partially reversible interventions*. These include hormone therapy to masculinize or feminize the body. Some hormone-induced changes may need reconstructive surgery to reverse the effect (e.g., gynaecomastia caused by estrogens), while other changes are not reversible (e.g., deepening of the voice caused by testosterone).

3. *Irreversible interventions*. These are surgical procedures.

A staged process is recommended to keep options open through the first two stages. Moving from one stage to another should not occur until there has been adequate time for adolescents and their parents to assimilate fully the effects of earlier interventions.

Fully Reversible Interventions

Adolescents may be eligible for puberty-suppressing hormones as soon as pubertal changes have begun. In order for adolescents and their parents to make an informed decision about pubertal delay, it is recommended that adolescents experience the onset of puberty to at least Tanner Stage 2. Some children may arrive at this stage at very young ages (e.g., 9 years of age). Studies

evaluating this approach have only included children who were at least 12 years of age (Cohen-Kettenis, Schagen, Steensma, de Vries, & Delemarre-van de Waal, 2011; de Vries, Steensma et al., 2010; Delemarre-van de Waal, van Weissenbruch, & Cohen Kettenis, 2004; Delemarre-van de Waal & Cohen-Kettenis, 2006).

Two goals justify intervention with puberty-suppressing hormones: (i) their use gives adolescents more time to explore their gender nonconformity and other developmental issues; and (ii) their use may facilitate transition by preventing the development of sex characteristics that are difficult or impossible to reverse if adolescents continue on to pursue sex reassignment.

Puberty suppression may continue for a few years, at which time a decision is made to either discontinue all hormone therapy or transition to a feminizing/masculinizing hormone regimen. Pubertal suppression does not inevitably lead to social transition or to sex reassignment.

Criteria for Puberty-Suppressing Hormones

In order for adolescents to receive puberty-suppressing hormones, the following minimum criteria must be met:

1. The adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed);

2. Gender dysphoria emerged or worsened with the onset of puberty;

3. Any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment;

4. The adolescent has given informed consent and, particularly when the adolescent has not reached the age of medical consent, the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process.

Regimens, Monitoring, and Risks for Puberty Suppression

For puberty suppression, adolescents with male genitalia should be treated with GnRH analogues, which stop luteinizing hormone secretion and therefore testosterone secretion. Alternatively, they may be treated with progestins (such as medroxyprogesterone) or with other medications that block testosterone secretion and/or neutralize testosterone action. Adolescents with female genitalia should be treated with GnRH analogues, which stop the production of estrogens and

progesterone. Alternatively, they may be treated with progestins (such as medroxyprogesterone). Continuous oral contraceptives (or depot medroxyprogesterone) may be used to suppress menses. In both groups of adolescents, use of GnRH analogues is the preferred treatment (Hembree et al., 2009), but their high cost is prohibitive for some patients.

During pubertal suppression, an adolescent's physical development should be carefully monitored—preferably by a pediatric endocrinologist—so that any necessary interventions can occur (e.g., to establish an adequate gender appropriate height, to improve iatrogenic low bone mineral density) (Hembree et al., 2009).

Early use of puberty-suppressing hormones may avert negative social and emotional consequences of gender dysphoria more effectively than their later use would. Intervention in early adolescence should be managed with pediatric endocrinological advice, when available. Adolescents with male genitalia who start GnRH analogues early in puberty should be informed that this could result in insufficient penile tissue for penile inversion vaginoplasty techniques (alternative techniques, such as the use of a skin graft or colon tissue, are available).

Neither puberty suppression nor allowing puberty to occur is a neutral act. On the one hand, functioning in later life can be compromised by the development of irreversible secondary sex characteristics during puberty and by years spent experiencing intense gender dysphoria. On the other hand, there are concerns about negative physical side effects of GnRH analogue use (e.g., on bone development and height). Although the very first results of this approach (as assessed for adolescents followed over 10 years) are promising (Cohen-Kettenis et al., 2011; Delemarre-van de Waal & Cohen-Kettenis, 2006), the long-term effects can only be determined when the earliest-treated patients reach the appropriate age.

Partially Reversible Interventions

Adolescents may be eligible to begin feminizing/masculinizing hormone therapy, preferably with parental consent. In many countries, 16-year-olds are legal adults for medical decision-making and do not require parental consent. Ideally, treatment decisions should be made among the adolescent, the family, and the treatment team.

Regimens for hormone therapy in gender dysphoric adolescents differ substantially from those used in adults (Hembree et al., 2009). The hormone regimens for youth are adapted to account for the somatic, emotional, and mental development that occurs throughout adolescence (Hembree et al., 2009).

Irreversible Interventions

Genital surgery should not be carried out until (i) patients reach the legal age of majority to give consent for medical procedures in a given country, and (ii) patients have lived continuously for at least 12 months in the gender role that is congruent with their gender identity. The age threshold should be seen as a minimum criterion and not an indication in and of itself for active intervention.

Chest surgery in FtM patients could be carried out earlier, preferably after ample time of living in the desired gender role and after one year of testosterone treatment. The intent of this suggested sequence is to give adolescents sufficient opportunity to experience and socially adjust in a more masculine gender role, before undergoing irreversible surgery. However, different approaches may be more suitable, depending on an adolescent's specific clinical situation and goals for gender identity expression.

Risks of Withholding Medical Treatment for Adolescents

Refusing timely medical interventions for adolescents might prolong gender dysphoria and contribute to an appearance that could provoke abuse and stigmatization. As the level of gender-related abuse is strongly associated with the degree of psychiatric distress during adolescence (Nuttbrock et al., 2010), withholding puberty suppression and subsequent feminizing or masculinizing hormone therapy is not a neutral option for adolescents.

VII
Mental Health

Transsexual, transgender, and gender-nonconforming people might seek the assistance of a mental health professional for any number of reasons. Regardless of a person's reason for seeking care, mental health professionals should have familiarity with gender nonconformity, act with appropriate cultural competence, and exhibit sensitivity in providing care.

This section of the *SOC* focuses on the role of mental health professionals in the care of adults seeking help for gender dysphoria and related concerns. Professionals working with gender dysphoric children, adolescents, and their families should consult section VI.

Competency of Mental Health Professionals Working with Adults Who Present with Gender Dysphoria

The training of mental health professionals competent to work with gender dysphoric adults rests upon basic general clinical competence in the assessment, diagnosis, and treatment of mental health concerns. Clinical training may occur within any discipline that prepares mental health professionals for clinical practice, such as psychology, psychiatry, social work, mental health counseling, marriage and family therapy, nursing, or family medicine with specific training in behavioral health and counseling. The following are recommended minimum credentials for mental health professionals who work with adults presenting with gender dysphoria:

1. A master's degree or its equivalent in a clinical behavioral science field. This degree, or a more advanced one, should be granted by an institution accredited by the appropriate national or regional accrediting board. The mental health professional should have documented credentials from a relevant licensing board or equivalent for that country.

2. Competence in using the *Diagnostic Statistical Manual of Mental Disorders* and/or the *International Classification of Diseases* for diagnostic purposes.

3. Ability to recognize and diagnose coexisting mental health concerns and to distinguish these from gender dysphoria.

4. Documented supervised training and competence in psychotherapy or counseling.

5. Knowledgeable about gender-nonconforming identities and expressions, and the assessment and treatment of gender dysphoria.

6. Continuing education in the assessment and treatment of gender dysphoria. This may include attending relevant professional meetings, workshops, or seminars; obtaining supervision from a mental health professional with relevant experience; or participating in research related to gender nonconformity and gender dysphoria.

In addition to the minimum credentials above, it is recommended that mental health professionals develop and maintain cultural competence to facilitate their work with transsexual, transgender, and gender-nonconforming clients. This may involve, for example, becoming knowledgeable about current community, advocacy, and public policy issues relevant to these clients and their families. Additionally, knowledge about sexuality, sexual health concerns, and the assessment and treatment of sexual disorders is preferred.

Mental health professionals who are new to the field (irrespective of their level of training and other experience) should work under the supervision of a mental health professional with established competence in the assessment and treatment of gender dysphoria.

Tasks of Mental Health Professionals Working with Adults Who Present with Gender Dysphoria

Mental health professionals may serve transsexual, transgender, and gender-nonconforming individuals and their families in many ways, depending on a client's needs. For example, mental health professionals may serve as a psychotherapist, counselor, or family therapist, or as a diagnostician/assessor, advocate, or educator.

Mental health professionals should determine a client's reasons for seeking professional assistance. For example, a client may be presenting for any combination of the following health care services: psychotherapeutic assistance to explore gender identity and expression or to facilitate a coming-out process; assessment and referral for feminizing/masculinizing medical interventions; psychological support for family members (partners, children, extended family); psychotherapy unrelated to gender concerns; or other professional services.

Below are general guidelines for common tasks that mental health professionals may fulfill in working with adults who present with gender dysphoria.

Tasks Related to Assessment and Referral

1. Assess Gender Dysphoria

Mental health professionals assess clients' gender dysphoria in the context of an evaluation of their psychosocial adjustment (Bockting et al., 2006; Lev, 2004, 2009). The evaluation includes, at a minimum, assessment of gender identity and gender dysphoria, history and development of gender dysphoric feelings, the impact of stigma attached to gender nonconformity on mental health, and the availability of support from family, friends, and peers (for example, in-person or online contact with other transsexual, transgender, or gender-nonconforming individuals or groups). The evaluation may result in no diagnosis, in a formal diagnosis related to gender dysphoria, and/or in other diagnoses that describe aspects of the client's health and psychosocial adjustment. The role

of mental health professionals includes making reasonably sure that the gender dysphoria is not secondary to, or better accounted for, by other diagnoses.

Mental health professionals with the competencies described above (hereafter called "a qualified mental health professional") are best prepared to conduct this assessment of gender dysphoria. However, this task may instead be conducted by another type of health professional who has appropriate training in behavioral health and is competent in the assessment of gender dysphoria, particularly when functioning as part of a multidisciplinary specialty team that provides access to feminizing/masculinizing hormone therapy. This professional may be the prescribing hormone therapy provider or a member of that provider's health care team.

2. Provide Information Regarding Options for Gender Identity and Expression and Possible Medical Interventions

An important task of mental health professionals is to educate clients regarding the diversity of gender identities and expressions and the various options available to alleviate gender dysphoria. Mental health professionals then may facilitate a process (or refer elsewhere) in which clients explore these various options, with the goals of finding a comfortable gender role and expression and becoming prepared to make a fully informed decision about available medical interventions, if needed. This process may include referral for individual, family, and group therapy and/or to community resources and avenues for peer support. The professional and the client discuss the implications, both short- and long-term, of any changes in gender role and use of medical interventions. These implications can be psychological, social, physical, sexual, occupational, financial, and legal (Bockting et al., 2006; Lev, 2004).

This task is also best conducted by a qualified mental health professional, but may be conducted by another health professional with appropriate training in behavioral health and with sufficient knowledge about gender-nonconforming identities and expressions and about possible medical interventions for gender dysphoria, particularly when functioning as part of a multidisciplinary specialty team that provides access to feminizing/masculinizing hormone therapy.

3. Assess, Diagnose, and Discuss Treatment Options for Coexisting Mental Health Concerns

Clients presenting with gender dysphoria may struggle with a range of mental health concerns (Gómez-Gil, Trilla, Salamero, Godás, & Valdés, 2009; Murad et al., 2010) whether related or unrelated to what is often a long history of gender dysphoria and/or chronic minority stress. Possible concerns include anxiety, depression, self-harm, a history of abuse and neglect, compulsivity, substance abuse, sexual concerns, personality disorders, eating disorders, psychotic disorders, and autistic spectrum disorders (Bockting et al., 2006; Nuttbrock et al., 2010; Robinow, 2009). Mental health professionals should screen for these and other mental health concerns and incorporate

the identified concerns into the overall treatment plan. These concerns can be significant sources of distress and, if left untreated, can complicate the process of gender identity exploration and resolution of gender dysphoria (Bockting et al., 2006; Fraser, 2009a; Lev, 2009). Addressing these concerns can greatly facilitate the resolution of gender dysphoria, possible changes in gender role, the making of informed decisions about medical interventions, and improvements in quality of life.

Some clients may benefit from psychotropic medications to alleviate symptoms or treat coexisting mental health concerns. Mental health professionals are expected to recognize this and either provide pharmacotherapy or refer to a colleague who is qualified to do so. The presence of coexisting mental health concerns does not necessarily preclude possible changes in gender role or access to feminizing/masculinizing hormones or surgery; rather, these concerns need to be optimally managed prior to, or concurrent with, treatment of gender dysphoria. In addition, clients should be assessed for their ability to provide educated and informed consent for medical treatments.

Qualified mental health professionals are specifically trained to assess, diagnose, and treat (or refer to treatment for) these coexisting mental health concerns. Other health professionals with appropriate training in behavioral health, particularly when functioning as part of a multidisciplinary specialty team providing access to feminizing/masculinizing hormone therapy, may also screen for mental health concerns and, if indicated, provide referral for comprehensive assessment and treatment by a qualified mental health professional.

4. If Applicable, Assess Eligibility, Prepare, and Refer for Hormone Therapy

The *SOC* provide criteria to guide decisions regarding feminizing/masculinizing hormone therapy (outlined in section VIII and Appendix C). Mental health professionals can help clients who are considering hormone therapy to be both psychologically prepared (e.g., client has made a fully informed decision with clear and realistic expectations; is ready to receive the service in line with the overall treatment plan; has included family and community as appropriate) and practically prepared (e.g., has been evaluated by a physician to rule out or address medical contraindications to hormone use; has considered the psychosocial implications). If clients are of childbearing age, reproductive options (section IX) should be explored before initiating hormone therapy.

It is important for mental health professionals to recognize that decisions about hormones are first and foremost a client's decisions—as are all decisions regarding healthcare. However, mental health professionals have a responsibility to encourage, guide, and assist clients with making fully informed decisions and becoming adequately prepared. To best support their clients' decisions, mental health professionals need to have functioning working relationships with their clients and sufficient information about them. Clients should receive prompt and attentive evaluation, with the goal of alleviating their gender dysphoria and providing them with appropriate medical services.

Referral for feminizing/masculinizing hormone therapy

People may approach a specialized provider in any discipline to pursue feminizing/masculinizing hormone therapy. However, transgender health care is an interdisciplinary field, and coordination of care and referral among a client's overall care team is recommended.

Hormone therapy can be initiated with a referral from a qualified mental health professional. Alternatively, a health professional who is appropriately trained in behavioral health and competent in the assessment of gender dysphoria may assess eligibility, prepare, and refer the patient for hormone therapy, particularly in the absence of significant coexisting mental health concerns and when working in the context of a multidisciplinary specialty team. The referring health professional should provide documentation—in the chart and/or referral letter—of the patient's personal and treatment history, progress, and eligibility. Health professionals who recommend hormone therapy share the ethical and legal responsibility for that decision with the physician who provides the service.

The recommended content of the referral letter for feminizing/masculinizing hormone therapy is as follows:

1. The client's general identifying characteristics;

2. Results of the client's psychosocial assessment, including any diagnoses;

3. The duration of the referring health professional's relationship with the client, including the type of evaluation and therapy or counseling to date;

4. An explanation that the criteria for hormone therapy have been met, and a brief description of the clinical rationale for supporting the client's request for hormone therapy;

5. A statement that informed consent has been obtained from the patient;

6. A statement that the referring health professional is available for coordination of care and welcomes a phone call to establish this.

For providers working within a multidisciplinary specialty team, a letter may not be necessary; rather, the assessment and recommendation can be documented in the patient's chart.

5. If Applicable, Assess Eligibility, Prepare, and Refer for Surgery

The *SOC* also provide criteria to guide decisions regarding breast/chest surgery and genital surgery (outlined in section XI and Appendix C). Mental health professionals can help clients who are

considering surgery to be both psychologically prepared (e.g., has made a fully informed decision with clear and realistic expectations; is ready to receive the service in line with the overall treatment plan; has included family and community as appropriate) and practically prepared (e.g., has made an informed choice about a surgeon to perform the procedure; has arranged aftercare). If clients are of childbearing age, reproductive options (section IX) should be explored before undergoing genital surgery.

The *SOC* do not state criteria for other surgical procedures, such as feminizing or masculinizing facial surgery; however, mental health professionals can play an important role in helping their clients to make fully informed decisions about the timing and implications of such procedures in the context of the overall coming-out or transition process.

It is important for mental health professionals to recognize that decisions about surgery are first and foremost a client's decisions—as are all decisions regarding healthcare. However, mental health professionals have a responsibility to encourage, guide, and assist clients with making fully informed decisions and becoming adequately prepared. To best support their clients' decisions, mental health professionals need to have functioning working relationships with their clients and sufficient information about them. Clients should receive prompt and attentive evaluation, with the goal of alleviating their gender dysphoria and providing them with appropriate medical services.

Referral for surgery

Surgical treatments for gender dysphoria can be initiated by a referral (one or two, depending on the type of surgery) from a qualified mental health professional. The mental health professional provides documentation—in the chart and/or referral letter—of the patient's personal and treatment history, progress, and eligibility. Mental health professionals who recommend surgery share the ethical and legal responsibility for that decision with the surgeon.

- One referral from a qualified mental health professional is needed for breast/chest surgery (e.g., mastectomy, chest reconstruction, or augmentation mammoplasty).

- Two referrals—from qualified mental health professionals who have independently assessed the patient—are needed for genital surgery (i.e., hysterectomy/salpingo-oophorectomy, orchiectomy, genital reconstructive surgeries). If the first referral is from the patient's psychotherapist, the second referral should be from a person who has only had an evaluative role with the patient. Two separate letters, or one letter signed by both (e.g., if practicing within the same clinic) may be sent. Each referral letter, however, is expected to cover the same topics in the areas outlined below.

The recommended content of the referral letters for surgery is as follows:

1. The client's general identifying characteristics;
2. Results of the client's psychosocial assessment, including any diagnoses;
3. The duration of the mental health professional's relationship with the client, including the type of evaluation and therapy or counseling to date;
4. An explanation that the criteria for surgery have been met, and a brief description of the clinical rationale for supporting the patient's request for surgery;
5. A statement about the fact that informed consent has been obtained from the patient;
6. A statement that the mental health professional is available for coordination of care and welcomes a phone call to establish this.

For providers working within a multidisciplinary specialty team, a letter may not be necessary, rather, the assessment and recommendation can be documented in the patient's chart.

Relationship of Mental Health Professionals with Hormone-Prescribing Physicians, Surgeons, and Other Health Professionals

It is ideal for mental health professionals to perform their work and periodically discuss progress and obtain peer consultation from other professionals (both in mental health care and other health disciplines) who are competent in the assessment and treatment of gender dysphoria. The relationship among professionals involved in a client's health care should remain collaborative, with coordination and clinical dialogue taking place as needed. Open and consistent communication may be necessary for consultation, referral, and management of postoperative concerns.

Tasks Related to Psychotherapy

1. Psychotherapy Is Not an Absolute Requirement for Hormone Therapy and Surgery

A mental health screening and/or assessment as outlined above is needed for referral to hormonal and surgical treatments for gender dysphoria. In contrast, psychotherapy—although highly recommended—is not a requirement.

The *SOC* do not recommend a minimum number of psychotherapy sessions prior to hormone therapy or surgery. The reasons for this are multifaceted (Lev, 2009). First, a minimum number of sessions tends to be construed as a hurdle, which discourages the genuine opportunity for personal growth. Second, mental health professionals can offer important support to clients throughout all phases of exploration of gender identity, gender expression, and possible transition—not just prior to any possible medical interventions. Third, clients and their psychotherapists differ in their abilities to attain similar goals in a specified time period.

2. Goals of Psychotherapy for Adults with Gender Concerns

The general goal of psychotherapy is to find ways to maximize a person's overall psychological well-being, quality of life, and self-fulfillment. Psychotherapy is not intended to alter a person's gender identity; rather, psychotherapy can help an individual to explore gender concerns and find ways to alleviate gender dysphoria, if present (Bockting et al., 2006; Bockting & Coleman, 2007; Fraser, 2009a; Lev, 2004). Typically, the overarching treatment goal is to help transsexual, transgender, and gender-nonconforming individuals achieve long-term comfort in their gender identity expression, with realistic chances for success in their relationships, education, and work. For additional details, see Fraser (Fraser, 2009c).

Therapy may consist of individual, couple, family, or group psychotherapy, the latter being particularly important to foster peer support.

3. Psychotherapy for Transsexual, Transgender, and Gender-Nonconforming Clients, Including Counseling and Support for Changes in Gender Role

Finding a comfortable gender role is, first and foremost, a psychosocial process. Psychotherapy can be invaluable in assisting transsexual, transgender, and gender-nonconforming individuals with all of the following: (i) clarifying and exploring gender identity and role, (ii) addressing the impact of stigma and minority stress on one's mental health and human development, and (iii) facilitating a coming-out process (Bockting & Coleman, 2007; Devor, 2004; Lev, 2004), which for some individuals may include changes in gender role expression and the use of feminizing/masculinizing medical interventions.

Mental health professionals can provide support and promote interpersonal skills and resilience in individuals and their families as they navigate a world that often is ill-prepared to accommodate and respect transgender, transsexual, and gender-nonconforming people. Psychotherapy can also aid in alleviating any coexisting mental health concerns (e.g., anxiety, depression) identified during screening and assessment.

For transsexual, transgender, and gender-nonconforming individuals who plan to change gender roles permanently and make a social gender role transition, mental health professionals can facilitate the development of an individualized plan with specific goals and timelines. While the experience of changing one's gender role differs from person to person, the social aspects of the experience are usually challenging—often more so than the physical aspects. Because changing gender role can have profound personal and social consequences, the decision to do so should include an awareness of what the familial, interpersonal, educational, vocational, economic, and legal challenges are likely to be, so that people can function successfully in their gender role.

Many transsexual, transgender, and gender-nonconforming people will present for care without ever having been related to, or accepted in, the gender role that is most congruent with their gender identity. Mental health professionals can help these clients to explore and anticipate the implications of changes in gender role, and to pace the process of implementing these changes. Psychotherapy can provide a space for clients to begin to express themselves in ways that are congruent with their gender identity and, for some clients, overcome fears about changes in gender expression. Calculated risks can be taken outside of therapy to gain experience and build confidence in the new role. Assistance with coming out to family and community (friends, school, workplace) can be provided.

Other transsexual, transgender, and gender-nonconforming individuals will present for care already having acquired experience (minimal, moderate, or extensive) living in a gender role that differs from that associated with their birth-assigned sex. Mental health professionals can help these clients to identify and work through potential challenges and foster optimal adjustment as they continue to express changes in their gender role.

4. Family Therapy or Support for Family Members

Decisions about changes in gender role and medical interventions for gender dysphoria have implications for, not only clients, but also their families (Emerson & Rosenfeld, 1996; Fraser, 2009a; Lev, 2004). Mental health professionals can assist clients with making thoughtful decisions about communicating with family members and others about their gender identity and treatment decisions. Family therapy may include work with spouses or partners, as well as with children and other members of a client's extended family.

Clients may also request assistance with their relationships and sexual health. For example, they may want to explore their sexuality and intimacy-related concerns.

Family therapy might be offered as part of the client's individual therapy and, if clinically appropriate, by the same provider. Alternatively, referrals can be made to other therapists with relevant expertise

for working with family members or to sources of peer support (e.g., in-person or offline support networks of partners or families).

5. Follow-Up Care Throughout Life

Mental health professionals may work with clients and their families at many stages of their lives. Psychotherapy may be helpful at different times and for various issues throughout the life cycle.

6. E-Therapy, Online Counseling, or Distance Counseling

Online or e-therapy has been shown to be particularly useful for people who have difficulty accessing competent in-person psychotherapeutic treatment and who may experience isolation and stigma (Derrig-Palumbo & Zeine, 2005; Fenichel et al., 2004; Fraser, 2009b). By extrapolation, e-therapy may be a useful modality for psychotherapy with transsexual, transgender, and gender-nonconforming people. E-therapy offers opportunities for potentially enhanced, expanded, creative, and tailored delivery of services; however, as a developing modality it may also carry unexpected risk. Telemedicine guidelines are clear in some disciplines in some parts of the United States (Fraser, 2009b; Maheu, Pulier, Wilhelm, McMenamin, & Brown-Connolly, 2005) but not all; the international situation is even less well-defined (Maheu et al., 2005). Until sufficient evidence-based data on this use of e-therapy is available, caution in its use is advised.

Mental health professionals engaging in e-therapy are advised to stay current with their particular licensing board, professional association, and country's regulations, as well as the most recent literature pertaining to this rapidly evolving medium. A more thorough description of the potential uses, processes, and ethical concerns related to e-therapy has been published (Fraser, 2009b).

Other Tasks of Mental Health Professionals

1. Educate and Advocate on Behalf of Clients Within Their Community (Schools, Workplaces, Other Organizations) and Assist Clients with Making Changes in Identity Documents

Transsexual, transgender, and gender-nonconforming people may face challenges in their professional, educational, and other types of settings as they actualize their gender identity and expression (Lev, 2004, 2009). Mental health professionals can play an important role by educating people in these settings regarding gender nonconformity and by advocating on behalf of their clients (Currah, Juang, & Minter, 2006; Currah & Minter, 2000). This role may involve consultation

with school counselors, teachers, and administrators, human resources staff, personnel managers and employers, and representatives from other organizations and institutions. In addition, health providers may be called upon to support changes in a client's name and/or gender marker on identity documents such as passports, driver's licenses, birth certificates, and diplomas.

2. Provide Information and Referral for Peer Support

For some transsexual, transgender, and gender-nonconforming people, an experience in peer support groups may be more instructive regarding options for gender expression than anything individual psychotherapy could offer (Rachlin, 2002). Both experiences are potentially valuable, and all people exploring gender issues should be encouraged to participate in community activities, if possible. Resources for peer support and information should be made available.

Culture and Its Ramifications for Assessment and Psychotherapy

Health professionals work in enormously different environments across the world. Forms of distress that cause people to seek professional assistance in any culture are understood and classified by people in terms that are products of their own cultures (Frank & Frank, 1993). Cultural settings also largely determine how such conditions are understood by mental health professionals. Cultural differences related to gender identity and expression can affect patients, mental health professionals, and accepted psychotherapy practice. WPATH recognizes that the *SOC* have grown out of a Western tradition and may need to be adapted depending on the cultural context.

Ethical Guidelines Related to Mental Health Care

Mental health professionals need to be certified or licensed to practice in a given country according to that country's professional regulations (Fraser, 2009b; Pope & Vasquez, 2011). Professionals must adhere to the ethical codes of their professional licensing or certifying organizations in all of their work with transsexual, transgender, and gender-nonconforming clients.

Treatment aimed at trying to change a person's gender identity and lived gender expression to become more congruent with sex assigned at birth has been attempted in the past (Gelder & Marks, 1969; Greenson, 1964), yet without success, particularly in the long-term (Cohen-Kettenis & Kuiper, 1984; Pauly, 1965). Such treatment is no longer considered ethical.

If mental health professionals are uncomfortable with, or inexperienced in, working with transsexual, transgender, and gender-nonconforming individuals and their families, they should refer clients to a competent provider or, at minimum, consult with an expert peer. If no local practitioners are available, consultation may be done via telehealth methods, assuming local requirements for distance consultation are met.

Issues of Access to Care

Qualified mental health professionals are not universally available; thus, access to quality care might be limited. WPATH aims to improve access and provides regular continuing education opportunities to train professionals from various disciplines to provide quality, transgender-specific health care. Providing mental health care from a distance through the use of technology may be one way to improve access (Fraser, 2009b).

In many places around the world, access to health care for transsexual, transgender, and gender-nonconforming people is also limited by a lack of health insurance or other means to pay for needed care. WPATH urges health insurance companies and other third-party payers to cover the medically necessary treatments to alleviate gender dysphoria (American Medical Association, 2008; Anton, 2009; The World Professional Association for Transgender Health, 2008).

When faced with a client who is unable to access services, referral to available peer support resources (offline and online) is recommended. Finally, harm-reduction approaches might be indicated to assist clients with making healthy decisions to improve their lives.

VIII
Hormone Therapy

Medical Necessity of Hormone Therapy

Feminizing/masculinizing hormone therapy—the administration of exogenous endocrine agents to induce feminizing or masculinizing changes—is a medically necessary intervention for many transsexual, transgender, and gender-nonconforming individuals with gender dysphoria

(Newfield, Hart, Dibble, & Kohler, 2006; Pfäfflin & Junge, 1998). Some people seek maximum feminization/masculinization, while others experience relief with an androgynous presentation resulting from hormonal minimization of existing secondary sex characteristics (Factor & Rothblum, 2008). Evidence for the psychosocial outcomes of hormone therapy is summarized in Appendix D.

Hormone therapy must be individualized based on a patient's goals, the risk/benefit ratio of medications, the presence of other medical conditions, and consideration of social and economic issues. Hormone therapy can provide significant comfort to patients who do not wish to make a social gender role transition or undergo surgery, or who are unable to do so (Meyer III, 2009). Hormone therapy is a recommended criterion for some, but not all, surgical treatments for gender dysphoria (see section XI and Appendix C).

Criteria for Hormone Therapy

Initiation of hormone therapy may be undertaken after a psychosocial assessment has been conducted and informed consent has been obtained by a qualified health professional, as outlined in section VII of the *SOC*. A referral is required from the mental health professional who performed the assessment, unless the assessment was done by a hormone provider who is also qualified in this area.

The criteria for hormone therapy are as follows:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country (if younger, follow the *SOC* outlined in section VI);
4. If significant medical or mental health concerns are present, they must be reasonably well-controlled.

As noted in section VII of the *SOC*, the presence of coexisting mental health concerns does not necessarily preclude access to feminizing/masculinizing hormones; rather, these concerns need to be managed prior to, or concurrent with, treatment of gender dysphoria.

In selected circumstances, it can be acceptable practice to provide hormones to patients who have not fulfilled these criteria. Examples include facilitating the provision of monitored therapy using hormones of known quality as an alternative to illicit or unsupervised hormone use or to patients

who have already established themselves in their affirmed gender and who have a history of prior hormone use. It is unethical to deny availability or eligibility for hormone therapy solely on the basis of blood seropositivity for blood-borne infections such as HIV or hepatitis B or C.

In rare cases, hormone therapy may be contraindicated due to serious individual health conditions. Health professionals should assist these patients with accessing nonhormonal interventions for gender dysphoria. A qualified mental health professional familiar with the patient is an excellent resource in these circumstances.

Informed Consent

Feminizing/masculinizing hormone therapy may lead to irreversible physical changes. Thus, hormone therapy should be provided only to those who are legally able to provide informed consent. This includes people who have been declared by a court to be emancipated minors, incarcerated people, and cognitively impaired people who are considered competent to participate in their medical decisions (Bockting et al., 2006). Providers should document in the medical record that comprehensive information has been provided and understood about all relevant aspects of the hormone therapy, including both possible benefits and risks and the impact on reproductive capacity.

Relationship Between the *Standards of Care* and Informed Consent Model Protocols

A number of community health centers in the United States have developed protocols for providing hormone therapy based on an approach that has become known as the Informed Consent Model (Callen Lorde Community Health Center, 2000, 2011; Fenway Community Health Transgender Health Program, 2007; Tom Waddell Health Center, 2006). These protocols are consistent with the guidelines presented in the WPATH *Standards of Care, Version 7*. The *SOC* are flexible clinical guidelines; they allow for tailoring of interventions to the needs of the individual receiving services and for tailoring of protocols to the approach and setting in which these services are provided (Ehrbar & Gorton, 2010).

Obtaining informed consent for hormone therapy is an important task of providers to ensure that patients understand the psychological and physical benefits and risks of hormone therapy, as well as its psychosocial implications. Providers prescribing the hormones or health professionals recommending the hormones should have the knowledge and experience to assess gender

dysphoria. They should inform individuals of the particular benefits, limitations, and risks of hormones, given the patient's age, previous experience with hormones, and concurrent physical or mental health concerns.

Screening for and addressing acute or current mental health concerns is an important part of the informed consent process. This may be done by a mental health professional or by an appropriately trained prescribing provider (see section VII of the *SOC*). The same provider or another appropriately trained member of the health care team (e.g., a nurse) can address the psychosocial implications of taking hormones when necessary (e.g., the impact of masculinization/feminization on how one is perceived and its potential impact on relationships with family, friends, and coworkers). If indicated, these providers will make referrals for psychotherapy and for the assessment and treatment of coexisting mental health concerns such as anxiety or depression.

The difference between the Informed Consent Model and *SOC, Version 7,* is that the *SOC* puts greater emphasis on the important role that mental health professionals can play in alleviating gender dysphoria and facilitating changes in gender role and psychosocial adjustment. This may include a comprehensive mental health assessment and psychotherapy, when indicated. In the Informed Consent Model, the focus is on obtaining informed consent as the threshold for the initiation of hormone therapy in a multidisciplinary, harm-reduction environment. Less emphasis is placed on the provision of mental health care until the patient requests it, unless significant mental health concerns are identified that would need to be addressed before hormone prescription.

Physical Effects of Hormone Therapy

Feminizing/masculinizing hormone therapy will induce physical changes that are more congruent with a patient's gender identity.

- In FtM patients, the following physical changes are expected to occur: deepened voice, clitoral enlargement (variable), growth in facial and body hair, cessation of menses, atrophy of breast tissue, and decreased percentage of body fat compared to muscle mass.

- In MtF patients, the following physical changes are expected to occur: breast growth (variable), decreased erectile function, decreased testicular size, and increased percentage of body fat compared to muscle mass.

Most physical changes, whether feminizing or masculinizing, occur over the course of two years. The amount of physical change and the exact timeline of effects can be highly variable. Tables 1a and 1b outline the approximate time course of these physical changes.

TABLE 1A: EFFECTS AND EXPECTED TIME COURSE OF MASCULINIZING HORMONES [A]

Effect	Expected onset[B]	Expected maximum effect[B]
Skin oiliness/acne	1–6 months	1–2 years
Facial/body hair growth	3–6 months	3–5 years
Scalp hair loss	>12 months[C]	Variable
Increased muscle mass/strength	6–12 months	2–5 years[D]
Body fat redistribution	3–6 months	2–5 years
Cessation of menses	2–6 months	n/a
Clitoral enlargement	3–6 months	1–2 years
Vaginal atrophy	3–6 months	1–2 years
Deepened voice	3–12 months	1–2 years

A Adapted with permission from Hembree et al.(2009). Copyright 2009, The Endocrine Society.
B Estimates represent published and unpublished clinical observations.
C Highly dependent on age and inheritance; may be minimal.
D Significantly dependent on amount of exercise.

TABLE 1B: EFFECTS AND EXPECTED TIME COURSE OF FEMINIZING HORMONES [A]

Effect	Expected onset[B]	Expected maximum effect[B]
Body fat redistribution	3–6 months	2–5 years
Decreased muscle mass/ strength	3–6 months	1–2 years[C]
Softening of skin/decreased oiliness	3–6 months	Unknown
Decreased libido	1–3 months	1–2 years
Decreased spontaneous erections	1–3 months	3–6 months
Male sexual dysfunction	Variable	Variable
Breast growth	3–6 months	2–3 years
Decreased testicular volume	3–6 months	2–3 years
Decreased sperm production	Variable	Variable
Thinning and slowed growth of body and facial hair	6–12 months	> 3 years[D]
Male pattern baldness	No regrowth, loss stops 1–3 months	1–2 years

[A] Adapted with permission from Hembree et al. (2009). Copyright 2009, The Endocrine Society.
[B] Estimates represent published and unpublished clinical observations.
[C] Significantly dependent on amount of exercise.
[D] Complete removal of male facial and body hair requires electrolysis, laser treatment, or both.

The degree and rate of physical effects depends in part on the dose, route of administration, and medications used, which are selected in accordance with a patient's specific medical goals (e.g., changes in gender role expression, plans for sex reassignment) and medical risk profile. There is no current evidence that response to hormone therapy—with the possible exception of voice deepening in FtM persons—can be reliably predicted based on age, body habitus, ethnicity, or family appearance. All other factors being equal, there is no evidence to suggest that any medically approved type or method of administering hormones is more effective than any other in producing the desired physical changes.

Risks of Hormone Therapy

All medical interventions carry risks. The likelihood of a serious adverse event is dependent on numerous factors: the medication itself, dose, route of administration, and a patient's clinical characteristics (age, comorbidities, family history, health habits). It is thus impossible to predict whether a given adverse effect will happen in an individual patient.

The risks associated with feminizing/masculinizing hormone therapy for the transsexual, transgender, and gender-nonconforming population as a whole are summarized in Table 2. Based on the level of evidence, risks are categorized as follows: (i) likely increased risk with hormone therapy, (ii) possibly increased risk with hormone therapy, or (iii) inconclusive or no increased risk. Items in the last category include those that may present risk, but for which the evidence is so minimal that no clear conclusion can be reached.

Additional detail about these risks can be found in Appendix B, which is based on two comprehensive, evidence-based literature reviews of masculinizing/feminizing hormone therapy (Feldman & Safer, 2009; Hembree et al., 2009), along with a large cohort study (Asscheman et al., 2011). These reviews can serve as detailed references for providers, along with other widely recognized, published clinical materials (Dahl, Feldman, Goldberg, & Jaberi, 2006; Ettner, Monstrey, & Eyler, 2007).

TABLE 2: RISKS ASSOCIATED WITH HORMONE THERAPY. BOLDED ITEMS ARE CLINICALLY SIGNIFICANT

Risk Level	Feminizing hormones	Masculinizing hormones
Likely increased risk	Venous thromboembolic disease[A] Gallstones Elevated liver enzymes Weight gain Hypertriglyceridemia	Polycythemia Weight gain Acne Androgenic alopecia (balding) Sleep apnea
Likely increased risk with presence of additional risk factors[B]	Cardiovascular disease	
Possible increased risk	Hypertension Hyperprolactinemia or prolactinoma	Elevated liver enzymes Hyperlipidemia
Possible increased risk with presence of additional risk factors[B]	Type 2 diabetes[A]	Destabilization of certain psychiatric disorders[C] Cardiovascular disease Hypertension Type 2 diabetes
No increased risk or inconclusive	Breast cancer	Loss of bone density Breast cancer Cervical cancer Ovarian cancer Uterine cancer

* **Note:** Risk is greater with oral estrogen administration than with transdermal estrogen administration.

A Risk is greater with oral estrogen administration than with transdermal estrogen administration.

B Additional risk factors include age.

C Includes bipolar, schizoaffective, and other disorders that may include manic or psychotic symptoms. This adverse event appears to be associated with higher doses or supraphysiologic blood levels of testosterone.

Competency of Hormone-Prescribing Physicians, Relationship with Other Health Professionals

Feminizing/masculinizing hormone therapy is best undertaken in the context of a complete approach to health care that includes comprehensive primary care and a coordinated approach to psychosocial issues (Feldman & Safer, 2009). While psychotherapy or ongoing counseling is not required for the initiation of hormone therapy, if a therapist is involved, then regular communication among health professionals is advised (with the patient's consent) to ensure that the transition process is going well, both physically and psychosocially.

With appropriate training, feminizing/masculinizing hormone therapy can be managed by a variety of providers, including nurse practitioners, physician assistants, and primary care physicians (Dahl et al., 2006). Medical visits relating to hormone maintenance provide an opportunity to deliver broader care to a population that is often medically underserved (Clements, Wilkinson, Kitano, & Marx, 1999; Feldman, 2007; Xavier, 2000). Many of the screening tasks and management of comorbidities associated with long-term hormone use, such as cardiovascular risk factors and cancer screening, fall more uniformly within the scope of primary care rather than specialist care (American Academy of Family Physicians, 2005; Eyler, 2007; World Health Organization, 2008), particularly in locations where dedicated gender teams or specialized physicians are not available.

Given the multidisciplinary needs of transsexual, transgender, and gender-nonconforming people seeking hormone therapy, as well as the difficulties associated with fragmentation of care in general (World Health Organization, 2008), WPATH strongly encourages the increased training and involvement of primary care providers in the area of feminizing/masculinizing hormone therapy. If hormones are prescribed by a specialist, there should be close communication with the patient's primary care provider. Conversely, an experienced hormone provider or endocrinologist should be involved if the primary care physician has no experience with this type of hormone therapy, or if the patient has a pre-existing metabolic or endocrine disorder that could be affected by endocrine therapy.

While formal training programs in transgender medicine do not yet exist, hormone providers have a responsibility to obtain appropriate knowledge and experience in this field. Clinicians can increase their experience and comfort in providing feminizing/masculinizing hormone therapy by co-managing care or consulting with a more experienced provider, or by providing more limited types of hormone therapy before progressing to initiation of hormone therapy. Because this field of medicine is evolving, clinicians should become familiar and keep current with the medical literature, and discuss emerging issues with colleagues. Such discussions might occur through networks established by WPATH and other national/local organizations.

Responsibilities of Hormone-Prescribing Physicians

In general, clinicians who prescribe hormone therapy should engage in the following tasks:

1. Perform an initial evaluation that includes discussion of a patient's physical transition goals, health history, physical examination, risk assessment, and relevant laboratory tests.

2. Discuss with patients the expected effects of feminizing/masculinizing medications and the possible adverse health effects. These effects can include a reduction in fertility (Feldman & Safer, 2009; Hembree et al., 2009). Therefore, reproductive options should be discussed with patients before starting hormone therapy (see section IX).

3. Confirm that patients have the capacity to understand the risks and benefits of treatment and are capable of making an informed decision about medical care.

4. Provide ongoing medical monitoring, including regular physical and laboratory examination to monitor hormone effectiveness and side effects.

5. Communicate as needed with a patient's primary care provider, mental health professional, and surgeon.

6. If needed, provide patients with a brief written statement indicating that they are under medical supervision and care that includes feminizing/masculinizing hormone therapy. Particularly during the early phases of hormone treatment, a patient may wish to carry this statement at all times to help prevent difficulties with the police and other authorities.

Depending on the clinical situation for providing hormones (see below), some of these responsibilities are less relevant. Thus, the degree of counseling, physical examinations, and laboratory evaluations should be individualized to a patient's needs.

Clinical Situations for Hormone Therapy

There are circumstances in which clinicians may be called upon to provide hormones without necessarily initiating or maintaining long-term feminizing/masculinizing hormone therapy. By acknowledging these different clinical situations (see below, from least to highest level of complexity), it may be possible to involve clinicians in feminizing/masculinizing hormone therapy who might not otherwise feel able to offer this treatment.

1. Bridging

Whether prescribed by another clinician or obtained through other means (e.g., purchased over the Internet), patients may present for care already on hormone therapy. Clinicians can provide a limited (1–6 month) prescription for hormones while helping patients find a provider who can prescribe long-term hormone therapy. Providers should assess a patient's current regimen for safety and drug interactions and substitute safer medications or doses when indicated (Dahl et al., 2006; Feldman & Safer, 2009). If hormones were previously prescribed, medical records should be requested (with the patient's permission) to obtain the results of baseline examinations and laboratory tests and any adverse events. Hormone providers should also communicate with any mental health professional who is currently involved in a patient's care. If a patient has never had a psychosocial assessment as recommended by the *SOC* (see section VII), clinicians should refer the patient to a qualified mental health professional if appropriate and feasible (Feldman & Safer, 2009). Providers who prescribe bridging hormones need to work with patients to establish limits as to the duration of bridging therapy.

2. Hormone Therapy Following Gonad Removal

Hormone replacement with estrogen or testosterone is usually continued lifelong after an oophorectomy or orchiectomy, unless medical contraindications arise. Because hormone doses are often decreased after these surgeries (Basson, 2001; Levy, Crown, & Reid, 2003; Moore, Wisniewski, & Dobs, 2003) and only adjusted for age and comorbid health concerns, hormone management in this situation is quite similar to hormone replacement in any hypogonadal patient.

3. Hormone Maintenance Prior to Gonad Removal

Once patients have achieved maximal feminizing/masculinizing benefits from hormones (typically two or more years), they remain on a maintenance dose. The maintenance dose is then adjusted for changes in health conditions, aging, or other considerations such as lifestyle changes (Dahl et al., 2006). When a patient on maintenance hormones presents for care, the provider should assess the patient's current regimen for safety and drug interactions and substitute safer medications or doses when indicated. The patient should continue to be monitored by physical examinations and laboratory testing on a regular basis, as outlined in the literature (Feldman & Safer, 2009; Hembree et al., 2009). The dose and form of hormones should be revisited regularly with any changes in the patient's health status and available evidence on the potential long-term risks of hormones (See *Hormone Regimens,* below).

4. Initiating Hormonal Feminization/Masculinization

This clinical situation requires the greatest commitment in terms of provider time and expertise. Hormone therapy must be individualized based on a patient's goals, the risk/benefit ratio of medications, the presence of other medical conditions, and consideration of social and economic issues. Although a wide variety of hormone regimens have been published (Dahl et al., 2006; Hembree et al., 2009; Moore et al., 2003), there are no published reports of randomized clinical trials comparing safety and efficacy. Despite this variation, a reasonable framework for initial risk assessment and ongoing monitoring of hormone therapy can be constructed, based on the efficacy and safety evidence presented above.

Risk Assessment and Modification for Initiating Hormone Therapy

The initial evaluation for hormone therapy assesses a patient's clinical goals and risk factors for hormone-related adverse events. During the risk assessment, the patient and clinician should develop a plan for reducing risks wherever possible, either prior to initiating therapy or as part of ongoing harm reduction.

All assessments should include a thorough physical exam, including weight, height, and blood pressure. The need for breast, genital, and rectal exams, which are sensitive issues for most transsexual, transgender, and gender-nonconforming patients, should be based on individual risks and preventive health care needs (Feldman & Goldberg, 2006; Feldman, 2007).

Preventive Care

Hormone providers should address preventive health care with patients, particularly if a patient does not have a primary care provider. Depending on a patient's age and risk profile, there may be appropriate screening tests or exams for conditions affected by hormone therapy. Ideally, these screening tests should be carried out prior to the start of hormone therapy.

Risk Assessment and Modification for Feminizing Hormone Therapy (MtF)

There are no absolute contraindications to feminizing therapy per se, but absolute contraindications exist for the different feminizing agents, particularly estrogen. These include previous venous thrombotic events related to an underlying hypercoagulable condition, history of estrogen-sensitive neoplasm, and end-stage chronic liver disease (Gharib et al., 2005).

Other medical conditions, as noted in Table 2 and Appendix B, can be exacerbated by estrogen or androgen blockade, and therefore should be evaluated and reasonably well controlled prior to starting hormone therapy (Feldman & Safer, 2009; Hembree et al., 2009). Clinicians should particularly attend to tobacco use, as it is associated with increased risk of venous thrombosis, which is further increased with estrogen use. Consultation with a cardiologist may be advisable for patients with known cardio- or cerebrovascular disease.

Baseline laboratory values are important to both assess initial risk and evaluate possible future adverse events. Initial labs should be based on the risks of feminizing hormone therapy outlined in Table 2, as well as individual patient risk factors, including family history. Suggested initial lab panels have been published (Feldman & Safer, 2009; Hembree et al., 2009). These can be modified for patients or health care systems with limited resources, and in otherwise healthy patients.

Risk Assessment and Modification for Masculinizing Hormone Therapy (FtM)

Absolute contraindications to testosterone therapy include pregnancy, unstable coronary artery disease, and untreated polycythemia with a hematocrit of 55% or higher (Carnegie, 2004). Because the aromatization of testosterone to estrogen may increase risk in patients with a history of breast or other estrogen dependent cancers (Moore et al., 2003), consultation with an oncologist may be indicated prior to hormone use. Comorbid conditions likely to be exacerbated by testosterone use should be evaluated and treated, ideally prior to starting hormone therapy (Feldman & Safer, 2009; Hembree et al., 2009). Consultation with a cardiologist may be advisable for patients with known cardio- or cerebrovascular disease. (Dhejne et al., 2011).

An increased prevalence of polycystic ovarian syndrome (PCOS) has been noted among FtM patients even in the absence of testosterone use (Baba et al., 2007; Balen, Schachter, Montgomery, Reid, & Jacobs, 1993; Bosinski et al., 1997). While there is no evidence that PCOS is related to the development of a transsexual, transgender, or gender-nonconforming identity, PCOS is associated with increased risk of diabetes, cardiac disease, high blood pressure, and ovarian and endometrial cancers (Cattrall & Healy, 2004). Signs and symptoms of PCOS should be evaluated prior to initiating testosterone therapy, as testosterone may affect many of these conditions. Testosterone can affect the developing fetus (*Physicians' Desk Reference,* 2010), and patients at risk of becoming pregnant require highly effective birth control.

Baseline laboratory values are important to both assess initial risk and evaluate possible future adverse events. Initial labs should be based on the risks of masculinizing hormone therapy outlined in Table 2, as well as individual patient risk factors, including family history. Suggested initial lab panels have been published (Feldman & Safer, 2009; Hembree et al., 2009). These can be modified for patients or health care systems with limited resources, and in otherwise healthy patients.

Clinical Monitoring During Hormone Therapy for Efficacy and Adverse Events

The purpose of clinical monitoring during hormone use is to assess the degree of feminization/masculinization and the possible presence of adverse effects of medication. However, as with the monitoring of any long-term medication, monitoring should take place in the context of comprehensive health care. Suggested clinical monitoring protocols have been published (Feldman & Safer, 2009; Hembree et al., 2009). Patients with comorbid medical conditions may need to be monitored more frequently. Healthy patients in geographically remote or resource-poor areas may be able to use alternative strategies, such as telehealth, or cooperation with local providers such as nurses and physician assistants. In the absence of other indications, health professionals may prioritize monitoring for those risks that are either likely to be increased by hormone therapy or possibly increased by hormone therapy but clinically serious in nature.

Efficacy and Risk Monitoring During Feminizing Hormone Therapy (MtF)

The best assessment of hormone efficacy is clinical response: Is a patient developing a feminized body while minimizing masculine characteristics, consistent with that patient's gender goals? In order to more rapidly predict the hormone dosages that will achieve clinical response, one can measure testosterone levels for suppression below the upper limit of the normal female range and estradiol levels within a premenopausal female range but well below supraphysiologic levels (Feldman & Safer, 2009; Hembree et al., 2009).

Monitoring for adverse events should include both clinical and laboratory evaluation. Follow-up should include careful assessment for signs of cardiovascular impairment and venous thromboembolism (VTE) through measurement of blood pressure, weight, and pulse; heart and lung exams; and examination of the extremities for peripheral edema, localized swelling, or pain (Feldman & Safer, 2009). Laboratory monitoring should be based on the risks of hormone therapy described above, a patient's individual comorbidities and risk factors, and the specific hormone regimen itself. Specific lab-monitoring protocols have been published (Feldman & Safer, 2009; Hembree et al., 2009).

Efficacy and Risk Monitoring During Masculinizing Hormone Therapy (FtM)

The best assessment of hormone efficacy is clinical response: Is a patient developing a masculinized body while minimizing feminine characteristics, consistent with that patient's gender goals? Clinicians can achieve a good clinical response with the least likelihood of adverse events by maintaining testosterone levels within the normal male range while avoiding supraphysiological

levels (Dahl et al., 2006; Hembree et al., 2009). For patients using intramuscular (IM) testosterone cypionate or enanthate, some clinicians check trough levels while others prefer midcycle levels (Dahl et al., 2006; Hembree et al., 2009; Tangpricha, Turner, Malabanan, & Holick, 2001; Tangpricha, Ducharme, Barber, & Chipkin, 2003).

Monitoring for adverse events should include both clinical and laboratory evaluation. Follow-up should include careful assessment for signs and symptoms of excessive weight gain, acne, uterine break-through bleeding, and cardiovascular impairment, as well as psychiatric symptoms in at-risk patients. Physical examinations should include measurement of blood pressure, weight, and pulse; and heart, lung, and skin exams (Feldman & Safer, 2009). Laboratory monitoring should be based on the risks of hormone therapy described above, a patient's individual comorbidities and risk factors, and the specific hormone regimen itself. Specific lab monitoring protocols have been published (Feldman & Safer, 2009; Hembree et al., 2009).

Hormone Regimens

To date, no controlled clinical trials of any feminizing/masculinizing hormone regimen have been conducted to evaluate safety or efficacy in producing physical transition. As a result, wide variation in doses and types of hormones have been published in the medical literature (Moore et al., 2003; Tangpricha et al., 2003; van Kesteren, Asscheman, Megens, & Gooren, 1997). In addition, access to particular medications may be limited by a patient's geographical location and/or social or econonomic situations. For these reasons, WPATH does not describe or endorse a particular feminizing/masculinizing hormone regimen. Rather, the medication classes and routes of administration used in most published regimens are broadly reviewed.

As outlined above, there are demonstrated safety differences in individual elements of various regimens. The Endocrine Society Guidelines (Hembree et al., 2009) and Feldman and Safer (2009) provide specific guidance regarding the types of hormones and suggested dosing to maintain levels within physiologic ranges for a patient's desired gender expression (based on goals of full feminization/masculinization). It is strongly recommend that hormone providers regularly review the literature for new information and use those medications that safely meet individual patient needs with available local resources.

Regimens for Feminizing Hormone Therapy (MtF)

Estrogen

Use of oral estrogen, and specifically ethinyl estradiol, appears to increase the risk of VTE. Because of this safety concern, ethinyl estradiol is not recommended for feminizing hormone therapy. Transdermal estrogen is recommended for those patients with risks factors for VTE. The risk of adverse events increases with higher doses, particular doses resulting in supraphysiologic levels (Hembree et al., 2009). Patients with co-morbid conditions that can be affected by estrogen should avoid oral estrogen if possible and be started at lower levels. Some patients may not be able to safely use the levels of estrogen needed to get the desired results. This possibility needs to be discussed with patients well in advance of starting hormone therapy.

Androgen-reducing medications ("anti-androgens")

A combination of estrogen and "anti-androgens" is the most commonly studied regimen for feminization. Androgen-reducing medications, from a variety of classes of drugs, have the effect of reducing either endogenous testosterone levels or testosterone activity, and thus diminishing masculine characteristics such as body hair. They minimize the dosage of estrogen needed to suppress testosterone, thereby reducing the risks associated with high-dose exogenous estrogen (Prior, Vigna, Watson, Diewold, & Robinow, 1986; Prior, Vigna, & Watson, 1989).

Common anti-androgens include the following:

- Spironolactone, an antihypertensive agent, directly inhibits testosterone secretion and androgen binding to the androgen receptor. Blood pressure and electrolytes need to be monitored because of the potential for hyperkalemia.

- Cyproterone acetate is a progestational compound with anti-androgenic properties. This medication is not approved in the United States because of concerns over potential hepatotoxicity, but it is widely used elsewhere (De Cuypere et al., 2005).

- GnRH agonists (e.g., goserelin, buserelin, triptorelin) are neurohormones that block the gonadtropin-releasing hormone receptor, thus blocking the release of follicle stimulating hormone and luteinizing hormone. This leads to highly effective gonadal blockade. However, these medications are expensive and only available as injectables or implants.

- 5-alpha reductase inhibitors (finasteride and dutasteride) block the conversion of testosterone to the more active agent, 5-alpha-dihydrotestosterone. These medications have beneficial effects on scalp hair loss, body hair growth, sebaceous glands, and skin consistency.

Cyproterone and spironolactone are the most commonly used anti-androgens and are likely the most cost-effective.

Progestins

With the exception of cyproterone, the inclusion of progestins in feminizing hormone therapy is controversial (Oriel, 2000). Because progestins play a role in mammary development on a cellular level, some clinicians believe that these agents are necessary for full breast development (Basson & Prior, 1998; Oriel, 2000). However, a clinical comparison of feminization regimens with and without progestins found that the addition of progestins neither enhanced breast growth nor lowered serum levels of free testosterone (Meyer et al., 1986). There are concerns regarding potential adverse effects of progestins, including depression, weight gain, and lipid changes (Meyer et al., 1986; Tangpricha et al., 2003). Progestins (especially medroxyprogesterone) are also suspected to increase breast cancer risk and cardiovascular risk in women (Rossouw et al., 2002). Micronized progesterone may be better tolerated and have a more favorable impact on the lipid profile than medroxyprogesterone does (de Lignières, 1999; Fitzpatrick, Pace, & Wiita, 2000).

Regimens for Masculinizing Hormone Therapy (FtM)

Testosterone

Testosterone generally can be given orally, transdermally, or parenterally (IM), although buccal and implantable preparations are also available. Oral testosterone undecanoate, available outside the United States, results in lower serum testosterone levels than nonoral preparations and has limited efficacy in suppressing menses (Feldman, 2005, April; Moore et al., 2003). Because intramuscular testosterone cypionate or enanthate are often administered every 2–4 weeks, some patients may notice cyclic variation in effects (e.g., fatigue and irritability at the end of the injection cycle, aggression or expansive mood at the beginning of the injection cycle), as well as more time outside the normal physiologic levels (Jockenhövel, 2004). This may be mitigated by using a lower but more frequent dosage schedule or by using a daily transdermal preparation (Dobs et al., 1999; Jockenhövel, 2004; Nieschlag et al., 2004). Intramuscular testosterone undecanoate (not currently available in the United States) maintains stable, physiologic testosterone levels over approximately 12 weeks and has been effective in both the setting of hypogonadism and in FtM individuals (Mueller, Kiesewetter, Binder, Beckmann, & Dittrich, 2007; Zitzmann, Saad, & Nieschlag, 2006). There is evidence that transdermal and intramuscular testosterone achieve similar masculinizing results, although the timeframe may be somewhat slower with transdermal preparations (Feldman, 2005, April). Especially as patients age, the goal is to use the lowest dose needed to maintain the desired clinical result, with appropriate precautions being made to maintain bone density.

Other agents

Progestins, most commonly medroxyprogesterone, can be used for a short period of time to assist with menstrual cessation early in hormone therapy. GnRH agonists can be used similarly, as well as for refractory uterine bleeding in patients without an underlying gynecological abnormality.

Bioidentical and Compounded Hormones

As discussion surrounding the use of bioidentical hormones in postmenopausal hormone replacement has heightened, interest has also increased in the use of similar compounds in feminizing/masculinizing hormone therapy. There is no evidence that custom compounded bioidentical hormones are safer or more effective than government agency-approved bioidentical hormones (Sood, Shuster, Smith, Vincent, & Jatoi, 2011). Therefore, it has been advised by the North American Menopause Society (2010) and others to assume that, whether the hormone is from a compounding pharmacy or not, if the active ingredients are similar, it should have a similar side-effect profile. WPATH concurs with this assessment.

IX
Reproductive Health

Many transgender, transsexual, and gender-nonconforming people will want to have children. Because feminizing/masculinizing hormone therapy limits fertility (Darney, 2008; Zhang, Gu, Wang, Cui, & Bremner, 1999), it is desirable for patients to make decisions concerning fertility before starting hormone therapy or undergoing surgery to remove/alter their reproductive organs. Cases are known of people who received hormone therapy and genital surgery and later regretted their inability to parent genetically related children (De Sutter, Kira, Verschoor, & Hotimsky, 2002).

Health care professionals—including mental health professionals recommending hormone therapy or surgery, hormone-prescribing physicians, and surgeons—should discuss reproductive options with patients prior to initiation of these medical treatments for gender dysphoria. These discussions should occur even if patients are not interested in these issues at the time of treatment, which may be more common for younger patients (De Sutter, 2009). Early discussions are desirable, but not always possible. If an individual has not had complete sex reassignment surgery, it may be possible to stop hormones long enough for natal hormones to recover, allowing

the production of mature gametes (Payer, Meyer, & Walker, 1979; Van den Broecke, Van der Elst, Liu, Hovatta, & Dhont, 2001).

Besides debate and opinion papers, very few research papers have been published on the reproductive health issues of individuals receiving different medical treatments for gender dysphoria. Another group who faces the need to preserve reproductive function in light of loss or damage to their gonads are people with malignancies that require removal of reproductive organs or use of damaging radiation or chemotherapy. Lessons learned from that group can be applied to people treated for gender dysphoria.

MtF patients, especially those who have not already reproduced, should be informed about sperm-preservation options and encouraged to consider banking their sperm prior to hormone therapy. In a study examining testes that were exposed to high-dose estrogen (Payer et al., 1979), findings suggest that stopping estrogen may allow the testes to recover. In an article reporting on the opinions of MtF individuals towards sperm freezing (De Sutter et al., 2002), the vast majority of 121 survey respondents felt that the availability of freezing sperm should be discussed and offered by the medical world. Sperm should be collected before hormone therapy or after stopping the therapy until the sperm count rises again. Cryopreservation should be discussed even if there is poor semen quality. In adults with azoospermia, a testicular biopsy with subsequent cryopreservation of biopsied material for sperm is possible, but may not be successful.

Reproductive options for FtM patients might include oocyte (egg) or embryo freezing. The frozen gametes and embryo could later be used with a surrogate woman to carry to pregnancy. Studies of women with polycystic ovarian disease suggest that the ovary can recover in part from the effects of high testosterone levels (Hunter & Sterrett, 2000). Stopping the testosterone briefly might allow for ovaries to recover enough to release eggs; success likely depends on the patient's age and duration of testosterone treatment. While not systematically studied, some FtM individuals are doing exactly that, and some have been able to become pregnant and deliver children (More, 1998).

Patients should be advised that these techniques are not available everywhere and can be very costly. Transsexual, transgender, and gender-nonconforming people should not be refused reproductive options for any reason.

A special group of individuals are prepubertal or pubertal adolescents who will never develop reproductive function in their natal sex due to blockers or cross-gender hormones. At this time there is no technique for preserving function from the gonads of these individuals.

X

Voice and Communication Therapy

Communication, both verbal and nonverbal, is an important aspect of human behavior and gender expression. Transsexual, transgender, and gender-nonconforming people might seek the assistance of a voice and communication specialist to develop vocal characteristics (e.g., pitch, intonation, resonance, speech rate, phrasing patterns) and non-verbal communication patterns (e.g., gestures, posture/movement, facial expressions) that facilitate comfort with their gender identity. Voice and communication therapy may help to alleviate gender dysphoria and be a positive and motivating step towards achieving one's goals for gender role expression.

Competency of Voice and Communication Specialists Working with Transsexual, Transgender, and Gender-Nonconforming Clients

Specialists may include speech-language pathologists, speech therapists, and speech-voice clinicians. In most countries the professional association for speech-language pathologists requires specific qualifications and credentials for membership. In some countries the government regulates practice through licensing, certification, or registration processes (American Speech-Language-Hearing Association, 2011; Canadian Association of Speech-Language Pathologists and Audiologists; Royal College of Speech Therapists, United Kingdom; Speech Pathology Australia).

The following are recommended minimum credentials for voice and communication specialists working with transsexual, transgender, and gender-nonconforming clients:

1. Specialized training and competence in the assessment and development of communication skills in transsexual, transgender, and gender-nonconforming clients.

2. A basic understanding of transgender health, including hormonal and surgical treatments for feminization/masculinization and trans-specific psychosocial issues as outlined in the *SOC*; and familiarity with basic sensitivity protocols such as the use of preferred gender pronoun and name (Canadian Association of Speech-Language Pathologists and Audiologists; Royal College of Speech Therapists, United Kingdom; Speech Pathology Australia).

3. Continuing education in the assessment and development of communication skills in transsexual, transgender, and gender-nonconforming clients. This may include attendance at professional meetings, workshops, or seminars; participation in research related to gender identity issues; independent study; or mentoring from an experienced, certified clinician.

Other professionals such as vocal coaches, theatre professionals, singing teachers, and movement experts may play a valuable adjunct role. Such professionals will ideally have experience working with, or be actively collaborating with, speech-language pathologists.

Assessment and Treatment Considerations

The overall purpose of voice and communication therapy is to help clients adapt their voice and communication in a way that is both safe and authentic, resulting in communication patterns that clients feel are congruent with their gender identity and that reflect their sense of self (Adler, Hirsch, & Mordaunt, 2006). It is essential that voice and communication specialists be sensitive to individual communication preferences. Communication—style, voice, choice of language, etc.—is personal. Individuals should not be counseled to adopt behaviors with which they are not comfortable or which do not feel authentic. Specialists can best serve their clients by taking the time to understand a person's gender concerns and goals for gender-role expression (American Speech-Language-Hearing Association, 2011; Canadian Association of Speech-Language Pathologists and Audiologists; Royal College of Speech Therapists, United Kingdom; Speech Pathology Australia).

Individuals may choose the communication behaviors that they wish to acquire in accordance with their gender identity. These decisions are also informed and supported by the knowledge of the voice and communication specialist and by the assessment data for a specific client (Hancock, Krissinger, & Owen, 2010). Assessment includes a client's self-evaluation and a specialist's evaluation of voice, resonance, articulation, spoken language, and non-verbal communication (Adler et al., 2006; Hancock et al., 2010).

Voice-and-communication treatment plans are developed by considering the available research evidence, the clinical knowledge and experience of the specialist, and the client's own goals and values (American Speech-Language-Hearing Association, 2011; Canadian Association of Speech-Language Pathologists and Audiologists; Royal College of Speech Therapists, United Kingdom; Speech Pathology Australia). Targets of treatment typically include pitch, intonation, loudness and stress patterns, voice quality, resonance, articulation, speech rate and phrasing, language, and nonverbal communication (Adler et al., 2006; Davies & Goldberg, 2006; de Bruin, Coerts, & Greven, 2000; Gelfer, 1999; McNeill, 2006; Oates & Dacakis, 1983). Treatment may involve individual and/or group sessions. The frequency and duration of treatment will vary according to a client's needs. Existing protocols for voice-and-communication treatment can be considered in

developing an individualized therapy plan (Carew, Dacakis, & Oates, 2007; Dacakis, 2000; Davies & Goldberg, 2006; Gelfer, 1999; McNeill, Wilson, Clark, & Deakin, 2008; Mount & Salmon, 1988).

Feminizing or masculinizing the voice involves non-habitual use of the voice production mechanism. Prevention measures are necessary to avoid the possibility of vocal misuse and long-term vocal damage. All voice and communication therapy services should therefore include a vocal health component (Adler et al., 2006).

Vocal Health Considerations After Voice Feminization Surgery

As noted in section XI, some transsexual, transgender, and gender-nonconforming people will undergo voice feminization surgery. (Voice deepening can be achieved through masculinizing hormone therapy, but feminizing hormones do not have an impact on the adult MtF voice.) There are varying degrees of satisfaction, safety, and long-term improvement in patients who have had such surgery. It is recommended that individuals undergoing voice feminization surgery also consult a voice and communication specialist to maximize the surgical outcome, help protect vocal health, and learn nonpitch related aspects of communication. Voice surgery procedures should include follow-up sessions with a voice and communication specialist who is licensed and/or credentialed by the board responsible for speech therapists/speech-language pathologists in that country (Kanagalingam et al., 2005; Neumann & Welzel, 2004).

XI
Surgery

Sex Reassignment Surgery Is Effective and Medically Necessary

Surgery – particularly genital surgery – is often the last and the most considered step in the treatment process for gender dysphoria. While many transsexual, transgender, and gender-nonconforming individuals find comfort with their gender identity, role, and expression without surgery, for many others surgery is essential and medically necessary to alleviate their gender dysphoria (Hage & Karim, 2000). For the latter group, relief from gender dysphoria cannot be achieved

without modification of their primary and/or secondary sex characteristics to establish greater congruence with their gender identity. Moreover, surgery can help patients feel more at ease in the presence of sex partners or in venues such as physicians' offices, swimming pools, or health clubs. In some settings, surgery might reduce risk of harm in the event of arrest or search by police or other authorities.

Follow-up studies have shown an undeniable beneficial effect of sex reassignment surgery on postoperative outcomes such as subjective well-being, cosmesis, and sexual function (De Cuypere et al., 2005; Gijs & Brewaeys, 2007; Klein & Gorzalka, 2009; Pfäfflin & Junge, 1998). Additional information on the outcomes of surgical treatments are summarized in Appendix D.

Ethical Questions Regarding Sex Reassignment Surgery

In ordinary surgical practice, pathological tissues are removed to restore disturbed functions, or alterations are made to body features to improve a patient's self image. Some people, including some health professionals, object on ethical grounds to surgery as a treatment for gender dysphoria, because these conditions are thought not to apply.

It is important that health professionals caring for patients with gender dysphoria feel comfortable about altering anatomically normal structures. In order to understand how surgery can alleviate the psychological discomfort and distress of individuals with gender dysphoria, professionals need to listen to these patients discuss their symptoms, dilemmas, and life histories. The resistance against performing surgery on the ethical basis of "above all do no harm" should be respected, discussed, and met with the opportunity to learn from patients themselves about the psychological distress of having gender dysphoria and the potential for harm caused by denying access to appropriate treatments.

Genital and breast/chest surgical treatments for gender dysphoria are not merely another set of elective procedures. Typical elective procedures involve only a private mutually consenting contract between a patient and a surgeon. Genital and breast/chest surgeries as medically necessary treatments for gender dysphoria are to be undertaken only after assessment of the patient by qualified mental health professionals, as outlined in section VII of the *SOC*. These surgeries may be performed once there is written documentation that this assessment has occurred and that the person has met the criteria for a specific surgical treatment. By following this procedure, mental health professionals, surgeons, and patients share responsibility for the decision to make irreversible changes to the body.

It is unethical to deny availability or eligibility for sex reassignment surgeries solely on the basis of blood seropositivity for blood-borne infections such as HIV or hepatitis C or B.

Relationship of Surgeons with Mental Health Professionals, Hormone-Prescribing Physicians (if Applicable), and Patients (Informed Consent)

The role of a surgeon in the treatment of gender dysphoria is not that of a mere technician. Rather, conscientious surgeons will have insight into each patient's history and the rationale that led to the referral for surgery. To that end, surgeons must talk at length with their patients and have close working relationships with other health professionals who have been actively involved in their clinical care.

Consultation is readily accomplished when a surgeon practices as part of an interdisciplinary health care team. In the absence of this, a surgeon must be confident that the referring mental health professional(s), and if applicable the physician who prescribes hormones, is/are competent in the assessment and treatment of gender dysphoria, because the surgeon is relying heavily on his/her/their expertise.

Once a surgeon is satisfied that the criteria for specific surgeries have been met (as outlined below), surgical treatment should be considered and a preoperative surgical consultation should take place. During this consultation, the procedure and postoperative course should be extensively discussed with the patient. Surgeons are responsible for discussing all of the following with patients seeking surgical treatments for gender dysphoria:

- The different surgical techniques available (with referral to colleagues who provide alternative options);
- The advantages and disadvantages of each technique;
- The limitations of a procedure to achieve "ideal" results; surgeons should provide a full range of before-and-after photographs of their own patients, including both successful and unsuccessful outcomes;
- The inherent risks and possible complications of the various techniques; surgeons should inform patients of their own complication rates with each procedure.

These discussions are the core of the informed consent process, which is both an ethical and legal requirement for any surgical procedure. Ensuring that patients have a realistic expectation of outcomes is important in achieving a result that will alleviate their gender dysphoria.

All of this information should be provided to patients in writing, in a language in which they are fluent, and in graphic illustrations. Patients should receive the information in advance (possibly

via the Internet) and be given ample time to review it carefully. The elements of informed consent should always be discussed face-to-face prior to the surgical intervention. Questions can then be answered and written informed consent can be provided by the patient. Because these surgeries are irreversibile, care should be taken to ensure that patients have sufficient time to absorb information fully before they are asked to provide informed consent. A minimum of 24 hours is suggested.

Surgeons should provide immediate aftercare and consultation with other physicians serving the patient in the future. Patients should work with their surgeon to develop an adequate aftercare plan for the surgery.

Overview of Surgical Procedures for the Treatment of Patients with Gender Dysphoria

For the Male-to-Female (MtF) Patient, Surgical Procedures May Include the Following:

1. Breast/chest surgery: augmentation mammoplasty (implants/lipofilling);

2. Genital surgery: penectomy, orchiectomy, vaginoplasty, clitoroplasty, vulvoplasty;

3. Nongenital, nonbreast surgical interventions: facial feminization surgery, liposuction, lipofilling, voice surgery, thyroid cartilage reduction, gluteal augmentation (implants/lipofilling), hair reconstruction, and various aesthetic procedures.

For the Female-to-Male (FtM) Patient, Surgical Procedures May Include the Following:

1. Breast/chest surgery: subcutaneous mastectomy, creation of a male chest;

2. Genital surgery: hysterectomy/salpingo-oophorectomy, reconstruction of the fixed part of the urethra, which can be combined with a metoidioplasty or with a phalloplasty (employing a pedicled or free vascularized flap), vaginectomy, scrotoplasty, and implantation of erection and/or testicular prostheses;

3. Nongenital, nonbreast surgical interventions: voice surgery (rare), liposuction, lipofilling, pectoral implants, and various aesthetic procedures.

Reconstructive Versus Aesthetic Surgery

The question of whether sex reassignment surgery should be considered "aesthetic" surgery or "reconstructive" surgery is pertinent not only from a philosophical point of view, but also from a financial point of view. Aesthetic or cosmetic surgery is mostly regarded as not medically necessary and therefore is typically paid for entirely by the patient. In contrast, reconstructive procedures are considered medically necessary—with unquestionable therapeutic results—and thus paid for partially or entirely by national health systems or insurance companies.

Unfortunately, in the field of plastic and reconstructive surgery (both in general and specifically for gender-related surgeries), there is no clear distinction between what is purely reconstructive and what is purely cosmetic. Most plastic surgery procedures actually are a mixture of both reconstructive and cosmetic components.

While most professionals agree that genital surgery and mastectomy cannot be considered purely cosmetic, opinions diverge as to what degree other surgical procedures (e.g., breast augmentation, facial feminization surgery) can be considered purely reconstructive. Although it may be much easier to see a phalloplasty or a vaginoplasty as an intervention to end lifelong suffering, for certain patients an intervention like a reduction rhinoplasty can have a radical and permanent effect on their quality of life, and therefore is much more medically necessary than for somebody without gender dysphoria.

Criteria for Surgeries

As for all of the *SOC*, the criteria for initiation of surgical treatments for gender dysphoria were developed to promote optimal patient care. While the *SOC* allow for an individualized approach to best meet a patient's health care needs, a criterion for all breast/chest and genital surgeries is documentation of persistent gender dysphoria by a qualified mental health professional. For some surgeries, additional criteria include preparation and treatment consisting of feminizing/masculinizing hormone therapy and one year of continuous living in a gender role that is congruent with one's gender identity.

These criteria are outlined below. Based on the available evidence and expert clinical consensus, different recommendations are made for different surgeries.

The *SOC* do not specify an order in which different surgeries should occur. The number and sequence of surgical procedures may vary from patient to patient, according to their clinical needs.

Criteria for Breast/Chest Surgery (One Referral)

Criteria for mastectomy and creation of a male chest in FtM patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country (if younger, follow the *SOC* for children and adolescents);
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.

Hormone therapy is not a prerequisite.

Criteria for breast augmentation (implants/lipofilling) in MtF patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country (if younger, follow the *SOC* for children and adolescents);
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.

Although not an explicit criterion, it is recommended that MtF patients undergo feminizing hormone therapy (minimum 12 months) prior to breast augmentation surgery. The purpose is to maximize breast growth in order to obtain better surgical (aesthetic) results.

Criteria for Genital Surgery (Two Referrals)

The criteria for genital surgery are specific to the type of surgery being requested.

Criteria for hysterectomy and salpingo-oophorectomy in FtM patients and for orchiectomy in MtF patients:

1. Persistent, well-documented gender dysphoria;

2. Capacity to make a fully informed decision and to consent for treatment;

3. Age of majority in a given country;

4. If significant medical or mental health concerns are present, they must be well controlled.

5. 12 continuous months of hormone therapy as appropriate to the patient's gender goals (unless hormones are not clinically indicated for the individual).

The aim of hormone therapy prior to gonadectomy is primarily to introduce a period of reversible estrogen or testosterone suppression, before the patient undergoes irreversible surgical intervention.

These criteria do not apply to patients who are having these procedures for medical indications other than gender dysphoria.

Criteria for metoidioplasty or phalloplasty in FtM patients and for vaginoplasty in MtF patients:

1. Persistent, well-documented gender dysphoria;

2. Capacity to make a fully informed decision and to consent for treatment;

3. Age of majority in a given country;

4. If significant medical or mental health concerns are present, they must be well controlled;

5. 12 continuous months of hormone therapy as appropriate to the patient's gender goals (unless hormones are not clinically indicated for the individual).

6. 12 continuous months of living in a gender role that is congruent with their gender identity.

Although not an explicit criterion, it is recommended that these patients also have regular visits with a mental health or other medical professional.

Rationale for a preoperative, 12-month experience of living in an identity-congruent gender role:

The criterion noted above for some types of genital surgeries—i.e., that patients engage in 12 continuous months of living in a gender role that is congruent with their gender identity—is based on expert clinical consensus that this experience provides ample opportunity for patients to experience and socially adjust in their desired gender role, before undergoing irreversible surgery. As noted in section VII, the social aspects of changing one's gender role are usually challenging—

often more so than the physical aspects. Changing gender role can have profound personal and social consequences, and the decision to do so should include an awareness of what the familial, interpersonal, educational, vocational, economic, and legal challenges are likely to be, so that people can function successfully in their gender role. Support from a qualified mental health professional and from peers can be invaluable in ensuring a successful gender role adaptation (Bockting, 2008).

The duration of 12 months allows for a range of different life experiences and events that may occur throughout the year (e.g., family events, holidays, vacations, season-specific work or school experiences). During this time, patients should present consistently, on a day-to-day basis and across all settings of life, in their desired gender role. This includes coming out to partners, family, friends, and community members (e.g., at school, work, other settings).

Health professionals should clearly document a patient's experience in the gender role in the medical chart, including the start date of living full time for those who are preparing for genital surgery. In some situations, if needed, health professionals may request verification that this criterion has been fulfilled: They may communicate with individuals who have related to the patient in an identity-congruent gender role, or request documentation of a legal name and/or gender marker change, if applicable.

Surgery for People with Psychotic Conditions and Other Serious Mental Illnesses

When patients with gender dysphoria are also diagnosed with severe psychiatric disorders and impaired reality testing (e.g., psychotic episodes, bipolar disorder, dissociative identity disorder, borderline personality disorder), an effort must be made to improve these conditions with psychotropic medications and/or psychotherapy before surgery is contemplated. (Dhejne et al., 2011). Reevaluation by a mental health professional qualified to assess and manage psychotic conditions should be conducted prior to surgery, describing the patient's mental status and readiness for surgery. It is preferable that this mental health professional be familiar with the patient. No surgery should be performed while a patient is actively psychotic (De Cuypere & Vercruysse, 2009).

Competency of Surgeons Performing Breast/Chest or Genital Surgery

Physicians who perform surgical treatments for gender dsyphoria should be urologists, gynecologists, plastic surgeons, or general surgeons, and board-certified as such by the relevant national

and/or regional association. Surgeons should have specialized competence in genital reconstructive techniques as indicated by documented supervised training with a more experienced surgeon. Even experienced surgeons must be willing to have their surgical skills reviewed by their peers. An official audit of surgical outcomes and publication of these results would be greatly reassuring to both referring health professionals and patients. Surgeons should regularly attend professional meetings where new techniques are presented. The internet is often effectively used by patients to share information on their experience with surgeons and their teams.

Ideally, surgeons should be knowledgeable about more than one surgical technique for genital reconstruction so that they, in consultation with patients, can choose the ideal technique for each individual. Alternatively, if a surgeon is skilled in a single technique and this procedure is either not suitable for or desired by a patient, the surgeon should inform the patient about other procedures and offer referral to another appropriately skilled surgeon.

Breast/Chest Surgery Techniques and Complications

Although breast/chest appearance is an important secondary sex characteristic, breast presence or size is not involved in the legal definitions of sex and gender and is not necessary for reproduction. The performance of breast/chest operations for treatment of gender dysphoria should be considered with the same care as beginning hormone therapy, as both produce relatively irreversible changes to the body.

For the MtF patient, a breast augmentation (sometimes called “chest reconstruction”) is not different from the procedure in a natal female patient. It is usually performed through implantation of breast prostheses and occasionally with the lipofilling technique. Infections and capsular fibrosis are rare complications of augmentation mammoplasty in MtF patients (Kanhai, Hage, Karim, & Mulder, 1999).

For the FtM patient, a mastectomy or “male chest contouring” procedure is available. For many FtM patients, this is the only surgery undertaken. When the amount of breast tissue removed requires skin removal, a scar will result and the patient should be so informed. Complications of subcutaneous mastectomy can include nipple necrosis, contour irregularities, and unsightly scarring (Monstrey et al., 2008).

Genital Surgery Techniques and Complications

Genital surgical procedures for the MtF patient may include orchiectomy, penectomy, vaginoplasty, clitoroplasty, and labiaplasty. Techniques include penile skin inversion, pedicled colosigmoid

transplant, and free skin grafts to line the neovagina. Sexual sensation is an important objective in vaginoplasty, along with creation of a functional vagina and acceptable cosmesis.

Surgical complications of MtF genital surgery may include complete or partial necrosis of the vagina and labia, fistulas from the bladder or bowel into the vagina, stenosis of the urethra, and vaginas that are either too short or too small for coitus. While the surgical techniques for creating a neovagina are functionally and aesthetically excellent, anorgasmia following the procedure has been reported, and a second stage labiaplasty may be needed for cosmesis (Klein & Gorzalka, 2009; Lawrence, 2006).

Genital surgical procedures for FtM patients may include hysterectomy, salpingo-oophorectomy, vaginectomy, metoidioplasty, scrotoplasty, urethroplasty, placement of testicular prostheses, and phalloplasty. For patients without former abdominal surgery, the laparoscopic technique for hysterectomy and salpingo-oophorectomy is recommended to avoid a lower-abdominal scar. Vaginal access may be difficult as most patients are nulliparous and have often not experienced penetrative intercourse. Current operative techniques for phalloplasty are varied. The choice of techniques may be restricted by anatomical or surgical considerations and by a client's financial considerations. If the objectives of phalloplasty are a neophallus of good appearance, standing micturition, sexual sensation, and/or coital ability, patients should be clearly informed that there are several separate stages of surgery and frequent technical difficulties, which may require additional operations. Even metoidioplasty, which in theory is a one-stage procedure for construction of a microphallus, often requires more than one operation. The objective of standing micturition with this technique can not always be ensured (Monstrey et al., 2009).

Complications of phalloplasty in FtMs may include frequent urinary tract stenoses and fistulas, and occasionally necrosis of the neophallus. Metoidioplasty results in a micropenis, without the capacity for standing urination. Phalloplasty, using a pedicled or a free vascularized flap, is a lengthy, multi-stage procedure with significant morbidity that includes frequent urinary complications and unavoidable donor site scarring. For this reason, many FtM patients never undergo genital surgery other than hysterectomy and salpingo-oophorectomy (Hage & De Graaf, 1993).

Even patients who develop severe surgical complications seldom regret having undergone surgery. The importance of surgery can be appreciated by the repeated finding that quality of surgical results is one of the best predictors of the overall outcome of sex reassignment (Lawrence, 2006).

Other Surgeries

Other surgeries for assisting in body feminization include reduction thyroid chondroplasty (reduction of the Adam's apple), voice modification surgery, suction-assisted lipoplasty (contour

modeling) of the waist, rhinoplasty (nose correction), facial bone reduction, face-lift, and blepharoplasty (rejuvenation of the eyelid). Other surgeries for assisting in body masculinization include liposuction, lipofilling, and pectoral implants. Voice surgery to obtain a deeper voice is rare but may be recommended in some cases, such as when hormone therapy has been ineffective.

Although these surgeries do not require referral by mental health professionals, such professionals can play an important role in assisting clients in making a fully informed decision about the timing and implications of such procedures in the context of the social transition.

Although most of these procedures are generally labeled "purely aesthetic," these same operations in an individual with severe gender dysphoria can be considered medically necessary, depending on the unique clinical situation of a given patient's condition and life situation. This ambiguity reflects reality in clinical situations, and allows for individual decisions as to the need and desirability of these procedures.

XII

Postoperative Care and Follow-Up

Long-term postoperative care and follow-up after surgical treatments for gender dysphoria are associated with good surgical and psychosocial outcomes (Monstrey et al., 2009). Follow-up is important to a patient's subsequent physical and mental health and to a surgeon's knowledge about the benefits and limitations of surgery. Surgeons who operate on patients coming from long distances should include personal follow-up in their care plan and attempt to ensure affordable local long-term aftercare in their patients' geographic region.

Postoperative patients may sometimes exclude themselves from follow-up by specialty providers, including the hormone-prescribing physician (for patients receiving hormones), not recognizing that these providers are often best able to prevent, diagnose, and treat medical conditions that are unique to hormonally and surgically treated patients. The need for follow-up equally extends to mental health professionals, who may have spent a longer period of time with the patient than any other professional and therefore are in an excellent position to assist in any postoperative adjustment difficulties. Health professionals should stress the importance of postoperative follow-up care with their patients and offer continuity of care.

Postoperative patients should undergo regular medical screening according to recommended guidelines for their age. This is discussed more in the next section.

XIII

Lifelong Preventive and Primary Care

Transsexual, transgender, and gender-nonconforming people need health care throughout their lives. For example, to avoid the negative secondary effects of having a gonadectomy at a relatively young age and/or receiving long-term, high-dose hormone therapy, patients need thorough medical care by providers experienced in primary care and transgender health. If one provider is not able to provide all services, ongoing communication among providers is essential.

Primary care and health maintenance issues should be addressed before, during, and after any possible changes in gender role and medical interventions to alleviate gender dysphoria. While hormone providers and surgeons play important roles in preventive care, every transsexual, transgender, and gender-nonconforming person should partner with a primary care provider for overall health care needs (Feldman, 2007).

General Preventive Health Care

Screening guidelines developed for the general population are appropriate for organ systems that are unlikely to be affected by feminizing/masculinizing hormone therapy. However, in areas such as cardiovascular risk factors, osteoporosis, and some cancers (breast, cervical, ovarian, uterine, and prostate), such general guidelines may either over- or underestimate the cost-effectiveness of screening individuals who are receiving hormone therapy.

Several resources provide detailed protocols for the primary care of patients undergoing feminizing/masculinizing hormone therapy, including therapy that is provided after sex reassignment surgeries (Center of Excellence for Transgender Health, UCSF, 2011; Feldman & Goldberg, 2006; Feldman, 2007; Gorton, Buth, & Spade, 2005). Clinicians should consult their national evidence-based guidelines and discuss screening with their patients in light of the effects of hormone therapy on their baseline risk.

Cancer Screening

Cancer screening of organ systems that are associated with sex can present particular medical and psychosocial challenges for transsexual, transgender, and gender-nonconforming patients and their health care providers. In the absence of large-scale prospective studies, providers are unlikely to have enough evidence to determine the appropriate type and frequency of cancer screenings for this population. Over-screening results in higher health care costs, high false positive rates, and often unnecessary exposure to radiation and/or diagnostic interventions such as biopsies. Under-screening results in diagnostic delay for potentially treatable cancers. Patients may find cancer screening gender affirming (such as mammograms for MtF patients) or both physically and emotionally painful (such as Pap smears offer continuity of care for FtM patients).

Urogenital Care

Gynecologic care may be necessary for transsexual, transgender, and gender-nonconforming people of both sexes. For FtM patients, such care is needed predominantly for individuals who have not had genital surgery. For MtF patients, such care is needed after genital surgery. While many surgeons counsel patients regarding postoperative urogenital care, primary care clinicians and gynecologists should also be familiar with the special genital concerns of this population.

All MtF patients should receive counseling regarding genital hygiene, sexuality, and prevention of sexually transmitted infections; those who have had genital surgery should also be counseled on the need for regular vaginal dilation or penetrative intercourse in order to maintain vaginal depth and width (van Trotsenburg, 2009). Due to the anatomy of the male pelvis, the axis and the dimensions of the neovagina differ substantially from those of a biologic vagina. This anatomic difference can affect intercourse if not understood by MtF patients and their partners (van Trotsenburg, 2009).

Lower urinary tract infections occur frequently in MtF patients who have had surgery because of the reconstructive requirements of the shortened urethra. In addition, these patients may suffer from functional disorders of the lower urinary tract; such disorders may be caused by damage of the autonomous nerve supply of the bladder floor during dissection between the rectum and the bladder, and by a change of the position of the bladder itself. A dysfunctional bladder (e.g., overactive bladder, stress or urge urinary incontinence) may occur after sex reassignment surgery (Hoebeke et al., 2005; Kuhn, Hiltebrand, & Birkhauser, 2007).

Most FtM patients do not undergo vaginectomy (colpectomy). For patients who take masculinizing hormones, despite considerable conversion of testosterone to estrogens, atrophic changes of the vaginal lining can be observed regularly and may lead to pruritus or burning. Examination can be

both physically and emotionally painful, but lack of treatment can seriously aggravate the situation. Gynecologists treating the genital complaints of FtM patients should be aware of the sensitivity that patients with a male gender identity and masculine gender expression might have around having genitals typically associated with the female sex.

XIV

Applicability of the *Standards of Care* to People Living in Institutional Environments

The *SOC* in their entirety apply to all transsexual, transgender, and gender-nonconforming people, irrespective of their housing situation. People should not be discriminated against in their access to appropriate health care based on where they live, including institutional environments such as prisons or long-/intermediate-term health care facilities (Brown, 2009). Health care for transsexual, transgender, and gender-nonconforming people living in an institutional environment should mirror that which would be available to them if they were living in a non-institutional setting within the same community.

All elements of assessment and treatment as described in the *SOC* can be provided to people living in institutions (Brown, 2009). Access to these medically necessary treatments should not be denied on the basis of institutionalization or housing arrangements. If the in-house expertise of health professionals in the direct or indirect employ of the institution does not exist to assess and/or treat people with gender dysphoria, it is appropriate to obtain outside consultation from professionals who are knowledgeable about this specialized area of health care.

People with gender dysphoria in institutions may also have coexisting mental health conditions (Cole et al., 1997). These conditions should be evaluated and treated appropriately.

People who enter an institution on an appropriate regimen of hormone therapy should be continued on the same, or similar, therapies and monitored according to the *SOC*. A "freeze frame" approach is not considered appropriate care in most situations *(Kosilek v. Massachusetts Department of Corrections/Maloney,* C.A. No. 92–12820-MLW, 2002). People with gender dysphoria who are deemed appropriate for hormone therapy (following the *SOC*) should be started on such therapy. The consequences of abrupt withdrawal of hormones or lack of initiation of hormone therapy when medically necessary include a high likelihood of negative outcomes such as surgical self-treatment by autocastration, depressed mood, dysphoria, and/or suicidality (Brown, 2010).

Reasonable accommodations to the institutional environment can be made in the delivery of care consistent with the *SOC*, if such accommodations do not jeopardize the delivery of medically necessary care to people with gender dysphoria. An example of a reasonable accommodation is the use of injectable hormones, if not medically contraindicated, in an environment where diversion of oral preparations is highly likely (Brown, 2009). Denial of needed changes in gender role or access to treatments, including sex reassignment surgery, on the basis of residence in an institution are not reasonable accommodations under the *SOC* (Brown, 2010).

Housing and shower/bathroom facilities for transsexual, transgender, and gender-nonconforming people living in institutions should take into account their gender identity and role, physical status, dignity, and personal safety. Placement in a single-sex housing unit, ward, or pod on the sole basis of the appearance of the external genitalia may not be appropriate and may place the individual at risk for victimization (Brown, 2009).

Institutions where transsexual, transgender, and gender-nonconforming people reside and receive health care should monitor for a tolerant and positive climate to ensure that residents are not under attack by staff or other residents.

XV

Applicability of the *Standards of Care* to People With Disorders of Sex Development

Terminology

The term *disorder of sex development* (DSD) refers to a somatic condition of atypical development of the reproductive tract (Hughes, Houk, Ahmed, Lee, & LWPES/ESPE Consensus Group, 2006). DSDs include the condition that used to be called *intersexuality*. Although the terminology was changed to DSD during an international consensus conference in 2005 (Hughes et al., 2006), disagreement about language use remains. Some people object strongly to the "disorder" label, preferring instead to view these congenital conditions as a matter of diversity (Diamond, 2009) and to continue using the terms *intersex* or *intersexuality*. In the *SOC*, WPATH uses the term DSD in an objective and value-free manner, with the goal of ensuring that health professionals recognize this medical term and use it to access relevant literature as the field progresses. WPATH remains

open to new terminology that will further illuminate the experience of members of this diverse population and lead to improvements in health care access and delivery.

Rationale for Addition to the *SOC*

Previously, individuals with a DSD who also met the *DSM-IV-TR's* behavioral criteria for Gender Identity Disorder (American Psychiatric Association, 2000) were excluded from that general diagnosis. Instead, they were categorized as having a "Gender Identity Disorder - Not Otherwise Specified." They were also excluded from the WPATH *Standards of Care*.

The current proposal for *DSM-5* (www.dsm5.org) is to replace the term *gender identity disorder* with *gender dysphoria*. Moreover, the proposed changes to the *DSM* consider gender dysphoric people with a DSD to have a subtype of gender dysphoria. This proposed categorization—which explicitly differentiates between gender dysphoric individuals with and without a DSD—is justified: In people with a DSD, gender dysphoria differs in its phenomenological presentation, epidemiology, life trajectories, and etiology (Meyer-Bahlburg, 2009).

Adults with a DSD and gender dysphoria have increasingly come to the attention of health professionals. Accordingly, a brief discussion of their care is included in this version of the *SOC*.

Health History Considerations

Health professionals assisting patients with both a DSD and gender dysphoria need to be aware that the medical context in which such patients have grown up is typically very different from that of people without a DSD.

Some people are recognized as having a DSD through the observation of gender-atypical genitals at birth. (Increasingly this observation is made during the prenatal period by way of imaging procedures such as ultrasound.) These infants then undergo extensive medical diagnostic procedures. After consultation among the family and health professionals—during which the specific diagnosis, physical and hormonal findings, and feedback from long-term outcome studies (Cohen-Kettenis, 2005; Dessens, Slijper, & Drop, 2005; Jurgensen, Hiort, Holterhus, & Thyen, 2007; Mazur, 2005; Meyer-Bahlburg, 2005; Stikkelbroeck et al., 2003; Wisniewski, Migeon, Malouf, & Gearhart, 2004) are considered—the newborn is assigned a sex, either male or female.

Other individuals with a DSD come to the attention of health professionals around the age of puberty through the observation of atypical development of secondary sex characteristics. This observation also leads to a specific medical evaluation.

The type of DSD and severity of the condition has significant implications for decisions about a patient's initial sex assignment, subsequent genital surgery, and other medical and psychosocial care (Meyer-Bahlburg, 2009). For instance, the degree of prenatal androgen exposure in individuals with a DSD has been correlated with the degree of masculinization of gender-related *behavior* (that is, *gender role and expression*); however, the correlation is only moderate, and considerable behavioral variability remains unaccounted for by prenatal androgen exposure (Jurgensen et al., 2007; Meyer-Bahlburg, Dolezal, Baker, Ehrhardt, & New, 2006). Notably, a similar correlation of prenatal hormone exposure with gender *identity* has not been demonstrated (e.g., Meyer-Bahlburg et al., 2004). This is underlined by the fact that people with the same (core) gender identity can vary widely in the degree of masculinization of their gender-related behavior.

Assessment and Treatment of Gender Dysphoria in People with Disorders of Sex Development

Very rarely are individuals with a DSD identified as having gender dysphoria *before* a DSD diagnosis has been made. Even so, a DSD diagnosis is typically apparent with an appropriate history and basic physical exam—both of which are part of a medical evaluation for the appropriateness of hormone therapy or surgical interventions for gender dysphoria. Mental health professionals should ask their clients presenting with gender dysphoria to have a physical exam, particularly if they are not currently seeing a primary care (or other health care) provider.

Most people with a DSD who are born with genital ambiguity do not develop gender dysphoria (e.g., Meyer-Bahlburg, Dolezal, et al., 2004; Wisniewski et al., 2004). However, some people with a DSD will develop chronic gender dysphoria and even undergo a change in their birth-assigned sex and/or their gender role (Meyer-Bahlburg, 2005; Wilson, 1999; Zucker, 1999). If there are persistent and strong indications that gender dysphoria is present, a comprehensive evaluation by clinicians skilled in the assessment and treatment of gender dysphoria is essential, irrespective of the patient's age. Detailed recommendations have been published for conducting such an assessment and for making treatment decisions to address gender dysphoria in the context of a DSD (Meyer-Bahlburg, 2011). Only after thorough assessment should steps be taken in the direction of changing a patient's birth-assigned sex or gender role.

Clinicians assisting these patients with treatment options to alleviate gender dysphoria may profit from the insights gained from providing care to patients without a DSD (Cohen-Kettenis, 2010).

However, certain criteria for treatment (e.g., age, duration of experience with living in the desired gender role) are usually not routinely applied to people with a DSD; rather, the criteria are interpreted in light of a patient's specific situation (Meyer-Bahlburg, 2011). In the context of a DSD, changes in birth-assigned sex and gender role have been made at any age between early elementary-school age and middle adulthood. Even genital surgery may be performed much earlier in these patients than in gender dysphoric individuals without a DSD if the surgery is well justified by the diagnosis, by the evidence-based gender-identity prognosis for the given syndrome and syndrome severity, and by the patient's wishes.

One reason for these treatment differences is that genital surgery in individuals with a DSD is quite common in infancy and adolescence. Infertility may already be present due to either early gonadal failure or to gonadectomy because of a malignancy risk. Even so, it is advisable for patients with a DSD to undergo a full social transition to another gender role only if there is a long-standing history of gender-atypical behavior, and if gender dysphoria and/or the desire to change one's gender role has been strong and persistent for a considerable period of time. Six months is the time period of full symptom expression required for the application of the gender dysphoria diagnosis proposed for *DSM-5* (Meyer-Bahlburg, 2011).

Additional Resources

The gender-relevant medical histories of people with a DSD are often complex. Their histories may include a great variety of inborn genetic, endocrine, and somatic atypicalities, as well as various hormonal, surgical, and other medical treatments. For this reason, many additional issues need to be considered in the psychosocial and medical care of such patients, regardless of the presence of gender dysphoria. Consideration of these issues is beyond what can be covered in the *SOC*. The interested reader is referred to existing publications (e.g., Cohen-Kettenis & Pfäfflin, 2003; Meyer-Bahlburg, 2002, 2008). Some families and patients also find it useful to consult or work with community support groups.

There is a very substantial medical literature on the medical management of patients with a DSD. Much of this literature has been produced by high-level specialists in pediatric endocrinology and urology, with input from specialized mental health professionals, especially in the area of gender. Recent international consensus conferences have addressed evidence-based care guidelines (including issues of gender and of genital surgery) for DSD in general (Hughes et al., 2006) and specifically for Congenital Adrenal Hyperplasia (Joint LWPES/ESPE CAH Working Group et al., 2002; Speiser et al., 2010). Others have addressed the research needs for DSD in general (Meyer-Bahlburg & Blizzard, 2004) and for selected syndromes such as 46,XXY (Simpson et al., 2003).

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APPENDIX A
GLOSSARY

Terminology in the area of health care for transsexual, transgender, and gender-nonconforming people is rapidly evolving; new terms are being introduced, and the definitions of existing terms are changing. Thus, there is often misunderstanding, debate, or disagreement about language in this field. Terms that may be unfamiliar or that have specific meanings in the *SOC* are defined below for the purpose of this document only. Others may adopt these definitions, but WPATH acknowledges that these terms may be defined differently in different cultures, communities, and contexts.

WPATH also acknowledges that many terms used in relation to this population are not ideal. For example, the terms *transsexual* and *transvestite*—and, some would argue, the more recent term *transgender*—have been applied to people in an objectifying fashion. Yet such terms have been more or less adopted by many people who are making their best effort to make themselves understood. By continuing to use these terms, WPATH intends only to ensure that concepts and processes are comprehensible, in order to facilitate the delivery of quality health care to transsexual, transgender, and gender-nonconforming people. WPATH remains open to new terminology that will further illuminate the experience of members of this diverse population and lead to improvements in health care access and delivery.

Bioidentical hormones: Hormones that are *structurally* identical to those found in the human body (ACOG Committee of Gynecologic Practice, 2005). The hormones used in bioidentical hormone therapy (BHT) are generally derived from plant sources and are structurally similar to endogenous human hormones, but they need to be commercially processed to become bioidentical.

Bioidentical compounded hormone therapy (BCHT): Use of hormones that are prepared, mixed, assembled, packaged, or labeled as a drug by a pharmacist and custom-made for a patient according to a physician's specifications. Government drug agency approval is not possible for each compounded product made for an individual consumer.

Cross-dressing (transvestism): Wearing clothing and adopting a gender role presentation that, in a given culture, is more typical of the other sex.

Disorders of sex development (DSD): Congenital conditions in which the development of chromosomal, gonadal, or anatomic sex is atypical. Some people strongly object to the "disorder" label and instead view these conditions as a matter of diversity (Diamond, 2009), preferring the terms *intersex* and *intersexuality*.

Female-to-Male (FtM): Adjective to describe individuals assigned female at birth who are changing or who have changed their body and/or gender role from birth-assigned female to a more masculine body or role.

Gender dysphoria: Distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b).

Gender identity: A person's intrinsic sense of being male (a boy or a man), female (a girl or woman), or an alternative gender (e.g., boygirl, girlboy, transgender, genderqueer, eunuch) (Bockting, 1999; Stoller, 1964).

Gender identity disorder: Formal diagnosis set forth by the *Diagnostic Statistical Manual of Mental Disorders, 4th Edition, Text Rev (DSM IV-TR)* (American Psychiatric Association, 2000). Gender identity disorder is characterized by a strong and persistent cross-gender identification and a persistent discomfort with one's sex or sense of inappropriateness in the gender role of that sex, causing clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Gender-nonconforming: Adjective to describe individuals whose gender identity, role, or expression differs from what is normative for their assigned sex in a given culture and historical period.

Gender role or expression: Characteristics in personality, appearance, and behavior that in a given culture and historical period are designated as masculine or feminine (that is, more typical of the male or female social role) (Ruble, Martin, & Berenbaum, 2006). While most individuals present socially in clearly masculine or feminine gender roles, some people present in an alternative gender role such as genderqueer or specifically transgender. All people tend to incorporate both masculine and feminine characteristics in their gender expression in varying ways and to varying degrees (Bockting, 2008).

Genderqueer: Identity label that may be used by individuals whose gender identity and/or role does not conform to a binary understanding of gender as limited to the categories of man or woman, male or female (Bockting, 2008).

Internalized transphobia: Discomfort with one's own transgender feelings or identity as a result of internalizing society's normative gender expectations.

Male-to-Female (MtF): Adjective to describe individuals assigned male at birth who are changing or who have changed their body and/or gender role from birth-assigned male to a more feminine body or role.

Natural hormones: Hormones that are derived from natural *sources* such as plants or animals. Natural hormones may or may not be bioidentical.

Sex: Sex is assigned at birth as male or female, usually based on the appearance of the external genitalia. When the external genitalia are ambiguous, other components of sex (internal genitalia, chromosomal and hormonal sex) are considered in order to assign sex (Grumbach, Hughes, & Conte, 2003; MacLaughlin & Donahoe, 2004; Money & Ehrhardt, 1972; Vilain, 2000). For most people, gender identity and expression are consistent with their sex assigned at birth; for transsexual, transgender, and gender-nonconforming individuals, gender identity or expression differ from their sex assigned at birth.

Sex reassignment surgery (gender affirmation surgery): Surgery to change primary and/or secondary sex characteristics to affirm a person's gender identity. Sex reassignment surgery can be an important part of medically necessary treatment to alleviate gender dysphoria.

Transgender: Adjective to describe a diverse group of individuals who cross or transcend culturally defined categories of gender. The gender identity of transgender people differs to varying degrees from the sex they were assigned at birth (Bockting, 1999).

Transition: Period of time when individuals change from the gender role associated with their sex assigned at birth to a different gender role. For many people, this involves learning how to live socially in another gender role; for others this means finding a gender role and expression that are most comfortable for them. Transition may or may not include feminization or masculinization of the body through hormones or other medical procedures. The nature and duration of transition are variable and individualized.

Transsexual: Adjective (often applied by the medical profession) to describe individuals who seek to change or who have changed their primary and/or secondary sex characteristics through femininizing or masculinizing medical interventions (hormones and/or surgery), typically accompanied by a permanent change in gender role.

APPENDIX B
OVERVIEW OF MEDICAL RISKS OF HORMONE THERAPY

The risks outlined below are based on two comprehensive, evidence-based literature reviews of masculinizing/feminizing hormone therapy (Feldman & Safer, 2009; Hembree et al., 2009), along with a large cohort study (Asscheman et al., 2011). These reviews can serve as detailed references for providers, along with other widely recognized, published clinical materials (e.g., Dahl et al., 2006; Ettner et al., 2007).

Risks of Feminizing Hormone Therapy (MtF)

Likely Increased Risk:

Venous thromboembolic disease

- Estrogen use increases the risk of venous thromboembolic events (VTE), particularly in patients who are over age 40, smokers, highly sedentary, obese, and who have underlying thrombophilic disorders.
- This risk is increased with the additional use of third generation progestins.
- This risk is decreased with use of the transdermal (versus oral) route of estradiol administration, which is recommended for patients at higher risk of VTE.

Cardiovascular, cerebrovascular disease

- Estrogen use increases the risk of cardiovascular events in patients over age 50 with underlying cardiovascular risk factors. Additional progestin use may increase this risk.

Lipids

- Oral estrogen use may markedly increase triglycerides in patients, increasing the risk of pancreatitis and cardiovascular events.
- Different routes of administration will have different metabolic effects on levels of HDL cholesterol, LDL cholesterol and lipoprotein(a).
- In general, clinical evidence suggests that MtF patients with pre-existing lipid disorders may benefit from the use of transdermal rather than oral estrogen.

Liver/gallbladder

- Estrogen and cyproterone acetate use may be associated with transient liver enzyme elevations and, rarely, clinical hepatotoxicity.
- Estrogen use increases the risk of cholelithiasis (gall stones) and subsequent cholecystectomy.

Possible Increased Risk:

Type 2 diabetes mellitus

- Feminizing hormone therapy, particularly estrogen, may increase the risk of type 2 diabetes, particularly among patients with a family history of diabetes or other risk factors for this disease.

Hypertension

- Estrogen use may increase blood pressure, but the effect on incidence of overt hypertension is unknown.
- Spironolactone reduces blood pressure and is recommended for at-risk or hypertensive patients desiring feminization.

Prolactinoma

- Estrogen use increases the risk of hyperprolactinemia among MtF patients in the first year of treatment, but this risk is unlikely thereafter.
- High-dose estrogen use may promote the clinical appearance of preexisting but clinically unapparent prolactinoma.

Inconclusive or No Increased Risk:

Items in this category include those that may present risk, but for which the evidence is so minimal that no clear conclusion can be reached.

Breast cancer

- MtF persons who have taken feminizing hormones do experience breast cancer, but it is unknown how their degree of risk compares to that of persons born with female genitalia.
- Longer duration of feminizing hormone exposure (i.e., number of years taking estrogen preparations), family history of breast cancer, obesity (BMI >35), and the use of progestins likely influence the level of risk.

Other Side Effects of Feminizing Therapy:

The following effects may be considered minor or even desired, depending on the patient, but are clearly associated with feminizing hormone therapy.

Fertility and sexual function

- Feminizing hormone therapy may impair fertility.
- Feminizing hormone therapy may decrease libido.
- Feminizing hormone therapy reduces nocturnal erections, with variable impact on sexually stimulated erections.

Risks of Anti-Androgen Medications:

Feminizing hormone regimens often include a variety of agents that affect testosterone production or action. These include GnRH agonists, progestins (including cyproterone acetate), spironolactone, and 5-alpha reductase inhibitors. An extensive discussion of the specific risks of these agents is beyond the scope of the *SOC*. However, both spironolactone and cyproterone acetate are widely used and deserve some comment.

Cyproterone acetate is a progestational compound with anti-androgenic properties (Gooren, 2005; Levy et al., 2003). Although widely used in Europe, it is not approved for use in the United States because of concerns about hepatotoxicity (Thole, Manso, Salgueiro, Revuelta, & Hidalgo, 2004). Spironolactone is commonly used as an anti-androgen in feminizing hormone therapy, particularly in regions where cyproterone is not approved for use (Dahl et al., 2006; Moore et al., 2003; Tangpricha et al., 2003). Spironolactone has a long history of use in treating hypertension and congestive heart failure. Its common side effects include hyperkalemia, dizziness, and gastrointestinal symptoms (*Physicians' Desk Reference*, 2007).

Risks of Masculinizing Hormone Therapy (FtM)

Likely Increased Risk:

Polycythemia

- Masculinizing hormone therapy involving testosterone or other androgenic steroids increases the risk of polycythemia (hematocrit > 50%), particularly in patients with other risk factors.
- Transdermal administration and adaptation of dosage may reduce this risk.

Weight gain/visceral fat

- Masculinizing hormone therapy can result in modest weight gain, with an increase in visceral fat.

Possible Increased Risk:

Lipids

- Testosterone therapy decreases HDL, but variably affects LDL and triglycerides.
- Supraphysiologic (beyond normal male range) serum levels of testosterone, often found with extended intramuscular dosing, may worsen lipid profiles, whereas transdermal administration appears to be more lipid neutral.
- Patients with underlying polycystic ovarian syndrome or dyslipidemia may be at increased risk of worsening dyslipidemia with testosterone therapy.

Liver

- Transient elevations in liver enzymes may occur with testosterone therapy.
- Hepatic dysfunction and malignancies have been noted with oral methyltestosterone. However, methyltestosterone is no longer available in most countries and should no longer be used.

Psychiatric

Masculinizing therapy involving testosterone or other androgenic steroids may increase the risk of hypomanic, manic, or psychotic symptoms in patients with underlying psychiatric disorders that include such symptoms. This adverse event appears to be associated with higher doses or supraphysiologic blood levels of testosterone.

Inconclusive or No Increased Risk:

Items in this category include those that may present risk, but for which the evidence is so minimal that no clear conclusion can be reached.

Osteoporosis

- Testosterone therapy maintains or increases bone mineral density among FtM patients prior to oophorectomy, at least in the first three years of treatment.
- There is an increased risk of bone density loss after oophorectomy, particularly if testosterone therapy is interrupted or insufficient. This includes patients utilizing solely oral testosterone.

Cardiovascular

- Masculinizing hormone therapy at normal physiologic doses does not appear to increase the risk of cardiovascular events among healthy patients.
- Masculinizing hormone therapy may increase the risk of cardiovascular disease in patients with underlying risks factors.

Hypertension

- Masculinizing hormone therapy at normal physiologic doses may increase blood pressure but does not appear to increase the risk of hypertension.
- Patients with risk factors for hypertension, such as weight gain, family history, or polycystic ovarian syndrome, may be at increased risk.

Type 2 diabetes mellitus

- Testosterone therapy does not appear to increase the risk of type 2 diabetes among FtM patients overall, unless other risk factors are present.
- Testosterone therapy may further increase the risk of type 2 diabetes in patients with other risk factors, such as significant weight gain, family history, and polycystic ovarian syndrome. There are no data that suggest or show an increase in risk in those with risk factors for dyslipidemia.

Breast cancer

- Testosterone therapy in FtM patients does not increase the risk of breast cancer.

Cervical cancer

- Testosterone therapy in FtM patients does not increase the risk of cervical cancer, although it may increase the risk of minimally abnormal Pap smears due to atrophic changes.

Ovarian cancer

- Analogous to persons born with female genitalia with elevated androgen levels, testosterone therapy in FtM patients may increase the risk of ovarian cancer, although evidence is limited.

Endometrial (uterine) cancer

- Testosterone therapy in FtM patients may increase the risk of endometrial cancer, although evidence is limited.

Other Side Effects of Masculinizing Therapy:

The following effects may be considered minor or even desired, depending on the patient, but are clearly associated with masculinization.

Fertility and sexual function

- Testosterone therapy in FtM patients reduces fertility, although the degree and reversibility are unknown.

- Testosterone therapy can induce permanent anatomic changes in the developing embryo or fetus.
- Testosterone therapy induces clitoral enlargement and increases libido.

Acne, androgenic alopecia

Acne and varying degrees of male pattern hair loss (androgenic alopecia) are common side effects of masculinizing hormone therapy.

APPENDIX C
SUMMARY OF CRITERIA FOR HORMONE THERAPY AND SURGERIES

As for all previous versions of the *SOC*, the criteria put forth in the *SOC* for hormone therapy and surgical treatments for gender dysphoria are clinical guidelines; individual health professionals and programs may modify them. Clinical departures from the *SOC* may come about because of a patient's unique anatomic, social, or psychological situation; an experienced health professional's evolving method of handling a common situation; a research protocol; lack of resources in various parts of the world; or the need for specific harm-reduction strategies. These departures should be recognized as such, explained to the patient, and documented through informed consent for quality patient care and legal protection. This documentation is also valuable to accumulate new data, which can be retrospectively examined to allow for health care—and the *SOC*—to evolve.

Criteria for Feminizing/Masculinizing Hormone Therapy (One Referral or Chart Documentation of Psychosocial Assessment)

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to give consent for treatment;
3. Age of majority in a given country (if younger, follow the *SOC* for children and adolescents);
4. If significant medical or mental concerns are present, they must be reasonably well controlled.

Criteria for Breast/Chest Surgery (One Referral)

Mastectomy and Creation of a Male Chest in FtM Patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to give consent for treatment;
3. Age of majority in a given country (if younger, follow the *SOC* for children and adolescents);
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.

Hormone therapy is not a prerequisite.

Breast Augmentation (Implants/Lipofilling) in MtF Patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to give consent for treatment;
3. Age of majority in a given country (if younger, follow the *SOC* for children and adolescents);
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.

Although not an explicit criterion, it is recommended that MtF patients undergo feminizing hormone therapy (minimum 12 months) prior to breast augmentation surgery. The purpose is to maximize breast growth in order to obtain better surgical (aesthetic) results.

Criteria for Genital Surgery (Two Referrals)

Hysterectomy and Salpingo-Oophorectomy in FtM Patients and Orchiectomy in MtF Patients:

1. Persistent, well documented gender dysphoria;
2. Capacity to make a fully informed decision and to give consent for treatment;

3. Age of majority in a given country;

4. If significant medical or mental health concerns are present, they must be well controlled;

5. 12 continuous months of hormone therapy as appropriate to the patient's gender goals (unless hormones are not clinically indicated for the individual).

The aim of hormone therapy prior to gonadectomy is primarily to introduce a period of reversible estrogen or testosterone suppression, before a patient undergoes irreversible surgical intervention.

These criteria do not apply to patients who are having these surgical procedures for medical indications other than gender dysphoria.

Metoidioplasty or Phalloplasty in FtM Patients and Vaginoplasty in MtF Patients:

1. Persistent, well documented gender dysphoria;

2. Capacity to make a fully informed decision and to give consent for treatment;

3. Age of majority in a given country;

4. If significant medical or mental health concerns are present, they must be well controlled;

5. 12 continuous months of hormone therapy as appropriate to the patient's gender goals (unless hormones are not clinically indicated for the individual);

6. 12 continuous months of living in a gender role that is congruent with their gender identity.

Although not an explicit criterion, it is recommended that these patients also have regular visits with a mental health or other medical professional.

The criterion noted above for some types of genital surgeries—that is, that patients engage in 12 continuous months of living in a gender role that is congruent with their gender identity—is based on expert clinical consensus that this experience provides ample opportunity for patients to experience and socially adjust in their desired gender role, before undergoing irreversible surgery.

APPENDIX D
EVIDENCE FOR CLINICAL OUTCOMES OF THERAPEUTIC APPROACHES

One of the real supports for any new therapy is an outcome analysis. Because of the controversial nature of sex reassignment surgery, this type of analysis has been very important. Almost all of the outcome studies in this area have been retrospective.

One of the first studies to examine the post-treatment psychosocial outcomes of transsexual patients was done in 1979 at Johns Hopkins University School of Medicine and Hospital (USA) (J. K. Meyer & Reter, 1979). This study focused on patients' occupational, educational, marital, and domiciliary stability. The results revealed several significant changes with treatment. These changes were not seen as positive; rather, they showed that many individuals who had entered the treatment program were no better off or were worse off in many measures after participation in the program. These findings resulted in closure of the treatment program at that hospital/medical school (Abramowitz, 1986).

Subsequently, a significant number of health professionals called for a standard for eligibility for sex reassignment surgery. This led to the formulation of the original *Standards of Care* of the Harry Benjamin International Gender Dysphoria Association (now WPATH) in 1979.

In 1981, Pauly published results from a large retrospective study of people who had undergone sex reassignment surgery. Participants in that study had much better outcomes: Among 83 FtM patients, 80.7% had a satisfactory outcome (i.e., patient self report of "improved social and emotional adjustment"), 6.0% unsatisfactory. Among 283 MtF patients, 71.4% had a satisfactory outcome, 8.1% unsatisfactory. This study included patients who were treated before the publication and use of the *Standards of Care*.

Since the *Standards of Care* have been in place, there has been a steady increase in patient satisfaction and decrease in dissatisfaction with the outcome of sex reassignment surgery. Studies conducted after 1996 focused on patients who were treated according to the *Standards of Care*. The findings of Rehman and colleagues (1999) and Krege and colleagues (2001) are typical of this body of work; none of the patients in these studies regretted having had surgery, and most reported being satisfied with the cosmetic and functional results of the surgery. Even patients who develop severe surgical complications seldom regret having undergone surgery. Quality of surgical results is one of the best predictors of the overall outcome of sex reassignment (Lawrence, 2003). The vast majority of follow-up studies have shown an undeniable beneficial effect of sex reassignment surgery on postoperative outcomes such as subjective well being, cosmesis, and sexual function (De Cuypere et al., 2005; Garaffa, Christopher, & Ralph, 2010; Klein & Gorzalka, 2009), although the specific magnitude of benefit is uncertain from

the currently available evidence. One study (Emory, Cole, Avery, Meyer, & Meyer, 2003) even showed improvement in patient income.

One troubling report (Newfield et al., 2006) documented lower scores on quality of life (measured with the SF-36) for FtM patients than for the general population. A weakness of that study is that it recruited its 384 participants by a general email rather than a systematic approach, and the degree and type of treatment were not recorded. Study participants who were taking testosterone had typically being doing so for less than 5 years. Reported quality of life was higher for patients who had undergone breast/chest surgery than for those who had not ($p<.001$). (A similar analysis was not done for genital surgery.) In other work, Kuhn and colleagues (2009) used the King's Health Questionnaire to assess the quality of life of 55 transsexual patients at 15 years after surgery. Scores were compared to those of 20 healthy female control patients who had undergone abdominal/pelvic surgery in the past. Quality of life scores for transsexual patients were the same or better than those of control patients for some subscales (emotions, sleep, incontinence, symptom severity, and role limitation), but worse in other domains (general health, physical limitation, and personal limitation).

Two long-term observational studies, both retrospective, compared the mortality and psychiatric morbidity of transsexual adults to those of general population samples (Asscheman et al., 2011; Dhejne et al., 2011). An analysis of data from the Swedish National Board of Health and Welfare information registry found that individuals who had received sex reassignment surgery (191 MtF and 133 FtM) had significantly higher rates of mortality, suicide, suicidal behavior, and psychiatric morbidity than those for a nontranssexual control group matched on age, immigrant status, prior psychiatric morbidity, and birth sex (Dhejne et al., 2011). Similarly, a study in the Netherlands reported a higher total mortality rate, including incidence of suicide, in both pre- and post-surgery transsexual patients (966 MtF and 365 MtF) than in the general population of that country (Asscheman et al., 2011). Neither of these studies questioned the efficacy of sex reassignment; indeed, both lacked an adequate comparison group of transsexuals who either did not receive treatment or who received treatment other than genital surgery. Moreover, transsexual people in these studies were treated as far back as the 1970s. However, these findings do emphasize the need to have good long-term psychological and psychiatric care available for this population. More studies are needed that focus on the outcomes of current assessment and treatment approaches for gender dysphoria.

It is difficult to determine the effectiveness of hormones alone in the relief of gender dysphoria. Most studies evaluating the effectiveness of masculinizing/feminizing hormone therapy on gender dysphoria have been conducted with patients who have also undergone sex reassignment surgery. Favorable effects of therapies that included both hormones and surgery were reported in a comprehensive review of over 3000 patients in 79 studies (mostly observational) conducted between 1961 and 1991 (Eldh, Berg, & Gustafsson, 1997; Gijs & Brewaeys, 2007; Murad et al., 2010; Pfäfflin & Junge, 1998). Patients operated on after 1986 did better than those before 1986; this reflects significant improvement in surgical complications (Eldh et al., 1997). Most patients have reported improved psychosocial outcomes, ranging between 87% for MtF patients and 97% for FtM patients (Green & Fleming, 1990).

Similar improvements were found in a Swedish study in which "almost all patients were satisfied with sex reassignment at 5 years, and 86% were assessed by clinicians at follow-up as stable or improved in global functioning" (Johansson, Sundbom, Höjerback, & Bodlund, 2010). Weaknesses of these earlier studies are their retrospective design and use of different criteria to evaluate outcomes.

A prospective study conducted in the Netherlands evaluated 325 consecutive adult and adolescent subjects seeking sex reassignment (Smith, Van Goozen, Kuiper, & Cohen-Kettenis, 2005). Patients who underwent sex reassignment therapy (both hormonal and surgical intervention) showed improvements in their mean gender dysphoria scores, measured by the Utrecht Gender Dysphoria Scale. Scores for body dissatisfaction and psychological function also improved in most categories. Fewer than 2% of patients expressed regret after therapy. This is the largest prospective study to affirm the results from retrospective studies that a combination of hormone therapy and surgery improves gender dysphoria and other areas of psychosocial functioning. There is a need for further research on the effects of hormone therapy without surgery, and without the goal of maximum physical feminization or masculinization.

Overall, studies have been reporting a steady improvement in outcomes as the field becomes more advanced. Outcome research has mainly focused on the outcome of sex reassignment surgery. In current practice there is a range of identity, role, and physical adaptations that could use additional follow-up or outcome research (Institute of Medicine, 2011).

APPENDIX E
DEVELOPMENT PROCESS FOR THE *STANDARDS OF CARE,* VERSION 7

The process of developing *Standards of Care, Version 7* began when an initial *SOC* "work group" was established in 2006. Members were invited to examine specific sections of *SOC, Version 6*. For each section, they were asked to review the relevant literature, identify where research was lacking and needed, and recommend potential revisions to the *SOC* as warranted by new evidence. Invited papers were submitted by the following authors: Aaron Devor, Walter Bockting, George Brown, Michael Brownstein, Peggy Cohen-Kettenis, Griet DeCuypere, Petra DeSutter, Jamie Feldman, Lin Fraser, Arlene Istar Lev, Stephen Levine, Walter Meyer, Heino Meyer-Bahlburg, Stan Monstrey, Loren Schechter, Mick van Trotsenburg, Sam Winter, and Ken Zucker. Some of these authors chose to add co-authors to assist them in their task.

Initial drafts of these papers were due June 1, 2007. Most were completed by September 2007, with the rest completed by the end of 2007. These manuscripts were then submitted to the *International*

Journal of Transgenderism (IJT). Each underwent the regular *IJT* peer review process. The final papers were published in Volume 11 (1–4) in 2009, making them available for discussion and debate.

After these articles were published, an *SOC* Revision Committee was established by the WPATH Board of Directors in 2010. The Revision Committee was first charged with debating and discussing the *IJT* background papers through a Google website. A subgroup of the Revision Committee was appointed by the Board of Directors to serve as the Writing Group. This group was charged with preparing the first draft of *SOC, Version 7* and continuing to work on revisions for consideration by the broader Revision Committee. The Board also appointed an International Advisory Group of transsexual, transgender, and gender-nonconforming individuals to give input on the revision.

A technical writer was hired to (1) review all of the recommendations for revision—both the original recommendations as outlined in the *IJT* articles and additional recommendations that emanated from the online discussion—and (2) create a survey to solicit further input on these potential revisions. From the survey results, the Writing Group was able to discern where these experts stood in terms of areas of agreement and areas in need of more discussion and debate. The technical writer then (3) created a very rough first draft of *SOC, Version 7* for the Writing Group to consider and build on.

The Writing Group met on March 4 and 5, 2011 in a face-to-face expert consultation meeting. They reviewed all recommended changes and debated and came to consensus on various controversial areas. Decisions were made based on the best available science and expert consensus. These decisions were incorporated into the draft, and additional sections were written by the Writing Group with the assistance of the technical writer.

The draft that emerged from the consultation meeting was then circulated among the Writing Group and finalized with the help of the technical writer. Once this initial draft was finalized, it was circulated among the broader *SOC* Revision Committee and the International Advisory Group. Discussion was opened up on the Google website and a conference call was held to resolve issues. Feedback from these groups was considered by the Writing Group, who then made further revisions. Two additional drafts were created and posted on the Google website for consideration by the broader *SOC* Revision Committee and the International Advisory Group. Upon completion of these three iterations of review and revision, the final document was presented to the WPATH Board of Directors for approval. The Board of Directors approved this version on September 14, 2011.

Funding

The *Standards of Care* revision process was made possible through a generous grant from the Tawani Foundation and a gift from an anonymous donor. These funds supported the following:

1. Costs of a professional technical writer;

2. Process of soliciting international input on proposed changes from gender identity professionals and the transgender community;

3. Working meeting of the Writing Group;

4. Process of gathering additional feedback and arriving at final expert consensus from the professional and transgender communities, the *Standards of Care, Version 7,* Revision Committee, and WPATH Board of Directors;

5. Costs of printing and distributing *Standards of Care, Version 7,* and posting a free downloadable copy on the WPATH website;

6. Plenary session to launch the *Standards of Care, Version 7,* at the 2011 WPATH Biennial Symposium in Atlanta, Georgia, USA.

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ISBN XXX-X-XXX-XXXXX-X

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Endocrine Treatment of Gender-Dysphoric/ Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline

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*Cosponsoring Associations: American Association of Clinical Endocrinologists, American Society of Andrology, European Society for Pediatric Endocrinology, European Society of Endocrinology, Pediatric Endocrine Society, and World Professional Association for Transgender Health.

Objective: To update the "Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline," published by the Endocrine Society in 2009.

Participants: The participants include an Endocrine Society–appointed task force of nine experts, a methodologist, and a medical writer.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation approach to describe the strength of recommendations and the quality of evidence. The task force commissioned two systematic reviews and used the best available evidence from other published systematic reviews and individual studies.

Consensus Process: Group meetings, conference calls, and e-mail communications enabled consensus. Endocrine Society committees, members and cosponsoring organizations reviewed and commented on preliminary drafts of the guidelines.

Conclusion: Gender affirmation is multidisciplinary treatment in which endocrinologists play an important role. Gender-dysphoric/gender-incongruent persons seek and/or are referred to endocrinologists to develop the physical characteristics of the affirmed gender. They require a safe and effective hormone regimen that will (1) suppress endogenous sex hormone secretion determined by the person's genetic/gonadal sex and (2) maintain sex hormone levels within the normal range for the person's affirmed gender. Hormone treatment is not recommended for prepubertal gender-dysphoric/gender-incongruent persons. Those clinicians who recommend gender-affirming endocrine treatments—appropriately trained diagnosing clinicians (required), a mental health provider for adolescents (required) and mental health

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 24 July 2017. Accepted 24 August 2017.
First Published Online 13 September 2017

Abbreviations: BMD, bone mineral density; DSD, disorder/difference of sex development; DSM, Diagnostic and Statistical Manual of Mental Disorders; GD, gender dysphoria; GnRH, gonadotropin-releasing hormone; ICD, International Statistical Classification of Diseases and Related Health Problems; MHP, mental health professional; VTE, venous thromboembolism.

professional for adults (recommended)—should be knowledgeable about the diagnostic criteria and criteria for gender-affirming treatment, have sufficient training and experience in assessing psychopathology, and be willing to participate in the ongoing care throughout the endocrine transition. We recommend treating gender-dysphoric/gender-incongruent adolescents who have entered puberty at Tanner Stage G2/B2 by suppression with gonadotropin-releasing hormone agonists. Clinicians may add gender-affirming hormones after a multidisciplinary team has confirmed the persistence of gender dysphoria/gender incongruence and sufficient mental capacity to give informed consent to this partially irreversible treatment. Most adolescents have this capacity by age 16 years old. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to age 16 years, although there is minimal published experience treating prior to 13.5 to 14 years of age. For the care of peripubertal youths and older adolescents, we recommend that an expert multidisciplinary team comprised of medical professionals and mental health professionals manage this treatment. The treating physician must confirm the criteria for treatment used by the referring mental health practitioner and collaborate with them in decisions about gender-affirming surgery in older adolescents. For adult gender-dysphoric/gender-incongruent persons, the treating clinicians (collectively) should have expertise in transgender-specific diagnostic criteria, mental health, primary care, hormone treatment, and surgery, as needed by the patient. We suggest maintaining physiologic levels of gender-appropriate hormones and monitoring for known risks and complications. When high doses of sex steroids are required to suppress endogenous sex steroids and/or in advanced age, clinicians may consider surgically removing natal gonads along with reducing sex steroid treatment. Clinicians should monitor both transgender males (female to male) and transgender females (male to female) for reproductive organ cancer risk when surgical removal is incomplete. Additionally, clinicians should persistently monitor adverse effects of sex steroids. For gender-affirming surgeries in adults, the treating physician must collaborate with and confirm the criteria for treatment used by the referring physician. Clinicians should avoid harming individuals (via hormone treatment) who have conditions other than gender dysphoria/gender incongruence and who may not benefit from the physical changes associated with this treatment. (***J Clin Endocrinol Metab*** **102: 3869–3903, 2017)**

Summary of Recommendations

1.0 Evaluation of youth and adults

1.1. We advise that only trained mental health professionals (MHPs) who meet the following criteria should diagnose gender dysphoria (GD)/gender incongruence in adults: (1) competence in using the Diagnostic and Statistical Manual of Mental Disorders (DSM) and/or the International Statistical Classification of Diseases and Related Health Problems (ICD) for diagnostic purposes, (2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings. (Ungraded Good Practice Statement)

1.2. We advise that only MHPs who meet the following criteria should diagnose GD/gender incongruence in children and adolescents: (1) training in child and adolescent developmental psychology and psychopathology, (2) competence in using the DSM and/or the ICD for diagnostic purposes, (3) the ability to make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (4) training in diagnosing psychiatric conditions, (5) the ability to undertake or refer for appropriate treatment, (6) the ability to psychosocially assess the person's understanding and social conditions that can impact gender-affirming hormone therapy, (7) a practice of regularly attending relevant professional meetings, and (8) knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents. (Ungraded Good Practice Statement)

1.3. We advise that decisions regarding the social transition of prepubertal youths with GD/gender incongruence are made with the assistance of an MHP or another experienced professional. (Ungraded Good Practice Statement).

doi: 10.1210/jc.2017-01658

1.4. We recommend against puberty blocking and gender-affirming hormone treatment in prepubertal children with GD/gender incongruence. (1 |⊕⊕◯◯)

1.5. We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults. (1 |⊕⊕⊕◯)

2.0 Treatment of adolescents

2.1. We suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment, and are requesting treatment should initially undergo treatment to suppress pubertal development. (2 |⊕⊕◯◯)

2.2. We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty. (2 |⊕⊕◯◯)

2.3. We recommend that, where indicated, GnRH analogues are used to suppress pubertal hormones. (1 |⊕⊕◯◯)

2.4. In adolescents who request sex hormone treatment (given this is a partly irreversible treatment), we recommend initiating treatment using a gradually increasing dose schedule after a multidisciplinary team of medical and MHPs has confirmed the persistence of GD/gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years. (1 |⊕⊕◯◯).

2.5. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to the age of 16 years in some adolescents with GD/gender incongruence, even though there are minimal published studies of gender-affirming hormone treatments administered before age 13.5 to 14 years. As with the care of adolescents ≥16 years of age, we recommend that an expert multidisciplinary team of medical and MHPs manage this treatment. (1 |⊕◯◯◯)

2.6. We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment. (2 |⊕⊕◯◯)

3.0 Hormonal therapy for transgender adults

3.1. We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and the criteria for the endocrine phase of gender transition before beginning treatment. (1 |⊕⊕⊕◯)

3.2. We recommend that clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment. (1 |⊕⊕⊕◯)

3.3. We suggest that clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender. (2 |⊕⊕◯◯)

3.4. We suggest that endocrinologists provide education to transgender individuals undergoing treatment about the onset and time course of physical changes induced by sex hormone treatment. (2 |⊕◯◯◯)

4.0 Adverse outcome prevention and long-term care

4.1. We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every 3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly. (2 |⊕⊕◯◯)

4.2. We suggest periodically monitoring prolactin levels in transgender females treated with estrogens. (2 |⊕⊕◯◯)

4.3. We suggest that clinicians evaluate transgender persons treated with hormones for cardiovascular risk factors using fasting lipid profiles, diabetes screening, and/or other diagnostic tools. (2 |⊕⊕◯◯)

4.4. We recommend that clinicians obtain bone mineral density (BMD) measurements when risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. (1 |⊕⊕◯◯)

4.5. We suggest that transgender females with no known increased risk of breast cancer follow breast-screening guidelines recommended for non-transgender females. (2 |⊕⊕◯◯)

4.6. We suggest that transgender females treated with estrogens follow individualized screening according to personal risk for prostatic disease and prostate cancer. (2 |⊕◯◯◯)

4.7. We advise that clinicians determine the medical necessity of including a total hysterectomy and oophorectomy as part of gender-affirming surgery. (Ungraded Good Practice Statement)

5.0 Surgery for sex reassignment and gender confirmation

5.1. We recommend that a patient pursue genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically necessary and would benefit the patient's overall health and/or well-being. (1 ⊕⊕◯◯)

5.2. We advise that clinicians approve genital gender-affirming surgery only after completion of at least 1 year of consistent and compliant hormone treatment, unless hormone therapy is not desired or medically contraindicated. (Ungraded Good Practice Statement)

5.3. We advise that the clinician responsible for endocrine treatment and the primary care provider ensure appropriate medical clearance of transgender individuals for genital gender-affirming surgery and collaborate with the surgeon regarding hormone use during and after surgery. (Ungraded Good Practice Statement)

5.4. We recommend that clinicians refer hormone-treated transgender individuals for genital surgery when: (1) the individual has had a satisfactory social role change, (2) the individual is satisfied about the hormonal effects, and (3) the individual desires definitive surgical changes. (1 ⊕◯◯◯)

5.5. We suggest that clinicians delay gender-affirming genital surgery involving gonadectomy and/or hysterectomy until the patient is at least 18 years old or legal age of majority in his or her country. (2 ⊕⊕◯◯).

5.6. We suggest that clinicians determine the timing of breast surgery for transgender males based upon the physical and mental health status of the individual. There is insufficient evidence to recommend a specific age requirement. (2 ⊕◯◯◯)

Changes Since the Previous Guideline

Both the current guideline and the one published in 2009 contain similar sections. Listed here are the sections contained in the current guideline and the corresponding number of recommendations: Introduction, Evaluation of Youth and Adults (5), Treatment of Adolescents (6), Hormonal Therapy for Transgender Adults (4), Adverse Outcomes Prevention and Long-term Care (7), and Surgery for Sex Reassignment and Gender Confirmation (6). The current introduction updates the diagnostic classification of "gender dysphoria/gender incongruence." It also reviews the development of "gender identity" and summarizes its natural development. The section on clinical evaluation of both youth and adults, defines in detail the professional qualifications required of those who diagnose and treat both adolescents and adults. We advise that decisions regarding the social transition of prepubertal youth are made with the assistance of a mental health professional or similarly experienced professional. We recommend against puberty blocking followed by gender-affirming hormone treatment of prepubertal children. Clinicians should inform pubertal children, adolescents, and adults seeking gender-confirming treatment of their options for fertility preservation. Prior to treatment, clinicians should evaluate the presence of medical conditions that may be worsened by hormone depletion and/or treatment. A multidisciplinary team, preferably composed of medical and mental health professionals, should monitor treatments. Clinicians evaluating transgender adults for endocrine treatment should confirm the diagnosis of persistent gender dysphoria/gender incongruence. Physicians should educate transgender persons regarding the time course of steroid-induced physical changes. Treatment should include periodic monitoring of hormone levels and metabolic parameters, as well as assessments of bone density and the impact upon prostate, gonads, and uterus. We also make recommendations for transgender persons who plan genital gender-affirming surgery.

Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee (CGS) of the Endocrine Society deemed the diagnosis and treatment of individuals with GD/gender incongruence a priority area for revision and appointed a task force to formulate evidence-based recommendations. The task force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation group, an international group with expertise in the development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The task force used the best available research evidence to develop the recommendations. The task force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase "we recommend" and the number 1, and weak recommendations use the phrase "we suggest" and the number 2. Cross-filled circles indicate the quality of the evidence, such that ⊕◯◯◯ denotes very low–quality evidence; ⊕⊕◯◯, low quality; ⊕⊕⊕◯, moderate quality; and ⊕⊕⊕⊕, high quality. The task force has confidence that persons who receive care according to the strong recommendations will derive, on average, more benefit than harm. Weak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence and the

doi: 10.1210/jc.2017-01658

values that the task force considered in making the recommendation. In some instances, there are remarks in which the task force offers technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the task force and their preferences; therefore, one should consider these remarks as suggestions.

In this guideline, the task force made several statements to emphasize the importance of shared decision-making, general preventive care measures, and basic principles of the treatment of transgender persons. They labeled these "Ungraded Good Practice Statement." Direct evidence for these statements was either unavailable or not systematically appraised and considered out of the scope of this guideline. The intention of these statements is to draw attention to these principles.

The Endocrine Society maintains a rigorous conflict-of-interest review process for developing clinical practice guidelines. All task force members must declare any potential conflicts of interest by completing a conflict-of-interest form. The CGS reviews all conflicts of interest before the Society's Council approves the members to participate on the task force and periodically during the development of the guideline. All others participating in the guideline's development must also disclose any conflicts of interest in the matter under study, and most of these participants must be without any conflicts of interest. The CGS and the task force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined as remuneration in any amount from commercial interests; grants; research support; consulting fees; salary; ownership interests [*e.g.*, stocks and stock options (excluding diversified mutual funds)]; honoraria and other payments for participation in speakers' bureaus, advisory boards, or boards of directors; and all other financial benefits. Completed forms are available through the Endocrine Society office.

The Endocrine Society provided the funding for this guideline; the task force received no funding or remuneration from commercial or other entities.

Commissioned Systematic Review

The task force commissioned two systematic reviews to support this guideline. The first one aimed to summarize the available evidence on the effect of sex steroid use in transgender individuals on lipids and cardiovascular outcomes. The review identified 29 eligible studies at moderate risk of bias. In transgender males (female to male), sex steroid therapy was associated with a statistically significant increase in serum triglycerides and low-density lipoprotein cholesterol levels. High-density lipoprotein cholesterol levels decreased significantly across all follow-up time periods. In transgender females (male to female), serum triglycerides were significantly higher without any changes in other parameters. Few myocardial infarction, stroke, venous thromboembolism (VTE), and death events were reported. These events were more frequent in transgender females. However, the quality of the evidence was low. The second review summarized the available evidence regarding the effect of sex steroids on bone health in transgender individuals and identified 13 studies. In transgender males, there was no statistically significant difference in the lumbar spine, femoral neck, or total hip BMD at 12 and 24 months compared with baseline values before initiating masculinizing hormone therapy. In transgender females, there was a statistically significant increase in lumbar spine BMD at 12 months and 24 months compared with baseline values before initiation of feminizing hormone therapy. There was minimal information on fracture rates. The quality of evidence was also low.

Introduction

Throughout recorded history (in the absence of an endocrine disorder) some men and women have experienced confusion and anguish resulting from rigid, forced conformity to sexual dimorphism. In modern history, there have been numerous ongoing biological, psychological, cultural, political, and sociological debates over various aspects of gender variance. The 20th century marked the emergence of a social awakening for men and women with the belief that they are "trapped" in the wrong body (3). Magnus Hirschfeld and Harry Benjamin, among others, pioneered the medical responses to those who sought relief from and a resolution to their profound discomfort. Although the term transsexual became widely known after Benjamin wrote "The Transsexual Phenomenon" (4), it was Hirschfeld who coined the term "transsexual" in 1923 to describe people who want to live a life that corresponds with their experienced gender vs their designated gender (5). Magnus Hirschfeld (6) and others (4, 7) have described other types of trans phenomena besides transsexualism. These early researchers proposed that the gender identity of these people was located somewhere along a unidimensional continuum. This continuum ranged from all male through "something in between" to all female. Yet such a classification does not take into account that people may have gender identities outside this continuum. For instance, some experience themselves as having both a male and female gender identity, whereas others completely renounce any gender classification (8, 9). There are also reports of individuals experiencing a continuous and rapid involuntary alternation between a male and female identity (10) or men who do not experience themselves as men but do not want to live as women (11, 12). In some countries, (*e.g.*, Nepal, Bangladesh, and Australia), these nonmale or nonfemale genders are officially recognized (13). Specific treatment protocols, however, have not yet been developed for these groups.

Instead of the term transsexualism, the current classification system of the American Psychiatric Association uses the term gender dysphoria in its diagnosis of persons who are not satisfied with their designated gender (14). The current version of the World Health Organization's ICD-10 still uses the term transsexualism when diagnosing adolescents and adults. However, for the ICD-11, the World Health Organization has proposed using the term "gender incongruence" (15).

Treating persons with GD/gender incongruence (15) was previously limited to relatively ineffective elixirs or creams. However, more effective endocrinology-based treatments became possible with the availability of testosterone in 1935 and diethylstilbestrol in 1938. Reports of individuals with GD/gender incongruence who were treated with hormones and gender-affirming surgery appeared in the press during the second half of the 20th century. The Harry Benjamin International Gender Dysphoria Association was founded in September 1979 and is now called the World Professional Association for Transgender Health (WPATH). WPATH published its first Standards of Care in 1979. These standards have since been regularly updated, providing guidance for treating persons with GD/gender incongruence (16).

Prior to 1975, few peer-reviewed articles were published concerning endocrine treatment of transgender persons. Since then, more than two thousand articles about various aspects of transgender care have appeared.

It is the purpose of this guideline to make detailed recommendations and suggestions, based on existing medical literature and clinical experience, that will enable treating physicians to maximize benefit and minimize risk when caring for individuals diagnosed with GD/gender incongruence.

In the future, we need more rigorous evaluations of the effectiveness and safety of endocrine and surgical protocols. Specifically, endocrine treatment protocols for GD/gender incongruence should include the careful assessment of the following: (1) the effects of prolonged delay of puberty in adolescents on bone health, gonadal function, and the brain (including effects on cognitive, emotional, social, and sexual development); (2) the effects of treatment in adults on sex hormone levels; (3) the requirement for and the effects of progestins and other agents used to suppress endogenous sex steroids during treatment; and (4) the risks and benefits of gender-affirming hormone treatment in older transgender people.

To successfully establish and enact these protocols, a commitment of mental health and endocrine investigators is required to collaborate in long-term, large-scale studies across countries that use the same diagnostic and inclusion criteria, medications, assay methods, and response assessment tools (*e.g.*, the European Network for the Investigation of Gender Incongruence) (17, 18).

Terminology and its use vary and continue to evolve. Table 1 contains the definitions of terms as they are used throughout this guideline.

Biological Determinants of Gender Identity Development

One's self-awareness as male or female changes gradually during infant life and childhood. This process of cognitive and affective learning evolves with interactions with parents, peers, and environment. A fairly accurate timetable exists outlining the steps in this process (19). Normative psychological literature, however, does not address if and when gender identity becomes crystallized and what factors contribute to the development of a gender identity that is not congruent with the gender of rearing. Results of studies from a variety of biomedical disciplines—genetic, endocrine, and neuroanatomic—support the concept that gender identity and/or gender expression (20) likely reflect a complex interplay of biological, environmental, and cultural factors (21, 22).

With respect to endocrine considerations, studies have failed to find differences in circulating levels of sex steroids between transgender and nontransgender individuals (23). However, studies in individuals with a disorder/difference of sex development (DSD) have informed our understanding of the role that hormones may play in gender identity outcome, even though most persons with GD/gender incongruence do not have a DSD. For example, although most 46,XX adult individuals with virilizing congenital adrenal hyperplasia caused by mutations in *CYP21A2* reported a female gender identity, the prevalence of GD/gender incongruence was much greater in this group than in the general population without a DSD. This supports the concept that there is a role for prenatal/postnatal androgens in gender development (24–26), although some studies indicate that prenatal androgens are more likely to affect gender behavior and sexual orientation rather than gender identity *per se* (27, 28).

Researchers have made similar observations regarding the potential role of androgens in the development of gender identity in other individuals with DSD. For example, a review of two groups of 46,XY persons, each with androgen synthesis deficiencies and female raised, reported transgender male (female-to-male) gender role changes in 56% to 63% and 39% to 64% of patients, respectively (29). Also, in 46,XY female-raised individuals with cloacal

doi: 10.1210/jc.2017-01658

Table 1. Definitions of Terms Used in This Guideline

Biological sex, biological male or female: These terms refer to physical aspects of maleness and femaleness. As these may not be in line with each other (*e.g.*, a person with XY chromosomes may have female-appearing genitalia), the terms biological sex and biological male or female are imprecise and should be avoided.

Cisgender: This means not transgender. An alternative way to describe individuals who are not transgender is "non-transgender people."

Gender-affirming (hormone) treatment: See "gender reassignment"

Gender dysphoria: This is the distress and unease experienced if gender identity and designated gender are not completely congruent (see Table 2). In 2013, the American Psychiatric Association released the fifth edition of the DSM-5, which replaced "gender identity disorder" with "gender dysphoria" and changed the criteria for diagnosis.

Gender expression: This refers to external manifestations of gender, expressed through one's name, pronouns, clothing, haircut, behavior, voice, or body characteristics. Typically, transgender people seek to make their gender expression align with their gender identity, rather than their designated gender.

Gender identity/experienced gender: This refers to one's internal, deeply held sense of gender. For transgender people, their gender identity does not match their sex designated at birth. Most people have a gender identity of man or woman (or boy or girl). For some people, their gender identity does not fit neatly into one of those two choices. Unlike gender expression (see below), gender identity is not visible to others.

Gender identity disorder: This is the term used for GD/gender incongruence in previous versions of DSM (see "gender dysphoria"). The ICD-10 still uses the term for diagnosing child diagnoses, but the upcoming ICD-11 has proposed using "gender incongruence of childhood."

Gender incongruence: This is an umbrella term used when the gender identity and/or gender expression differs from what is typically associated with the designated gender. Gender incongruence is also the proposed name of the gender identity–related diagnoses in ICD-11. Not all individuals with gender incongruence have gender dysphoria or seek treatment.

Gender variance: See "gender incongruence"

Gender reassignment: This refers to the treatment procedure for those who want to adapt their bodies to the experienced gender by means of hormones and/or surgery. This is also called gender-confirming or gender-affirming treatment.

Gender-reassignment surgery (gender-confirming/gender-affirming surgery): These terms refer only to the surgical part of gender-confirming/gender-affirming treatment.

Gender role: This refers to behaviors, attitudes, and personality traits that a society (in a given culture and historical period) designates as masculine or feminine and/or that society associates with or considers typical of the social role of men or women.

Sex designated at birth: This refers to sex assigned at birth, usually based on genital anatomy.

Sex: This refers to attributes that characterize biological maleness or femaleness. The best known attributes include the sex-determining genes, the sex chromosomes, the H-Y antigen, the gonads, sex hormones, internal and external genitalia, and secondary sex characteristics.

Sexual orientation: This term describes an individual's enduring physical and emotional attraction to another person. Gender identity and sexual orientation are not the same. Irrespective of their gender identity, transgender people may be attracted to women (gynephilic), attracted to men (androphilic), bisexual, asexual, or queer.

Transgender: This is an umbrella term for people whose gender identity and/or gender expression differs from what is typically associated with their sex designated at birth. Not all transgender individuals seek treatment.

Transgender male (also: trans man, female-to-male, transgender male): This refers to individuals assigned female at birth but who identify and live as men.

Transgender woman (also: trans woman, male-to female, transgender female): This refers to individuals assigned male at birth but who identify and live as women.

Transition: This refers to the process during which transgender persons change their physical, social, and/or legal characteristics consistent with the affirmed gender identity. Prepubertal children may choose to transition socially.

Transsexual: This is an older term that originated in the medical and psychological communities to refer to individuals who have permanently transitioned through medical interventions or desired to do so.

exstrophy and penile agenesis, the occurrence of transgender male changes was significantly more prevalent than in the general population (30, 31). However, the fact that a high percentage of individuals with the same conditions did not change gender suggests that cultural factors may play a role as well.

With respect to genetics and gender identity, several studies have suggested heritability of GD/gender incongruence (32, 33). In particular, a study by Heylens *et al.* (33) demonstrated a 39.1% concordance rate for gender identity disorder (based on the DSM-IV criteria) in 23 monozygotic twin pairs but no concordance in 21 same-sex dizygotic or seven opposite-sex twin pairs. Although numerous investigators have sought to identify specific genes associated with GD/gender incongruence, such studies have been inconsistent and without strong statistical significance (34–38).

Studies focusing on brain structure suggest that the brain phenotypes of people with GD/gender incongruence differ in various ways from control males and females, but that there is not a complete sex reversal in brain structures (39).

In summary, although there is much that is still unknown with respect to gender identity and its expression, compelling studies support the concept that biologic factors, in addition to environmental factors, contribute to this fundamental aspect of human development.

Natural History of Children With GD/Gender Incongruence

With current knowledge, we cannot predict the psychosexual outcome for any specific child. Prospective follow-up studies show that childhood GD/gender incongruence does not invariably persist into adolescence and adulthood (so-called "desisters"). Combining all outcome studies to date, the GD/gender incongruence of a minority of prepubertal children appears to persist in adolescence (20, 40). In adolescence, a significant number of these desisters identify as homosexual or bisexual. It may be that children who only showed some gender nonconforming characteristics have been included in the follow-up studies, because the DSM-IV text revision criteria for a diagnosis were rather broad. However, the persistence of GD/gender incongruence into adolescence is more likely if it had been extreme in childhood (41, 42). With the newer, stricter criteria of the DSM-5 (Table 2), persistence rates may well be different in future studies.

1.0 Evaluation of Youth and Adults

Gender-affirming treatment is a multidisciplinary effort. After evaluation, education, and diagnosis, treatment may include mental health care, hormone therapy, and/or surgical therapy. Together with an MHP, hormone-prescribing clinicians should examine the psychosocial impact of the potential changes on people's lives, including mental health, friends, family, jobs, and their role in society. Transgender individuals should be encouraged to experience living in the new gender role and assess whether this improves their quality of life. Although the focus of this guideline is gender-affirming hormone therapy, collaboration with appropriate professionals responsible for each aspect of treatment maximizes a successful outcome.

Diagnostic assessment and mental health care

GD/gender incongruence may be accompanied with psychological or psychiatric problems (43–51). It is therefore necessary that clinicians who prescribe hormones and are involved in diagnosis and psychosocial assessment meet the following criteria: (1) are competent in using the DSM and/or the ICD for diagnostic purposes, (2) are able to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) are trained in diagnosing psychiatric conditions, (4) undertake or refer for appropriate treatment, (5) are able to do a psychosocial assessment of the patient's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) regularly attend relevant professional meetings.

Because of the psychological vulnerability of many individuals with GD/gender incongruence, it is important that mental health care is available before, during, and sometimes also after transitioning. For children and adolescents, an MHP who has training/experience in child and adolescent gender development (as well as child and adolescent psychopathology) should make the diagnosis, because assessing GD/gender incongruence in children and adolescents is often extremely complex.

During assessment, the clinician obtains information from the individual seeking gender-affirming treatment. In the case

Table 2. DSM-5 Criteria for Gender Dysphoria in Adolescents and Adults

A. A marked incongruence between one's experienced/expressed gender and natal gender of at least 6 mo in duration, as manifested by at least two of the following:
   1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)
   2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)
   3. A strong desire for the primary and/or secondary sex characteristics of the other gender
   4. A strong desire to be of the other gender (or some alternative gender different from one's designated gender)
   5. A strong desire to be treated as the other gender (or some alternative gender different from one's designated gender)
   6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's designated gender)

B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:
   1. The condition exists with a disorder of sex development.
   2. The condition is posttransitional, in that the individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one sex-related medical procedure or treatment regimen—namely, regular sex hormone treatment or gender reassignment surgery confirming the desired gender (*e.g.*, penectomy, vaginoplasty in natal males; mastectomy or phalloplasty in natal females).

Reference: American Psychiatric Association (14).

doi: 10.1210/jc.2017-01658

of adolescents, the clinician also obtains information from the parents or guardians regarding various aspects of the child's general and psychosexual development and current functioning. On the basis of this information, the clinician:

- decides whether the individual fulfills criteria for treatment (see Tables 2 and 3) for GD/gender incongruence (DSM-5) or transsexualism (DSM-5 and/or ICD-10);
- informs the individual about the possibilities and limitations of various kinds of treatment (hormonal/surgical and nonhormonal), and if medical treatment is desired, provides correct information to prevent unrealistically high expectations;
- assesses whether medical interventions may result in unfavorable psychological and social outcomes.

In cases in which severe psychopathology, circumstances, or both seriously interfere with the diagnostic work or make satisfactory treatment unlikely, clinicians should assist the adolescent in managing these other issues. Literature on postoperative regret suggests that besides poor quality of surgery, severe psychiatric comorbidity and lack of support may interfere with positive outcomes (52–56).

For adolescents, the diagnostic procedure usually includes a complete psychodiagnostic assessment (57) and an assessment of the decision-making capability of the youth. An evaluation to assess the family's ability to endure stress, give support, and deal with the complexities of the adolescent's situation should be part of the diagnostic phase (58).

Social transitioning

A change in gender expression and role (which may involve living part time or full time in another gender role that is consistent with one's gender identity) may test the person's resolve, the capacity to function in the affirmed gender, and the adequacy of social, economic, and psychological supports. It assists both the individual and the clinician in their judgments about how to proceed (16). During social transitioning, the person's feelings about the social transformation (including coping with the responses of others) is a major focus of the counseling. The optimal timing for social transitioning may differ between individuals. Sometimes people wait until they start gender-affirming hormone treatment to make social transitioning easier, but individuals increasingly start social transitioning long before they receive medically supervised, gender-affirming hormone treatment.

Criteria

Adolescents and adults seeking gender-affirming hormone treatment and surgery should satisfy certain criteria before proceeding (16). Criteria for gender-affirming hormone therapy for adults are in Table 4, and criteria for gender-affirming hormone therapy for adolescents are in Table 5. Follow-up studies in adults meeting these criteria indicate a high satisfaction rate with treatment (59). However, the quality of evidence is usually low. A few follow-up studies on adolescents who fulfilled these criteria also indicated good treatment results (60–63).

Recommendations for Those Involved in the Gender-Affirming Hormone Treatment of Individuals With GD/Gender Incongruence

1.1. We advise that only trained MHPs who meet the following criteria should diagnose GD/gender incongruence in adults: (1) competence in using the DSM and/or the ICD for diagnostic purposes, (2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings. (Ungraded Good Practice Statement)

1.2. We advise that only MHPs who meet the following criteria should diagnose GD/gender incongruence in children and adolescents: (1) training in child and adolescent developmental psychology and psychopathology, (2) competence in using the DSM and/or ICD for diagnostic

Table 3. ICD-10 Criteria for Transsexualism

Transsexualism (F64.0) has three criteria:
1. The desire to live and be accepted as a member of the opposite sex, usually accompanied by the wish to make his or her body as congruent as possible with the preferred sex through surgery and hormone treatments.
2. The transsexual identity has been present persistently for at least 2 y.
3. The disorder is not a symptom of another mental disorder or a genetic, DSD, or chromosomal abnormality.

Table 4. Criteria for Gender-Affirming Hormone Therapy for Adults

1. Persistent, well-documented gender dysphoria/gender incongruence
2. The capacity to make a fully informed decision and to consent for treatment
3. The age of majority in a given country (if younger, follow the criteria for adolescents)
4. Mental health concerns, if present, must be reasonably well controlled

Reproduced from World Professional Association for Transgender Health (16).

purposes, (3) the ability to make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (4) training in diagnosing psychiatric conditions, (5) the ability to undertake or refer for appropriate treatment, (6) the ability to psychosocially assess the person's understanding and social conditions that can impact gender-affirming hormone therapy, (7) a practice of regularly attending relevant professional meetings, and (8) knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents. (Ungraded Good Practice Statement)

Evidence

Individuals with gender identity issues may have psychological or psychiatric problems (43–48, 50, 51, 64, 65). It is therefore necessary that clinicians making the diagnosis are able to make a distinction between GD/gender incongruence and conditions that have similar features. Examples of conditions with similar features are body dysmorphic disorder, body identity integrity disorder (a condition in which individuals have a sense that their anatomical configuration as an able-bodied person is somehow wrong or inappropriate) (66), or certain forms of eunuchism (in which a person is preoccupied with or engages in castration and/or penectomy for

Table 5. Criteria for Gender-Affirming Hormone Therapy for Adolescents

Adolescents are eligible for GnRH agonist treatment if:

1. A qualified MHP has confirmed that:
- the adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed),
- gender dysphoria worsened with the onset of puberty,
- any coexisting psychological, medical, or social problems that could interfere with treatment (*e.g.*, that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment,
- the adolescent has sufficient mental capacity to give informed consent to this (reversible) treatment,

2. And the adolescent:
- has been informed of the effects and side effects of treatment (including potential loss of fertility if the individual subsequently continues with sex hormone treatment) and options to preserve fertility,
- has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,

3. And a pediatric endocrinologist or other clinician experienced in pubertal assessment
- agrees with the indication for GnRH agonist treatment,
- has confirmed that puberty has started in the adolescent (Tanner stage ≥G2/B2),
- has confirmed that there are no medical contraindications to GnRH agonist treatment.

Adolescents are eligible for subsequent sex hormone treatment if:

1. A qualified MHP has confirmed:
- the persistence of gender dysphoria,
- any coexisting psychological, medical, or social problems that could interfere with treatment (*e.g.*, that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start sex hormone treatment,
- the adolescent has sufficient mental capacity (which most adolescents have by age 16 years) to estimate the consequences of this (partly) irreversible treatment, weigh the benefits and risks, and give informed consent to this (partly) irreversible treatment,

2. And the adolescent:
- has been informed of the (irreversible) effects and side effects of treatment (including potential loss of fertility and options to preserve fertility),
- has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,

3. And a pediatric endocrinologist or other clinician experienced in pubertal induction:
- agrees with the indication for sex hormone treatment,
- has confirmed that there are no medical contraindications to sex hormone treatment.

Reproduced from World Professional Association for Transgender Health (16).

doi: 10.1210/jc.2017-01658

reasons that are not gender identity related) (11). Clinicians should also be able to diagnose psychiatric conditions accurately and ensure that these conditions are treated appropriately, particularly when the conditions may complicate treatment, affect the outcome of gender-affirming treatment, or be affected by hormone use.

Values and preferences

The task force placed a very high value on avoiding harm from hormone treatment in individuals who have conditions other than GD/gender incongruence and who may not benefit from the physical changes associated with this treatment and placed a low value on any potential benefit these persons believe they may derive from hormone treatment. This justifies the good practice statement.

1.3. We advise that decisions regarding the social transition of prepubertal youths with GD/gender incongruence are made with the assistance of an MHP or another experienced professional. (Ungraded Good Practice Statement).

1.4. We recommend against puberty blocking and gender-affirming hormone treatment in prepubertal children with GD/gender incongruence. (1 |⊕⊕◯◯)

Evidence

In most children diagnosed with GD/gender incongruence, it did not persist into adolescence. The percentages differed among studies, probably dependent on which version of the DSM clinicians used, the patient's age, the recruitment criteria, and perhaps cultural factors. However, the large majority (about 85%) of prepubertal children with a childhood diagnosis did not remain GD/gender incongruent in adolescence (20). If children have completely socially transitioned, they may have great difficulty in returning to the original gender role upon entering puberty (40). Social transition is associated with the persistence of GD/gender incongruence as a child progresses into adolescence. It may be that the presence of GD/gender incongruence in prepubertal children is the earliest sign that a child is destined to be transgender as an adolescent/adult (20). However, social transition (in addition to GD/gender incongruence) has been found to contribute to the likelihood of persistence.

This recommendation, however, does not imply that children should be discouraged from showing gender-variant behaviors or should be punished for exhibiting such behaviors. In individual cases, an early complete social transition may result in a more favorable outcome, but there are currently no criteria to identify the GD/gender-incongruent children to whom this applies. At the present time, clinical experience suggests that persistence of GD/gender incongruence can only be reliably assessed after the first signs of puberty.

Values and preferences

The task force placed a high value on avoiding harm with gender-affirming hormone therapy in prepubertal children with GD/gender incongruence. This justifies the strong recommendation in the face of low-quality evidence.

1.5. We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults. (1 |⊕⊕⊕◯)

Remarks

Persons considering hormone use for gender affirmation need adequate information about this treatment in general and about fertility effects of hormone treatment in particular to make an informed and balanced decision (67, 68). Because young adolescents may not feel qualified to make decisions about fertility and may not fully understand the potential effects of hormonal interventions, consent and protocol education should include parents, the referring MHP(s), and other members of the adolescent's support group. To our knowledge, there are no formally evaluated decision aids available to assist in the discussion and decision regarding the future fertility of adolescents or adults beginning gender-affirming treatment.

Treating early pubertal youth with GnRH analogs will temporarily impair spermatogenesis and oocyte maturation. Given that an increasing number of transgender youth want to preserve fertility potential, delaying or temporarily discontinuing GnRH analogs to promote gamete maturation is an option. This option is often not preferred, because mature sperm production is associated with later stages of puberty and with the significant development of secondary sex characteristics.

For those designated male at birth with GD/gender incongruence and who are in early puberty, sperm production and the development of the reproductive tract are insufficient for the cryopreservation of sperm. However, prolonged pubertal suppression using GnRH analogs is reversible and clinicians should inform these individuals that sperm production can be initiated following prolonged gonadotropin suppression. This can be accomplished by spontaneous gonadotropin recovery after

cessation of GnRH analogs or by gonadotropin treatment and will probably be associated with physical manifestations of testosterone production, as stated above. Note that there are no data in this population concerning the time required for sufficient spermatogenesis to collect enough sperm for later fertility. In males treated for precocious puberty, spermarche was reported 0.7 to 3 years after cessation of GnRH analogs (69). In adult men with gonadotropin deficiency, sperm are noted in seminal fluid by 6 to 12 months of gonadotropin treatment. However, sperm numbers when partners of these patients conceive are far below the "normal range" (70, 71).

In girls, no studies have reported long-term, adverse effects of pubertal suppression on ovarian function after treatment cessation (72, 73). Clinicians should inform adolescents that no data are available regarding either time to spontaneous ovulation after cessation of GnRH analogs or the response to ovulation induction following prolonged gonadotropin suppression.

In males with GD/gender incongruence, when medical treatment is started in a later phase of puberty or in adulthood, spermatogenesis is sufficient for cryopreservation and storage of sperm. *In vitro* spermatogenesis is currently under investigation. Restoration of spermatogenesis after prolonged estrogen treatment has not been studied.

In females with GD/gender incongruence, the effect of prolonged treatment with exogenous testosterone on ovarian function is uncertain. There have been reports of an increased incidence of polycystic ovaries in transgender males, both prior to and as a result of androgen treatment (74–77), although these reports were not confirmed by others (78). Pregnancy has been reported in transgender males who have had prolonged androgen treatment and have discontinued testosterone but have not had genital surgery (79, 80). A reproductive endocrine gynecologist can counsel patients before gender-affirming hormone treatment or surgery regarding potential fertility options (81). Techniques for cryopreservation of oocytes, embryos, and ovarian tissue continue to improve, and oocyte maturation of immature tissue is being studied (82).

2.0 Treatment of Adolescents

During the past decade, clinicians have progressively acknowledged the suffering of young adolescents with GD/gender incongruence. In some forms of GD/gender incongruence, psychological interventions may be useful and sufficient. However, for many adolescents with GD/gender incongruence, the pubertal physical changes are unbearable. As early medical intervention may prevent psychological harm, various clinics have decided to start treating young adolescents with GD/gender incongruence with puberty-suppressing medication (a GnRH analog). As compared with starting gender-affirming treatment long after the first phases of puberty, a benefit of pubertal suppression at early puberty may be a better psychological and physical outcome.

In girls, the first physical sign of puberty is the budding of the breasts followed by an increase in breast and fat tissue. Breast development is also associated with the pubertal growth spurt, and menarche occurs ~2 years later. In boys, the first physical change is testicular growth. A testicular volume ≥4 mL is seen as consistent with the initiation of physical puberty. At the beginning of puberty, estradiol and testosterone levels are still low and are best measured in the early morning with an ultrasensitive assay. From a testicular volume of 10 mL, daytime testosterone levels increase, leading to virilization (83). Note that pubic hair and/or axillary hair/odor may not reflect the onset of gonadarche; instead, it may reflect adrenarche alone.

2.1. We suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment (Table 5), and are requesting treatment should initially undergo treatment to suppress pubertal development. (2 ⊕⊕◯◯)

2.2. We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty (Tanner stages G2/B2). (2 ⊕⊕◯◯)

Evidence

Pubertal suppression can expand the diagnostic phase by a long period, giving the subject more time to explore options and to live in the experienced gender before making a decision to proceed with gender-affirming sex hormone treatments and/or surgery, some of which is irreversible (84, 85). Pubertal suppression is fully reversible, enabling full pubertal development in the natal gender, after cessation of treatment, if appropriate. The experience of full endogenous puberty is an undesirable condition for the GD/gender-incongruent individual and may seriously interfere with healthy psychological functioning and well-being. Treating GD/gender-incongruent adolescents entering puberty with GnRH analogs has been shown to improve psychological functioning in several domains (86).

Another reason to start blocking pubertal hormones early in puberty is that the physical outcome is improved compared with initiating physical transition after puberty has been completed (60, 62). Looking like a man or woman when living as the opposite sex creates difficult

doi: 10.1210/jc.2017-01658

barriers with enormous life-long disadvantages. We therefore advise starting suppression in early puberty to prevent the irreversible development of undesirable secondary sex characteristics. However, adolescents with GD/gender incongruence should experience the first changes of their endogenous spontaneous puberty, because their emotional reaction to these first physical changes has diagnostic value in establishing the persistence of GD/gender incongruence (85). Thus, Tanner stage 2 is the optimal time to start pubertal suppression. However, pubertal suppression treatment in early puberty will limit the growth of the penis and scrotum, which will have a potential effect on future surgical treatments (87).

Clinicians can also use pubertal suppression in adolescents in later pubertal stages to stop menses in transgender males and prevent facial hair growth in transgender females. However, in contrast to the effects in early pubertal adolescents, physical sex characteristics (such as more advanced breast development in transgender boys and lowering of the voice and outgrowth of the jaw and brow in transgender girls) are not reversible.

Values and preferences

These recommendations place a high value on avoiding an unsatisfactory physical outcome when secondary sex characteristics have become manifest and irreversible, a higher value on psychological well-being, and a lower value on avoiding potential harm from early pubertal suppression.

Remarks

Table 6 lists the Tanner stages of breast and male genital development. Careful documentation of hallmarks of pubertal development will ensure precise timing when initiating pubertal suppression once puberty has started. Clinicians can use pubertal LH and sex steroid levels to confirm that puberty has progressed sufficiently before starting pubertal suppression (88). Reference ranges for sex steroids by Tanner stage may vary depending on the assay used. Ultrasensitive sex steroid and gonadotropin assays will help clinicians document early pubertal changes.

Irreversible and, for GD/gender-incongruent adolescents, undesirable sex characteristics in female puberty are breasts, female body habitus, and, in some cases, relative short stature. In male puberty, they are a prominent Adam's apple; low voice; male bone configuration, such as a large jaw, big feet and hands, and tall stature; and male hair pattern on the face and extremities.

2.3. We recommend that, where indicated, GnRH analogues are used to suppress pubertal hormones. (1 |⊕⊕◯◯)

Evidence

Clinicians can suppress pubertal development and gonadal function most effectively via gonadotropin suppression using GnRH analogs. GnRH analogs are long-acting agonists that suppress gonadotropins by GnRH receptor desensitization after an initial increase of gonadotropins during ~10 days after the first and (to a lesser degree) the second injection (89). Antagonists immediately suppress pituitary gonadotropin secretion (90, 91). Long-acting GnRH analogs are the currently preferred treatment option. Clinicians may consider long-acting GnRH antagonists when evidence on their safety and efficacy in adolescents becomes available.

During GnRH analog treatment, slight development of secondary sex characteristics may regress, and in a later phase of pubertal development, it will stop. In girls, breast tissue will become atrophic, and menses will stop. In boys, virilization will stop, and testicular volume may decrease (92).

An advantage of using GnRH analogs is the reversibility of the intervention. If, after extensive exploration of his/her transition wish, the individual no longer desires transition, they can discontinue pubertal suppression. In subjects with

Table 6. Tanner Stages of Breast Development and Male External Genitalia

The description of Tanner stages for breast development:
1. Prepubertal
2. Breast and papilla elevated as small mound; areolar diameter increased
3. Breast and areola enlarged, no contour separation
4. Areola and papilla form secondary mound
5. Mature; nipple projects, areola part of general breast contour

For penis and testes:
1. Prepubertal, testicular volume <4 mL
2. Slight enlargement of penis; enlarged scrotum, pink, texture altered, testes 4–6 mL
3. Penis longer, testes larger (8–12 mL)
4. Penis and glans larger, including increase in breadth; testes larger (12–15 mL), scrotum dark
5. Penis adult size; testicular volume > 15 ml

Adapted from Lawrence (56).

precocious puberty, spontaneous pubertal development has been shown to resume after patients discontinue taking GnRH analogs (93).

Recommendations 2.1 to 2.3 are supported by a prospective follow-up study from The Netherlands. This report assessed mental health outcomes in 55 transgender adolescents/young adults (22 transgender females and 33 transgender males) at three time points: (1) before the start of GnRH agonist (average age of 14.8 years at start of treatment), (2) at initiation of gender-affirming hormones (average age of 16.7 years at start of treatment), and (3) 1 year after "gender-reassignment surgery" (average age of 20.7 years) (63). Despite a decrease in depression and an improvement in general mental health functioning, GD/gender incongruence persisted through pubertal suppression, as previously reported (86). However, following sex hormone treatment and gender-reassignment surgery, GD/gender incongruence was resolved and psychological functioning steadily improved (63). Furthermore, well-being was similar to or better than that reported by age-matched young adults from the general population, and none of the study participants regretted treatment. This study represents the first long-term follow-up of individuals managed according to currently existing clinical practice guidelines for transgender youth, and it underscores the benefit of the multidisciplinary approach pioneered in The Netherlands; however, further studies are needed.

Side effects

The primary risks of pubertal suppression in GD/gender-incongruent adolescents may include adverse effects on bone mineralization (which can theoretically be reversed with sex hormone treatment), compromised fertility if the person subsequently is treated with sex hormones, and unknown effects on brain development. Few data are available on the effect of GnRH analogs on BMD in adolescents with GD/gender incongruence. Initial data in GD/gender-incongruent subjects demonstrated no change of absolute areal BMD during 2 years of GnRH analog therapy but a decrease in BMD *z* scores (85). A recent study also suggested suboptimal bone mineral accrual during GnRH analog treatment. The study reported a decrease in areal BMD *z* scores and of bone mineral apparent density *z* scores (which takes the size of the bone into account) in 19 transgender males treated with GnRH analogs from a mean age of 15.0 years (standard deviation = 2.0 years) for a median duration of 1.5 years (0.3 to 5.2 years) and in 15 transgender females treated from 14.9 (±1.9) years for 1.3 years (0.5 to 3.8 years), although not all changes were statistically significant (94). There was incomplete catch-up at age 22 years after sex hormone treatment from age 16.6 (±1.4) years for a median duration of 5.8 years (3.0 to 8.0 years) in transgender females and from age 16.4 (±2.3) years for 5.4 years (2.8 to 7.8 years) in transgender males. Little is known about more prolonged use of GnRH analogs. Researchers reported normal BMD *z* scores at age 35 years in one individual who used GnRH analogs from age 13.7 years until age 18.6 years before initiating sex hormone treatment (65).

Additional data are available from individuals with late puberty or GnRH analog treatment of other indications. Some studies reported that men with constitutionally delayed puberty have decreased BMD in adulthood (95). However, other studies reported that these men have normal BMD (96, 97). Treating adults with GnRH analogs results in a decrease of BMD (98). In children with central precocious puberty, treatment with GnRH analogs has been found to result in a decrease of BMD during treatment by some (99) but not others (100). Studies have reported normal BMD after discontinuing therapy (69, 72, 73, 101, 102). In adolescents treated with growth hormone who are small for gestational age and have normal pubertal timing, 2-year GnRH analog treatments did not adversely affect BMD (103). Calcium supplementation may be beneficial in optimizing bone health in GnRH analog–treated individuals (104). There are no studies of vitamin D supplementation in this context, but clinicians should offer supplements to vitamin D–deficient adolescents. Physical activity, especially during growth, is important for bone mass in healthy individuals (103) and is therefore likely to be beneficial for bone health in GnRH analog–treated subjects.

GnRH analogs did not induce a change in body mass index standard deviation score in GD/gender-incongruent adolescents (94) but caused an increase in fat mass and decrease in lean body mass percentage (92). Studies in girls treated for precocious puberty also reported a stable body mass index standard deviation score during treatment (72) and body mass index and body composition comparable to controls after treatment (73).

Arterial hypertension has been reported as an adverse effect in a few girls treated with GnRH analogs for precocious/early puberty (105, 106). Blood pressure monitoring before and during treatment is recommended.

Individuals may also experience hot flashes, fatigue, and mood alterations as a consequence of pubertal suppression. There is no consensus on treatment of these side effects in this context.

It is recommended that any use of pubertal blockers (and subsequent use of sex hormones, as detailed below) include a discussion about implications for fertility (see recommendation 1.3). Transgender adolescents may

doi: 10.1210/jc.2017-01658

want to preserve fertility, which may be otherwise compromised if puberty is suppressed at an early stage and the individual completes phenotypic transition with the use of sex hormones.

Limited data are available regarding the effects of GnRH analogs on brain development. A single cross-sectional study demonstrated no compromise of executive function (107), but animal data suggest there may be an effect of GnRH analogs on cognitive function (108).

Values and preferences

Our recommendation of GnRH analogs places a higher value on the superior efficacy, safety, and reversibility of the pubertal hormone suppression achieved (as compared with the alternatives) and a relatively lower value on limiting the cost of therapy. Of the available alternatives, depot and oral progestin preparations are effective. Experience with this treatment dates back prior to the emergence of GnRH analogs for treating precocious puberty in papers from the 1960s and early 1970s (109–112). These compounds are usually safe, but some side effects have been reported (113–115). Only two recent studies involved transgender youth (116, 117). One of these studies described the use of oral lynestrenol monotherapy followed by the addition of testosterone treatment in transgender boys who were at Tanner stage B4 or further at the start of treatment (117). They found lynestrenol safe, but gonadotropins were not fully suppressed. The study reported metrorrhagia in approximately half of the individuals, mainly in the first 6 months. Acne, headache, hot flashes, and fatigue were other frequent side effects. Another progestin that has been studied in the United States is medroxyprogesterone. This agent is not as effective as GnRH analogs in lowering endogenous sex hormones either and may be associated with other side effects (116). Progestin preparations may be an acceptable treatment for persons without access to GnRH analogs or with a needle phobia. If GnRH analog treatment is not available (insurance denial, prohibitive cost, or other reasons), postpubertal, transgender female adolescents may be treated with an antiandrogen that directly suppresses androgen synthesis or action (see adult section).

Remarks

Measurements of gonadotropin and sex steroid levels give precise information about gonadal axis suppression, although there is insufficient evidence for any specific short-term monitoring scheme in children treated with GnRH analogs (88). If the gonadal axis is not completely suppressed—as evidenced by (for example) menses, erections, or progressive hair growth—the interval of GnRH analog treatment can be shortened or the dose increased. During treatment, adolescents should be monitored for negative effects of delaying puberty, including a halted growth spurt and impaired bone mineral accretion. Table 7 illustrates a suggested clinical protocol.

Anthropometric measurements and X-rays of the left hand to monitor bone age are informative for evaluating growth. To assess BMD, clinicians can perform dual-energy X-ray absorptiometry scans.

2.4. In adolescents who request sex hormone treatment (given this is a partly irreversible treatment), we recommend initiating treatment using a gradually increasing dose schedule (see Table 8) after a multidisciplinary team of medical and MHPs has confirmed the persistence of GD/gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years (Table 5). (1 |⊕⊕◯◯)

2.5. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to the age of 16 years in some adolescents with GD/gender incongruence, even though there are minimal published studies of gender-affirming hormone treatments administered before age 13.5 to 14 years. As with the care of adolescents ≥16 years of age, we recommend that an expert multidisciplinary team of medical and MHPs manage this treatment. (1 |⊕◯◯◯)

2.6. We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment (Table 9). (2 |⊕⊕◯◯)

Table 7. Baseline and Follow-Up Protocol During Suppression of Puberty

Every 3–6 mo
Anthropometry: height, weight, sitting height, blood pressure, Tanner stages
Every 6–12 mo
Laboratory: LH, FSH, E2/T, 25OH vitamin D
Every 1–2 y
Bone density using DXA
Bone age on X-ray of the left hand (if clinically indicated)

Adapted from Hembree *et al.* (118).

Abbreviations: DXA, dual-energy X-ray absorptiometry; E2, estradiol; FSH, follicle stimulating hormone; LH, luteinizing hormone; T, testosterone;

Table 8. Protocol Induction of Puberty

Induction of female puberty with oral 17β-estradiol, increasing the dose every 6 mo:
- 5 μg/kg/d
- 10 μg/kg/d
- 15 μg/kg/d
- 20 μg/kg/d
- Adult dose = 2–6 mg/d
- *In postpubertal transgender female adolescents, the dose of 17β-estradiol can be increased more rapidly:*
  - 1 mg/d for 6 mo
  - 2 mg/d

Induction of female puberty with transdermal 17β-estradiol, increasing the dose every 6 mo (new patch is placed every 3.5 d):
- 6.25–12.5 μg/24 h (cut 25-μg patch into quarters, then halves)
- 25 μg/24 h
- 37.5 μg/24 h
- Adult dose = 50–200 μg/24 h
- *For alternatives once at adult dose, see Table 11.*
- *Adjust maintenance dose to mimic physiological estradiol levels (see Table 15).*

Induction of male puberty with testosterone esters increasing the dose every 6 mo (IM or SC):
- 25 mg/m^2/2 wk (or alternatively, half this dose weekly, or double the dose every 4 wk)
- 50 mg/m^2/2 wk
- 75 mg/m^2/2 wk
- 100 mg/m^2/2 wk
- Adult dose = 100–200 mg every 2 wk
- *In postpubertal transgender male adolescents the dose of testosterone esters can be increased more rapidly:*
  - 75 mg/2 wk for 6 mo
  - 125 mg/2 wk
- *For alternatives once at adult dose, see Table 11.*
- *Adjust maintenance dose to mimic physiological testosterone levels (see Table 14).*

Adapted from Hembree *et al.* (118).

Abbreviations: IM, intramuscularly; SC, subcutaneously.

Evidence

Adolescents develop competence in decision making at their own pace. Ideally, the supervising medical professionals should individually assess this competence, although no objective tools to make such an assessment are currently available.

Many adolescents have achieved a reasonable level of competence by age 15 to 16 years (119), and in many countries 16-year-olds are legally competent with regard to medical decision making (120). However, others believe that although some capacities are generally achieved before age 16 years, other abilities (such as good risk assessment) do not develop until well after 18 years (121). They suggest that health care procedures should be divided along a matrix of relative risk, so that younger adolescents can be allowed to decide about low-risk procedures, such as most diagnostic tests and common therapies, but not about high-risk procedures, such as most surgical procedures (121).

Currently available data from transgender adolescents support treatment with sex hormones starting at age 16 years (63, 122). However, some patients may incur potential risks by waiting until age 16 years. These include the potential risk to bone health if puberty is suppressed

Table 9. Baseline and Follow-up Protocol During Induction of Puberty

Every 3–6 mo
- •Anthropometry: height, weight, sitting height, blood pressure, Tanner stages

Every 6–12 mo
- •In transgender males: hemoglobin/hematocrit, lipids, testosterone, 25OH vitamin D
- •In transgender females: prolactin, estradiol, 25OH vitamin D

Every 1–2 y
- •BMD using DXA
- •Bone age on X-ray of the left hand (if clinically indicated)

BMD should be monitored into adulthood (until the age of 25–30 y or until peak bone mass has been reached).
For recommendations on monitoring once pubertal induction has been completed, see Tables 14 and 15.

Adapted from Hembree *et al.* (118).

Abbreviation: DXA, dual-energy X-ray absorptiometry.

doi: 10.1210/jc.2017-01658

for 6 to 7 years before initiating sex hormones (*e.g.*, if someone reached Tanner stage 2 at age 9-10 years old). Additionally, there may be concerns about inappropriate height and potential harm to mental health (emotional and social isolation) if initiation of secondary sex characteristics must wait until the person has reached 16 years of age. However, only minimal data supporting earlier use of gender-affirming hormones in transgender adolescents currently exist (63). Clearly, long-term studies are needed to determine the optimal age of sex hormone treatment in GD/gender-incongruent adolescents.

The MHP who has followed the adolescent during GnRH analog treatment plays an essential role in assessing whether the adolescent is eligible to start sex hormone therapy and capable of consenting to this treatment (Table 5). Support of the family/environment is essential. Prior to the start of sex hormones, clinicians should discuss the implications for fertility (see recommendation 1.5). Throughout pubertal induction, an MHP and a pediatric endocrinologist (or other clinician competent in the evaluation and induction of pubertal development) should monitor the adolescent. In addition to monitoring therapy, it is also important to pay attention to general adolescent health issues, including healthy life style choices, such as not smoking, contraception, and appropriate vaccinations (*e.g.*, human papillomavirus).

For the induction of puberty, clinicians can use a similar dose scheme for hypogonadal adolescents with GD/gender incongruence as they use in other individuals with hypogonadism, carefully monitoring for desired and undesired effects (Table 8). In transgender female adolescents, transdermal 17β-estradiol may be an alternative for oral 17β-estradiol. It is increasingly used for pubertal induction in hypogonadal females. However, the absence of low-dose estrogen patches may be a problem. As a result, individuals may need to cut patches to size themselves to achieve appropriate dosing (123). In transgender male adolescents, clinicians can give testosterone injections intramuscularly or subcutaneously (124, 125).

When puberty is initiated with a gradually increasing schedule of sex steroid doses, the initial levels will not be high enough to suppress endogenous sex steroid secretion. Gonadotropin secretion and endogenous production of testosterone may resume and interfere with the effectiveness of estrogen treatment, in transgender female adolescents (126, 127). Therefore, continuation of GnRH analog treatment is advised until gonadectomy. Given that GD/gender-incongruent adolescents may opt not to have gonadectomy, long-term studies are necessary to examine the potential risks of prolonged GnRH analog treatment. Alternatively, in transgender male adolescents, GnRH analog treatment can be discontinued once an adult dose of testosterone has been reached and the individual is well virilized. If uterine bleeding occurs, a progestin can be added. However, the combined use of a GnRH analog (for ovarian suppression) and testosterone may enable phenotypic transition with a lower dose of testosterone in comparison with testosterone alone. If there is a wish or need to discontinue GnRH analog treatment in transgender female adolescents, they may be treated with an antiandrogen that directly suppresses androgen synthesis or action (see section 3.0 "Hormonal Therapy for Transgender Adults").

Values and preferences

The recommendation to initiate pubertal induction only when the individual has sufficient mental capacity (roughly age 16 years) to give informed consent for this partly irreversible treatment places a higher value on the ability of the adolescent to fully understand and oversee the partially irreversible consequences of sex hormone treatment and to give informed consent. It places a lower value on the possible negative effects of delayed puberty. We may not currently have the means to weigh adequately the potential benefits of waiting until around age 16 years to initiate sex hormones vs the potential risks/harm to BMD and the sense of social isolation from having the timing of puberty be so out of sync with peers (128).

Remarks

Before starting sex hormone treatment, effects on fertility and options for fertility preservation should be discussed. Adult height may be a concern in transgender adolescents. In a transgender female adolescent, clinicians may consider higher doses of estrogen or a more rapid tempo of dose escalation during pubertal induction. There are no established treatments yet to augment adult height in a transgender male adolescent with open epiphyses during pubertal induction. It is not uncommon for transgender adolescents to present for clinical services after having completed or nearly completed puberty. In such cases, induction of puberty with sex hormones can be done more rapidly (see Table 8). Additionally, an adult dose of testosterone in transgender male adolescents may suffice to suppress the gonadal axis without the need to use a separate agent. At the appropriate time, the multidisciplinary team should adequately prepare the adolescent for transition to adult care.

3.0 Hormonal Therapy for Transgender Adults

The two major goals of hormonal therapy are (1) to reduce endogenous sex hormone levels, and thus reduce

the secondary sex characteristics of the individual's designated gender, and (2) to replace endogenous sex hormone levels consistent with the individual's gender identity by using the principles of hormone replacement treatment of hypogonadal patients. The timing of these two goals and the age at which to begin treatment with the sex hormones of the chosen gender is codetermined in collaboration with both the person pursuing transition and the health care providers. The treatment team should include a medical provider knowledgeable in transgender hormone therapy, an MHP knowledgeable in GD/gender incongruence and the mental health concerns of transition, and a primary care provider able to provide care appropriate for transgender individuals. The physical changes induced by this sex hormone transition are usually accompanied by an improvement in mental well-being (129, 130).

3.1. We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and the criteria for the endocrine phase of gender transition before beginning treatment. (1 |⊕⊕⊕◯)

3.2. We recommend that clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment (Table 10). (1 |⊕⊕⊕◯)

3.3. We suggest that clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender. (2 |⊕⊕◯◯)

Evidence

It is the responsibility of the treating clinician to confirm that the person fulfills criteria for treatment. The treating clinician should become familiar with the terms and criteria presented in Tables 1–5 and take a thorough history from the patient in collaboration with the other members of the treatment team. The treating clinician must ensure that the desire for transition is appropriate; the consequences, risks, and benefits of treatment are well understood; and the desire for transition persists. They also need to discuss fertility preservation options (see recommendation 1.3) (67, 68).

Transgender males

Clinical studies have demonstrated the efficacy of several different androgen preparations to induce masculinization in transgender males (Appendix A) (113, 114, 131–134). Regimens to change secondary sex characteristics follow the general principle of hormone replacement treatment of male hypogonadism (135). Clinicians can use either parenteral or transdermal preparations to achieve testosterone values in the normal male range (this is dependent on the specific assay, but is typically 320 to 1000 ng/dL) (Table 11) (136). Sustained supraphysiologic levels of testosterone increase the risk of adverse reactions (see section 4.0 "Adverse Outcome Prevention and Long-Term Care") and should be avoided.

Similar to androgen therapy in hypogonadal men, testosterone treatment in transgender males results in increased muscle mass and decreased fat mass, increased facial hair and acne, male pattern baldness in those genetically predisposed, and increased sexual desire (137).

Table 10. Medical Risks Associated With Sex Hormone Therapy

Transgender female: estrogen
Very high risk of adverse outcomes:
•Thromboembolic disease
Moderate risk of adverse outcomes:
•Macroprolactinoma
•Breast cancer
•Coronary artery disease
•Cerebrovascular disease
•Cholelithiasis
•Hypertriglyceridemia
Transgender male: testosterone
Very high risk of adverse outcomes:
•Erythrocytosis (hematocrit > 50%)
Moderate risk of adverse outcomes:
•Severe liver dysfunction (transaminases > threefold upper limit of normal)
•Coronary artery disease
•Cerebrovascular disease
•Hypertension
•Breast or uterine cancer

doi: 10.1210/jc.2017-01658

Table 11. Hormone Regimens in Transgender Persons

Transgender females[a]	
Estrogen	
Oral	
Estradiol	2.0–6.0 mg/d
Transdermal	
Estradiol transdermal patch (New patch placed every 3–5 d)	0.025–0.2 mg/d
Parenteral	
Estradiol valerate or cypionate	5–30 mg IM every 2 wk 2–10 mg IM every week
Anti-androgens	
Spironolactone	100–300 mg/d
Cyproterone acetate[b]	25–50 mg/d
GnRH agonist	3.75 mg SQ (SC) monthly 11.25 mg SQ (SC) 3-monthly
Transgender males	
Testosterone	
Parenteral testosterone	
Testosterone enanthate or cypionate	100–200 mg SQ (IM) every 2 wk or SQ (SC) 50% per week
Testosterone undecanoate[c]	1000 mg every 12 wk
Transdermal testosterone	
Testosterone gel 1.6%[d]	50–100 mg/d
Testosterone transdermal patch	2.5–7.5 mg/d

Abbreviations: IM, intramuscularly; SQ, sequentially; SC, subcutaneously.

[a]Estrogens used with or without antiandrogens or GnRH agonist.

[b]Not available in the United States.

[c]One thousand milligrams initially followed by an injection at 6 wk then at 12-wk intervals.

[d]Avoid cutaneous transfer to other individuals.

In transgender males, testosterone will result in clitoromegaly, temporary or permanent decreased fertility, deepening of the voice, cessation of menses (usually), and a significant increase in body hair, particularly on the face, chest, and abdomen. Cessation of menses may occur within a few months with testosterone treatment alone, although high doses of testosterone may be required. If uterine bleeding continues, clinicians may consider the addition of a progestational agent or endometrial ablation (138). Clinicians may also administer GnRH analogs or depot medroxyprogesterone to stop menses prior to testosterone treatment.

Transgender females

The hormone regimen for transgender females is more complex than the transgender male regimen (Appendix B). Treatment with physiologic doses of estrogen alone is insufficient to suppress testosterone levels into the normal range for females (139). Most published clinical studies report the need for adjunctive therapy to achieve testosterone levels in the female range (21, 113, 114, 132–134, 139, 140).

Multiple adjunctive medications are available, such as progestins with antiandrogen activity and GnRH agonists (141). Spironolactone works by directly blocking androgens during their interaction with the androgen receptor (114, 133, 142). It may also have estrogenic activity (143). Cyproterone acetate, a progestational compound with antiandrogenic properties (113, 132, 144), is widely used in Europe. 5α-Reductase inhibitors do not reduce testosterone levels and have adverse effects (145).

Dittrich *et al.* (141) reported that monthly doses of the GnRH agonist goserelin acetate in combination with estrogen were effective in reducing testosterone levels with a low incidence of adverse reactions in 60 transgender females. Leuprolide and transdermal estrogen were as effective as cyproterone and transdermal estrogen in a comparative retrospective study (146).

Patients can take estrogen as oral conjugated estrogens, oral 17β-estradiol, or transdermal 17β-estradiol. Among estrogen options, the increased risk of thromboembolic events associated with estrogens in general seems most concerning with ethinyl estradiol specifically (134, 140, 141), which is why we specifically suggest that it not be used in any transgender treatment plan. Data distinguishing among other estrogen options are less well established although there is some thought that oral routes of administration are more thrombogenic due to the "first pass effect" than are transdermal and parenteral routes, and that the risk of thromboembolic events is dose-dependent. Injectable estrogen and sublingual

estrogen may benefit from avoiding the first pass effect, but they can result in more rapid peaks with greater overall periodicity and thus are more difficult to monitor (147, 148). However, there are no data demonstrating that increased periodicity is harmful otherwise.

Clinicians can use serum estradiol levels to monitor oral, transdermal, and intramuscular estradiol. Blood tests cannot monitor conjugated estrogens or synthetic estrogen use. Clinicians should measure serum estradiol and serum testosterone and maintain them at the level for premenopausal females (100 to 200 pg/mL and <50 ng/dL, respectively). The transdermal preparations and injectable estradiol cypionate or valerate preparations may confer an advantage in older transgender females who may be at higher risk for thromboembolic disease (149).

Values

Our recommendation to maintain levels of gender-affirming hormones in the normal adult range places a high value on the avoidance of the long-term complications of pharmacologic doses. Those patients receiving endocrine treatment who have relative contraindications to hormones should have an in-depth discussion with their physician to balance the risks and benefits of therapy.

Remarks

Clinicians should inform all endocrine-treated individuals of all risks and benefits of gender-affirming hormones prior to initiating therapy. Clinicians should strongly encourage tobacco use cessation in transgender females to avoid increased risk of VTE and cardiovascular complications. We strongly discourage the unsupervised use of hormone therapy (150).

Not all individuals with GD/gender incongruence seek treatment as described (*e.g.*, male-to-eunuchs and individuals seeking partial transition). Tailoring current protocols to the individual may be done within the context of accepted safety guidelines using a multidisciplinary approach including mental health. No evidence-based protocols are available for these groups (151). We need prospective studies to better understand treatment options for these persons.

3.4. We suggest that endocrinologists provide education to transgender individuals undergoing treatment about the onset and time course of physical changes induced by sex hormone treatment. (2 |⊕○○○)

Evidence

Transgender males

Physical changes that are expected to occur during the first 1 to 6 months of testosterone therapy include cessation of menses, increased sexual desire, increased facial and body hair, increased oiliness of skin, increased muscle, and redistribution of fat mass. Changes that occur within the first year of testosterone therapy include deepening of the voice (152, 153), clitoromegaly, and male pattern hair loss (in some cases) (114, 144, 154, 155) (Table 12).

Transgender females

Physical changes that may occur in transgender females in the first 3 to 12 months of estrogen and antiandrogen therapy include decreased sexual desire, decreased spontaneous erections, decreased facial and body hair (usually mild), decreased oiliness of skin, increased breast tissue growth, and redistribution of fat mass (114, 139, 149, 154, 155, 161) (Table 13). Breast development is generally maximal at 2 years after initiating hormones (114, 139, 149, 155). Over a long period of time, the prostate gland and testicles will undergo atrophy.

Although the time course of breast development in transgender females has been studied (150), precise information about other changes induced by sex hormones is lacking (141). There is a great deal of variability among individuals, as evidenced during pubertal development. We all know that a major concern for transgender females is breast development. If we work with estrogens, the result will be often not what the transgender female expects.

Alternatively, there are transgender females who report an anecdotal improved breast development, mood, or sexual desire with the use of progestogens. However, there have been no well-designed studies of the role of progestogens in feminizing hormone regimens, so the question is still open.

Our knowledge concerning the natural history and effects of different cross-sex hormone therapies on breast

Table 12. Masculinizing Effects in Transgender Males

Effect	Onset	Maximum
Skin oiliness/acne	1–6 mo	1–2 y
Facial/body hair growth	6–12 mo	4–5 y
Scalp hair loss	6–12 mo	—[a]
Increased muscle mass/strength	6–12 mo	2–5 y
Fat redistribution	1–6 mo	2–5 y
Cessation of menses	1–6 mo	—[b]
Clitoral enlargement	1–6 mo	1–2 y
Vaginal atrophy	1–6 mo	1–2 y
Deepening of voice	6–12 mo	1–2 y

Estimates represent clinical observations: Toorians *et al.* (149), Asscheman *et al.* (156), Gooren *et al.* (157), Wierckx *et al.* (158).

[a] Prevention and treatment as recommended for biological men.

[b] Menorrhagia requires diagnosis and treatment by a gynecologist.

doi: 10.1210/jc.2017-01658

Table 13. Feminizing Effects in Transgender Females

Effect	Onset	Maximum
Redistribution of body fat	3–6 mo	2–3 y
Decrease in muscle mass and strength	3–6 mo	1–2 y
Softening of skin/decreased oiliness	3–6 mo	Unknown
Decreased sexual desire	1–3 mo	3–6 mo
Decreased spontaneous erections	1–3 mo	3–6 mo
Male sexual dysfunction	Variable	Variable
Breast growth	3–6 mo	2–3 y
Decreased testicular volume	3–6 mo	2–3 y
Decreased sperm production	Unknown	>3 y
Decreased terminal hair growth	6–12 mo	>3 y[a]
Scalp hair	Variable	—[b]
Voice changes	None	—[c]

Estimates represent clinical observations: Toorians *et al.* (149), Asscheman *et al.* (156), Gooren *et al.* (157).

[a]Complete removal of male sexual hair requires electrolysis or laser treatment or both.

[b]Familial scalp hair loss may occur if estrogens are stopped.

[c]Treatment by speech pathologists for voice training is most effective.

development in transgender females is extremely sparse and based on the low quality of evidence. Current evidence does not indicate that progestogens enhance breast development in transgender females, nor does evidence prove the absence of such an effect. This prevents us from drawing any firm conclusion at this moment and demonstrates the need for further research to clarify these important clinical questions (162).

Values and preferences

Transgender persons have very high expectations regarding the physical changes of hormone treatment and are aware that body changes can be enhanced by surgical procedures (*e.g.*, breast, face, and body habitus). Clear expectations for the extent and timing of sex hormone–induced changes may prevent the potential harm and expense of unnecessary procedures.

4.0 Adverse Outcome Prevention and Long-Term Care

Hormone therapy for transgender males and females confers many of the same risks associated with sex hormone replacement therapy in nontransgender persons. The risks arise from and are worsened by inadvertent or intentional use of supraphysiologic doses of sex hormones, as well as use of inadequate doses of sex hormones to maintain normal physiology (131, 139).

4.1. We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every 3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly. (2 |⊕⊕◯◯)

Evidence

Pretreatment screening and appropriate regular medical monitoring are recommended for both transgender males and females during the endocrine transition and periodically thereafter (26, 155). Clinicians should monitor weight and blood pressure, conduct physical exams, and assess routine health questions, such as tobacco use, symptoms of depression, and risk of adverse events such as deep vein thrombosis/pulmonary embolism and other adverse effects of sex steroids.

Transgender males

Table 14 contains a standard monitoring plan for transgender males on testosterone therapy (154, 159). Key issues include maintaining testosterone levels in the physiologic normal male range and avoiding adverse events resulting from excess testosterone therapy, particularly erythrocytosis, sleep apnea, hypertension, excessive weight gain, salt retention, lipid changes, and excessive or cystic acne (135).

Because oral 17-alkylated testosterone is not recommended, serious hepatic toxicity is not anticipated with parenteral or transdermal testosterone use (163, 164). Past concerns regarding liver toxicity with testosterone have been alleviated with subsequent reports that indicate the risk of serious liver disease is minimal (144, 165, 166).

Transgender females

Table 15 contains a standard monitoring plan for transgender females on estrogens, gonadotropin suppression, or antiandrogens (160). Key issues include avoiding supraphysiologic doses or blood levels of estrogen that may lead to increased risk for thromboembolic disease, liver dysfunction, and hypertension. Clinicians should monitor serum estradiol levels using laboratories participating in external quality control, as measurements of estradiol in blood can be very challenging (167).

VTE may be a serious complication. A study reported a 20-fold increase in venous thromboembolic disease in a large cohort of Dutch transgender subjects (161). This increase may have been associated with the use of the synthetic estrogen, ethinyl estradiol (149). The incidence decreased when clinicians stopped administering ethinyl estradiol (161). Thus, the use of synthetic estrogens and conjugated estrogens is undesirable because of the inability to regulate doses by measuring serum levels and the risk of thromboembolic disease. In a German gender clinic, deep vein thrombosis occurred in 1 of 60 of transgender females treated with a GnRH analog and oral

Table 14. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Male

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of virilization and for development of adverse reactions.
2. Measure serum testosterone every 3 mo until levels are in the normal physiologic male range:[a]
   a. For testosterone enanthate/cypionate injections, the testosterone level should be measured midway between injections. The target level is 400–700 ng/dL to 400 ng/dL. Alternatively, measure peak and trough levels to ensure levels remain in the normal male range.
   b. For parenteral testosterone undecanoate, testosterone should be measured just before the following injection. If the level is <400 ng/dL, adjust dosing interval.
   c. For transdermal testosterone, the testosterone level can be measured no sooner than after 1 wk of daily application (at least 2 h after application).
3. Measure hematocrit or hemoglobin at baseline and every 3 mo for the first year and then one to two times a year. Monitor weight, blood pressure, and lipids at regular intervals.
4. Screening for osteoporosis should be conducted in those who stop testosterone treatment, are not compliant with hormone therapy, or who develop risks for bone loss.
5. If cervical tissue is present, monitoring as recommended by the American College of Obstetricians and Gynecologists.
6. Ovariectomy can be considered after completion of hormone transition.
7. Conduct sub- and periareolar annual breast examinations if mastectomy performed. If mastectomy is not performed, then consider mammograms as recommended by the American Cancer Society.

[a] Adapted from Lapauw *et al.* (154) and Ott *et al.* (159).

estradiol (141). The patient who developed a deep vein thrombosis was found to have a homozygous C677 T mutation in the methylenetetrahydrofolate reductase gene. In an Austrian gender clinic, administering gender-affirming hormones to 162 transgender females and 89 transgender males was not associated with VTE, despite an 8.0% and 5.6% incidence of thrombophilia (159). A more recent multinational study reported only 10 cases of VTE from a cohort of 1073 subjects (168). Thrombophilia screening of transgender persons initiating hormone treatment should be restricted to those with a personal or family history of VTE (159). Monitoring D-dimer levels during treatment is not recommended (169).

4.2. We suggest periodically monitoring prolactin levels in transgender females treated with estrogens. (2 l⊕⊕◯◯)

Evidence

Estrogen therapy can increase the growth of pituitary lactrotroph cells. There have been several reports of prolactinomas occurring after long-term, high-dose estrogen therapy (170–173). Up to 20% of transgender females treated with estrogens may have elevations in prolactin levels associated with enlargement of the pituitary gland (156). In most cases, the serum prolactin levels will return to the normal range with a reduction or discontinuation of the estrogen therapy or discontinuation of cyproterone acetate (157, 174, 175).

The onset and time course of hyperprolactinemia during estrogen treatment are not known. Clinicians should measure prolactin levels at baseline and then at least annually during the transition period and every 2 years thereafter. Given that only a few case studies reported prolactinomas, and prolactinomas were not reported in large cohorts of estrogen-treated persons, the risk is likely to be very low. Because the major presenting findings of microprolactinomas (hypogonadism and sometimes gynecomastia) are not apparent in transgender females, clinicians may perform radiologic examinations of the pituitary in those patients whose prolactin levels persistently increase despite stable or reduced estrogen levels. Some transgender individuals receive psychotropic medications that can increase prolactin levels (174).

Table 15. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Female

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of feminization and for development of adverse reactions.
2. Measure serum testosterone and estradiol every 3 mo.
   a. Serum testosterone levels should be <50 ng/dL.
   b. Serum estradiol should not exceed the peak physiologic range: 100–200 pg/mL.
3. For individuals on spironolactone, serum electrolytes, particularly potassium, should be monitored every 3 mo in the first year and annually thereafter.
4. Routine cancer screening is recommended, as in nontransgender individuals (all tissues present).
5. Consider BMD testing at baseline (160). In individuals at low risk, screening for osteoporosis should be conducted at age 60 years or in those who are not compliant with hormone therapy.

This table presents strong recommendations and does not include lower level recommendations.

doi: 10.1210/jc.2017-01658

4.3. We suggest that clinicians evaluate transgender persons treated with hormones for cardiovascular risk factors using fasting lipid profiles, diabetes screening, and/or other diagnostic tools. (2 ⊕⊕◯◯)

Evidence

Transgender males

Administering testosterone to transgender males results in a more atherogenic lipid profile with lowered high-density lipoprotein cholesterol and higher triglyceride and low-density lipoprotein cholesterol values (176–179). Studies of the effect of testosterone on insulin sensitivity have mixed results (178, 180). A randomized, open-label uncontrolled safety study of transgender males treated with testosterone undecanoate demonstrated no insulin resistance after 1 year (181, 182). Numerous studies have demonstrated the effects of sex hormone treatment on the cardiovascular system (160, 179, 183, 184). Long-term studies from The Netherlands found no increased risk for cardiovascular mortality (161). Likewise, a meta-analysis of 19 randomized trials in nontransgender males on testosterone replacement showed no increased incidence of cardiovascular events (185). A systematic review of the literature found that data were insufficient (due to very low–quality evidence) to allow a meaningful assessment of patient-important outcomes, such as death, stroke, myocardial infarction, or VTE in transgender males (176). Future research is needed to ascertain the potential harm of hormonal therapies (176). Clinicians should manage cardiovascular risk factors as they emerge according to established guidelines (186).

Transgender females

A prospective study of transgender females found favorable changes in lipid parameters with increased high-density lipoprotein and decreased low-density lipoprotein concentrations (178). However, increased weight, blood pressure, and markers of insulin resistance attenuated these favorable lipid changes. In a meta-analysis, only serum triglycerides were higher at ≥24 months without changes in other parameters (187). The largest cohort of transgender females (mean age 41 years, followed for a mean of 10 years) showed no increase in cardiovascular mortality despite a 32% rate of tobacco use (161).

Thus, there is limited evidence to determine whether estrogen is protective or detrimental on lipid and glucose metabolism in transgender females (176). With aging, there is usually an increase of body weight. Therefore, as with nontransgender individuals, clinicians should monitor and manage glucose and lipid metabolism and blood pressure regularly according to established guidelines (186).

4.4. We recommend that clinicians obtain BMD measurements when risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. (1 ⊕⊕◯◯)

Evidence

Transgender males

Baseline bone mineral measurements in transgender males are generally in the expected range for their pretreatment gender (188). However, adequate dosing of testosterone is important to maintain bone mass in transgender males (189, 190). In one study (190), serum LH levels were inversely related to BMD, suggesting that low levels of sex hormones were associated with bone loss. Thus, LH levels in the normal range may serve as an indicator of the adequacy of sex steroid administration to preserve bone mass. The protective effect of testosterone may be mediated by peripheral conversion to estradiol, both systemically and locally in the bone.

Transgender females

A baseline study of BMD reported T scores less than −2.5 in 16% of transgender females (191). In aging males, studies suggest that serum estradiol more positively correlates with BMD than does testosterone (192, 193) and is more important for peak bone mass (194). Estrogen preserves BMD in transgender females who continue on estrogen and antiandrogen therapies (188, 190, 191, 195, 196).

Fracture data in transgender males and females are not available. Transgender persons who have undergone gonadectomy may choose not to continue consistent sex steroid treatment after hormonal and surgical sex reassignment, thereby becoming at risk for bone loss. There have been no studies to determine whether clinicians should use the sex assigned at birth or affirmed gender for assessing osteoporosis (*e.g.*, when using the FRAX tool). Although some researchers use the sex assigned at birth (with the assumption that bone mass has usually peaked for transgender people who initiate hormones in early adulthood), this should be assessed on a case-by-case basis until there are more data available. This assumption will be further complicated by the increasing prevalence of transgender people who undergo hormonal transition at a pubertal age or soon after puberty. Sex for comparison within risk assessment tools may be based on the age at which hormones were initiated and the length of exposure to hormones. In some cases, it may be

reasonable to assess risk using both the male and female calculators and using an intermediate value. Because all subjects underwent normal pubertal development, with known effects on bone size, reference values for birth sex were used for all participants (154).

4.5. We suggest that transgender females with no known increased risk of breast cancer follow breast-screening guidelines recommended for those designated female at birth. (2 ⊕⊕◯◯)

4.6. We suggest that transgender females treated with estrogens follow individualized screening according to personal risk for prostatic disease and prostate cancer. (2 ⊕◯◯◯)

Evidence

Studies have reported a few cases of breast cancer in transgender females (197–200). A Dutch study of 1800 transgender females followed for a mean of 15 years (range of 1 30 years) found one case of breast cancer. The Women's Health Initiative study reported that females taking conjugated equine estrogen without progesterone for 7 years did not have an increased risk of breast cancer as compared with females taking placebo (137).

In transgender males, a large retrospective study conducted at the U.S. Veterans Affairs medical health system identified seven breast cancers (194). The authors reported that this was not above the expected rate of breast cancers in cisgender females in this cohort. Furthermore, they did report one breast cancer that developed in a transgender male patient after mastectomy, supporting the fact that breast cancer can occur even after mastectomy. Indeed, there have been case reports of breast cancer developing in subareolar tissue in transgender males, which occurred after mastectomy (201, 202).

Women with primary hypogonadism (Turner syndrome) treated with estrogen replacement exhibited a significantly decreased incidence of breast cancer as compared with national standardized incidence ratios (203, 204). These studies suggest that estrogen therapy does not increase the risk of breast cancer in the short term (<20 to 30 years). We need long-term studies to determine the actual risk, as well as the role of screening mammograms. Regular examinations and gynecologic advice should determine monitoring for breast cancer.

Prostate cancer is very rare before the age of 40, especially with androgen deprivation therapy (205). Childhood or pubertal castration results in regression of the prostate and adult castration reverses benign prostate hypertrophy (206). Although van Kesteren *et al.* (207) reported that estrogen therapy does not induce hypertrophy or premalignant changes in the prostates of transgender females, studies have reported cases of benign prostatic hyperplasia in transgender females treated with estrogens for 20 to 25 years (208, 209). Studies have also reported a few cases of prostate carcinoma in transgender females (210–214).

Transgender females may feel uncomfortable scheduling regular prostate examinations. Gynecologists are not trained to screen for prostate cancer or to monitor prostate growth. Thus, it may be reasonable for transgender females who transitioned after age 20 years to have annual screening digital rectal examinations after age 50 years and prostate-specific antigen tests consistent with U.S. Preventive Services Task Force Guidelines (215).

4.7. We advise that clinicians determine the medical necessity of including a total hysterectomy and oophorectomy as part of gender-affirming surgery. (Ungraded Good Practice Statement)

Evidence

Although aromatization of testosterone to estradiol in transgender males has been suggested as a risk factor for endometrial cancer (216), no cases have been reported. When transgender males undergo hysterectomy, the uterus is small and there is endometrial atrophy (217, 218). Studies have reported cases of ovarian cancer (219, 220). Although there is limited evidence for increased risk of reproductive tract cancers in transgender males, health care providers should determine the medical necessity of a laparoscopic total hysterectomy as part of a gender-affirming surgery to prevent reproductive tract cancer (221).

Values

Given the discomfort that transgender males experience accessing gynecologic care, our recommendation for the medical necessity of total hysterectomy and oophorectomy places a high value on eliminating the risks of female reproductive tract disease and cancer and a lower value on avoiding the risks of these surgical procedures (related to the surgery and to the potential undesirable health consequences of oophorectomy) and their associated costs.

Remarks

The sexual orientation and type of sexual practices will determine the need and types of gynecologic care required following transition. Additionally, in certain countries, the approval required to change the sex in a birth certificate for transgender males may be dependent on having a complete hysterectomy. Clinicians should help patients research nonmedical administrative criteria and

doi: 10.1210/jc.2017-01658

provide counseling. If individuals decide not to undergo hysterectomy, screening for cervical cancer is the same as all other females.

5.0 Surgery for Sex Reassignment and Gender Confirmation

For many transgender adults, genital gender-affirming surgery may be the necessary step toward achieving their ultimate goal of living successfully in their desired gender role. The type of surgery falls into two main categories: (1) those that directly affect fertility and (2) those that do not. Those that change fertility (previously called sex reassignment surgery) include genital surgery to remove the penis and gonads in the male and removal of the uterus and gonads in the female. The surgeries that effect fertility are often governed by the legal system of the state or country in which they are performed. Other gender-conforming surgeries that do not directly affect fertility are not so tightly governed.

Gender-affirming surgical techniques have improved markedly during the past 10 years. Reconstructive genital surgery that preserves neurologic sensation is now the standard. The satisfaction rate with surgical reassignment of sex is now very high (187). Additionally, the mental health of the individual seems to be improved by participating in a treatment program that defines a pathway of gender-affirming treatment that includes hormones and surgery (130, 144) (Table 16).

Surgery that affects fertility is irreversible. The World Professional Association for Transgender Health Standards of Care (222) emphasizes that the "threshold of 18 should not be seen as an indication in itself for active intervention." If the social transition has not been satisfactory, if the person is not satisfied with or is ambivalent about the effects of sex hormone treatment, or if the person is ambivalent about surgery then the individual should not be referred for surgery (223, 224).

Gender-affirming genital surgeries for transgender females that affect fertility include gonadectomy, penectomy, and creation of a neovagina (225, 226). Surgeons often invert the skin of the penis to form the wall of the vagina, and several literatures reviews have reported on outcomes (227). Sometimes there is inadequate tissue to form a full neovagina, so clinicians have revisited using intestine and found it to be successful (87, 228, 229). Some newer vaginoplasty techniques may involve autologuous oral epithelial cells (230, 231).

The scrotum becomes the labia majora. Surgeons use reconstructive surgery to fashion the clitoris and its hood, preserving the neurovascular bundle at the tip of the penis as the neurosensory supply to the clitoris. Some surgeons are also creating a sensate pedicled-spot adding a G spot to the neovagina to increase sensation (232). Most recently, plastic surgeons have developed techniques to fashion labia minora. To further complete the feminization, uterine transplants have been proposed and even attempted (233).

Neovaginal prolapse, rectovaginal fistula, delayed healing, vaginal stenosis, and other complications do sometimes occur (234, 235). Clinicians should strongly remind the transgender person to use their dilators to maintain the depth and width of the vagina throughout the postoperative period. Genital sexual responsivity and other aspects of sexual function are usually preserved following genital gender-affirming surgery (236, 237).

Ancillary surgeries for more feminine or masculine appearance are not within the scope of this guideline. Voice therapy by a speech language pathologist is available to transform speech patterns to the affirmed gender (148). Spontaneous voice deepening occurs during testosterone treatment of transgender males (152, 238). No studies have compared the effectiveness of speech therapy, laryngeal surgery, or combined treatment.

Breast surgery is a good example of gender-confirming surgery that does not affect fertility. In all females, breast size exhibits a very broad spectrum. For transgender females to make the best informed decision, clinicians should delay breast augmentation surgery until the patient has completed at least 2 years of estrogen therapy, because the breasts continue to grow during that time (141, 155).

Another major procedure is the removal of facial and masculine-appearing body hair using either electrolysis or

Table 16. Criteria for Gender-Affirming Surgery, Which Affects Fertility

1. Persistent, well-documented gender dysphoria
2. Legal age of majority in the given country
3. Having continuously and responsibly used gender-affirming hormones for 12 mo (if there is no medical contraindication to receiving such therapy)
4. Successful continuous full-time living in the new gender role for 12 mo
5. If significant medical or mental health concerns are present, they must be well controlled
6. Demonstrable knowledge of all practical aspects of surgery (*e.g.*, cost, required lengths of hospitalizations, likely complications, postsurgical rehabilitation)

laser treatments. Other feminizing surgeries, such as that to feminize the face, are now becoming more popular (239–241).

In transgender males, clinicians usually delay gender-affirming genital surgeries until after a few years of androgen therapy. Those surgeries that affect fertility in this group include oophorectomy, vaginectomy, and complete hysterectomy. Surgeons can safely perform them vaginally with laparoscopy. These are sometimes done in conjunction with the creation of a neopenis. The cosmetic appearance of a neopenis is now very good, but the surgery is multistage and very expensive (242, 243). Radial forearm flap seems to be the most satisfactory procedure (228, 244). Other flaps also exist (245). Surgeons can make neopenile erections possible by reinervation of the flap and subsequent contraction of the muscle, leading to stiffening of the neopenis (246, 247), but results are inconsistent (248). Surgeons can also stiffen the penis by imbedding some mechanical device (*e.g.*, a rod or some inflatable apparatus) (249, 250). Because of these limitations, the creation of a neopenis has often been less than satisfactory. Recently, penis transplants are being proposed (233).

In fact, most transgender males do not have any external genital surgery because of the lack of access, high cost, and significant potential complications. Some choose a metaoidioplasty that brings forward the clitoris, thereby allowing them to void in a standing position without wetting themselves (251, 252). Surgeons can create the scrotum from the labia majora with good cosmetic effect and can implant testicular prostheses (253).

The most important masculinizing surgery for the transgender male is mastectomy, and it does not affect fertility. Breast size only partially regresses with androgen therapy (155). In adults, discussions about mastectomy usually take place after androgen therapy has started. Because some transgender male adolescents present after significant breast development has occurred, they may also consider mastectomy 2 years after they begin androgen therapy and before age 18 years. Clinicians should individualize treatment based on the physical and mental health status of the individual. There are now newer approaches to mastectomy with better outcomes (254, 255). These often involve chest contouring (256). Mastectomy is often necessary for living comfortably in the new gender (256).

5.1. We recommend that a patient pursue genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically necessary and would benefit the patient's overall health and/or well-being. (1 |⊕⊕◯◯)

5.2. We advise that clinicians approve genital gender-affirming surgery only after completion of at least 1 year of consistent and compliant hormone treatment, unless hormone therapy is not desired or medically contraindicated. (Ungraded Good Practice Statement)

5.3. We advise that the clinician responsible for endocrine treatment and the primary care provider ensure appropriate medical clearance of transgender individuals for genital gender-affirming surgery and collaborate with the surgeon regarding hormone use during and after surgery. (Ungraded Good Practice Statement)

5.4. We recommend that clinicians refer hormone-treated transgender individuals for genital surgery when: (1) the individual has had a satisfactory social role change, (2) the individual is satisfied about the hormonal effects, and (3) the individual desires definitive surgical changes. (1 |⊕◯◯◯)

5.5. We suggest that clinicians delay gender-affirming genital surgery involving gonadectomy and/or hysterectomy until the patient is at least 18 years old or legal age of majority in his or her country. (2 |⊕⊕◯◯).

5.6. We suggest that clinicians determine the timing of breast surgery for transgender males based upon the physical and mental health status of the individual. There is insufficient evidence to recommend a specific age requirement. (2 |⊕◯◯◯)

Evidence

Owing to the lack of controlled studies, incomplete follow-up, and lack of valid assessment measures, evaluating various surgical approaches and techniques is difficult. However, one systematic review including a large numbers of studies reported satisfactory cosmetic and functional results for vaginoplasty/neovagina construction (257). For transgender males, the outcomes are less certain. However, the problems are now better understood (258). Several postoperative studies report significant long-term psychological and psychiatric pathology (259–261). One study showed satisfaction with breasts, genitals, and femininity increased significantly and showed the importance of surgical treatment as a key therapeutic option for transgender females (262). Another analysis demonstrated that, despite the young average age at death following surgery and the relatively larger number of individuals with somatic morbidity, the study does not allow for determination of

doi: 10.1210/jc.2017-01658

causal relationships between, for example, specific types of hormonal or surgical treatment received and somatic morbidity and mortality (263). Reversal surgery in regretful male-to-female transsexuals after sexual reassignment surgery represents a complex, multistage procedure with satisfactory outcomes. Further insight into the characteristics of persons who regret their decision postoperatively would facilitate better future selection of applicants eligible for sexual reassignment surgery. We need more studies with appropriate controls that examine long-term quality of life, psychosocial outcomes, and psychiatric outcomes to determine the long-term benefits of surgical treatment.

When a transgender individual decides to have gender-affirming surgery, both the hormone prescribing clinician and the MHP must certify that the patient satisfies criteria for gender-affirming surgery (Table 16).

There is some concern that estrogen therapy may cause an increased risk for venous thrombosis during or following surgery (176). For this reason, the surgeon and the hormone-prescribing clinician should collaborate in making a decision about the use of hormones before and following surgery. One study suggests that preoperative factors (such as compliance) are less important for patient satisfaction than are the physical postoperative results (56). However, other studies and clinical experience dictate that individuals who do not follow medical instructions and do not work with their physicians toward a common goal do not achieve treatment goals (264) and experience higher rates of postoperative infections and other complications (265, 266). It is also important that the person requesting surgery feels comfortable with the anatomical changes that have occurred during hormone therapy. Dissatisfaction with social and physical outcomes during the hormone transition may be a contraindication to surgery (223).

An endocrinologist or experienced medical provider should monitor transgender individuals after surgery. Those who undergo gonadectomy will require hormone replacement therapy, surveillance, or both to prevent adverse effects of chronic hormone deficiency.

Financial Disclosures of the Task Force*

Wylie C. Hembree (chair)—financial or business/organizational interests: none declared, significant financial interest or leadership position: none declared. **Peggy T. Cohen-Kettenis**—financial or business/organizational interests: none declared, significant financial interest or leadership position: none declared. **Louis Gooren**—financial or business/organizational interests: none declared, significant financial interest or leadership position: none declared. **Sabine E. Hannema**—financial or business/organizational interests: none declared, significant financial interest or leadership position: Ferring Pharmaceuticals Inc. (lecture/conference), Pfizer (lecture). **Walter J. Meyer**—financial or business/organizational interests: none declared, significant financial interest or leadership position: none declared. **M. Hassan Murad****—financial or business/organizational interests: Mayo Clinic, Evidence-based Practice Center, significant financial interest or leadership position: none declared. **Stephen M. Rosenthal**—financial or business/organizational interests: AbbVie (consultant), National Institutes of Health (grantee), significant financial interest or leadership position: Pediatric Endocrine Society (immediate past president). **Joshua D. Safer, FACP**—financial or business/organizational interests: none declared, significant financial interest or leadership position: none declared. **Vin Tangpricha**—financial or business/organizational interests: Cystic Fibrosis Foundation (grantee), National Institutes of Health (grantee), significant financial interest or leadership position, Elsevier *Journal of Clinical and Translational Endocrinology* (editor). **Guy G. T'Sjoen**—financial or business/organizational interests: none declared, significant financial interest or leadership position: none declared.* Financial, business, and organizational disclosures of the task force cover the year prior to publication. Disclosures prior to this time period are archived.**Evidence-based reviews for this guideline were prepared under contract with the Endocrine Society.

Acknowledgments

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Disclosure Summary: See Financial Disclosures.

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PLOS ONE

DEFENDANT'S EXHIBIT 20

RESEARCH ARTICLE

Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria

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OPEN ACCESS

Citation: Littman L (2018) Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria. PLoS ONE 13(8): e0202330. https://doi.org/10.1371/journal.pone.0202330

Editor: Daniel Romer, University of Pennsylvania, UNITED STATES

Received: October 7, 2017

Accepted: August 1, 2018

Published: August 16, 2018

Data Availability Statement: The data cannot be made available due to ethical and regulatory restrictions. The study participants did not provide consent to have their responses shared publicly, shared in public databases, or shared with outside researchers. The Program for the Protection of Human Subjects (PPHS) at the Icahn School of Medicine at Mount Sinai is not permitting the sharing of data beyond what is reported in the paper owing to the sensitive nature of the collected information, the context of the study topic, its release's possible impact on the participants' reputation and standing in the community, and the

Abstract

Purpose

In on-line forums, parents have reported that their children seemed to experience a sudden or rapid onset of gender dysphoria, appearing for the first time during puberty or even after its completion. Parents describe that the onset of gender dysphoria seemed to occur in the context of belonging to a peer group where one, multiple, or even all of the friends have become gender dysphoric and transgender-identified during the same timeframe. Parents also report that their children exhibited an increase in social media/internet use prior to disclosure of a transgender identity. Recently, clinicians have reported that post-puberty presentations of gender dysphoria in natal females that appear to be rapid in onset is a phenomenon that they are seeing more and more in their clinic. Academics have raised questions about the role of social media in the development of gender dysphoria. The purpose of this study was to collect data about parents' observations, experiences, and perspectives about their adolescent and young adult (AYA) children showing signs of an apparent sudden or rapid onset of gender dysphoria that began during or after puberty, and develop hypotheses about factors that may contribute to the onset and/or expression of gender dysphoria among this demographic group.

Methods

For this descriptive, exploratory study, recruitment information with a link to a 90-question survey, consisting of multiple-choice, Likert-type and open-ended questions was placed on three websites where parents had reported sudden or rapid onsets of gender dysphoria occurring in their teen or young adult children. The study's eligibility criteria included parental response that their child had a sudden or rapid onset of gender dysphoria and parental indication that their child's gender dysphoria began during or after puberty. To maximize the chances of finding cases meeting eligibility criteria, the three websites (4thwavenow, transgender trend, and youthtranscriticalprofessionals) were selected for targeted recruitment. Website moderators and potential participants were encouraged to share the recruitment information and link to the survey with any individuals or communities that they thought

risk of participant recognition through linkage of details. As participants' identifiers were not collected it is not possible to contact participants and ask for their consent to disclose at this time. For any questions about restriction on data sharing, please contact PPHS at the Icahn School of Medicine at Mount Sinai (IRB@mssm.edu).

Funding: The author received no specific funding for this work.

Competing interests: Lisa Littman, MD, MPH, provides public health consulting on topics unrelated to this research. She is a member of several professional organizations including the American College of Preventive Medicine (ACPM), the American Public Health Association (APHA), the Society for Adolescent Health and Medicine (SAHM), the Society of Family Planning (SFP), the International Academy of Sex Research (IASR), and the World Professional Association for Transgender Health (WPATH).

might include eligible participants to expand the reach of the project through snowball sampling techniques. Data were collected anonymously via SurveyMonkey. Quantitative findings are presented as frequencies, percentages, ranges, means and/or medians. Open-ended responses from two questions were targeted for qualitative analysis of themes.

Results

There were 256 parent-completed surveys that met study criteria. The AYA children described were predominantly natal female (82.8%) with a mean age of 16.4 years at the time of survey completion and a mean age of 15.2 when they announced a transgender-identification. Per parent report, 41% of the AYAs had expressed a non-heterosexual sexual orientation before identifying as transgender. Many (62.5%) of the AYAs had reportedly been diagnosed with at least one mental health disorder or neurodevelopmental disability prior to the onset of their gender dysphoria (range of the number of pre-existing diagnoses 0–7). In 36.8% of the friendship groups described, parent participants indicated that the majority of the members became transgender-identified. Parents reported subjective declines in their AYAs' mental health (47.2%) and in parent-child relationships (57.3%) since the AYA "came out" and that AYAs expressed a range of behaviors that included: expressing distrust of non-transgender people (22.7%); stopping spending time with non-transgender friends (25.0%); trying to isolate themselves from their families (49.4%), and only trusting information about gender dysphoria from transgender sources (46.6%). Most (86.7%) of the parents reported that, along with the sudden or rapid onset of gender dysphoria, their child either had an increase in their social media/internet use, belonged to a friend group in which one or multiple friends became transgender-identified during a similar time-frame, or both

Conclusion

This descriptive, exploratory study of parent reports provides valuable detailed information that allows for the generation of hypotheses about factors that may contribute to the onset and/or expression of gender dysphoria among AYAs. Emerging hypotheses include the possibility of a potential new subcategory of gender dysphoria (referred to as rapid-onset gender dysphoria) that has not yet been clinically validated and the possibility of social influences and maladaptive coping mechanisms. Parent-child conflict may also explain some of the findings. More research that includes data collection from AYAs, parents, clinicians and third party informants is needed to further explore the roles of social influence, maladaptive coping mechanisms, parental approaches, and family dynamics in the development and duration of gender dysphoria in adolescents and young adults.

Introduction

In recent years, a number of parents have begun reporting in online discussion groups such as 4thwavenow in the US (https://4thwavenow.com) and Transgender Trend in the UK (https://www.transgendertrend.com) that their adolescent and young adult (AYA) children, who have had no histories of childhood gender identity issues, experienced a perceived sudden or rapid

onset of gender dysphoria. Parents have described clusters of gender dysphoria in pre-existing friend groups with multiple or even all members of a friend group becoming gender dysphoric and transgender-identified in a pattern that seems statistically unlikely based on previous research [1–8]. Parents describe a process of immersion in social media, such as "binge-watching" YouTube transition videos and excessive use of Tumblr, immediately preceding their child becoming gender dysphoric [1–2, 9]. These types of presentations have not been described in the research literature for gender dysphoria [1–10] and raise the question of whether social influences may be contributing to or even driving these occurrences of gender dysphoria in some populations of adolescents and young adults. (Note: The terminology of "natal sex", including the terms "natal female" and "natal male", will be used throughout this article. Natal sex refers to an individual's sex as it was observed and documented at the time of birth. Some researchers also use the terminology "assigned at birth".)

Background

Gender dysphoria in adolescents

Gender dysphoria (GD) is defined as an individual's persistent discomfort with their biological sex or assigned gender [11]. Two types of gender dysphoria studied include early-onset gender dysphoria, where the symptoms of gender dysphoria begin in early childhood, and late-onset gender dysphoria, where the symptoms begin after puberty [11]. Late-onset gender dysphoria that occurs during adolescence is now called adolescent-onset gender dysphoria. The majority of adolescents who present for care for gender dysphoria are individuals who experienced early-onset gender dysphoria that persisted or worsened with puberty although an atypical presentation has been described where adolescents who did not experience childhood symptoms present with new symptoms in adolescence [7, 12]. Adolescent-onset of gender dysphoria has only recently been reported in the literature for natal females [5,10, 13–14]. In fact, prior to 2012, there were little to no research studies about adolescent females with gender dysphoria first beginning in adolescence [10]. Thus, far more is known about adolescents with early-onset gender dysphoria than adolescents with adolescent-onset gender dysphoria [6, 15]. Although not all research studies on gender dysphoric adolescents exclude those with adolescent-onset gender dysphoria [10], it is important to note that most of the studies on adolescents, particularly those about gender dysphoria persistence and desistance rates and outcomes for the use of puberty suppression, cross-sex hormones, and surgery only included subjects whose gender dysphoria began in childhood and subjects with adolescent-onset gender dysphoria would not have met inclusion criteria for these studies [16–24]. Therefore, most of the research on adolescents with gender dysphoria to date is not generalizable to adolescents experiencing adolescent-onset gender dysphoria [16–24] and the outcomes for individuals with adolescent-onset gender dysphoria, including persistence and desistence rates and outcomes for treatments, are currently unknown.

As recently as 2012, there were only two clinics (one in Canada and one in the Netherlands) that had gathered enough data to provide empirical information about the main issues for gender dysphoric adolescents [25]. Both institutions concluded that the management of adolescent-onset gender dysphoria is more complicated than the management of early-onset gender dysphoria and that individuals with adolescent-onset are more likely to have significant psychopathology [25]. The presentation of gender dysphoria can occur in the context of severe psychiatric disorders, developmental difficulties, or as part of large-scale identity issues and, for these patients, medical transition might not be advisable [13]. The APA Task Force on the Treatment of Gender Identity Disorder notes that adolescents with gender dysphoria "should be screened carefully to detect the emergence of the desire for sex reassignment in the context

of trauma as well as for any disorder (such as schizophrenia, mania, psychotic depression) that may produce gender confusion. When present, such psychopathology must be addressed and taken into account prior to assisting the adolescent's decision as to whether or not to pursue sex reassignment or actually assisting the adolescent with the gender transition." [25].

Demographic and clinical changes for gender dysphoria

Although, by 2013, there was research documenting that a significant number of natal males experienced gender dysphoria that began during or after puberty, there was little information about this type of presentation for natal females [5]. Starting in the mid-2000s there has been a substantial change in demographics of patients presenting for care with most notably an increase in adolescent females and an inversion of the sex ratio from one favoring natal males to one favoring natal females [26–28]. And now, some clinicians have noted that they are seeing increasingly in their clinic, the phenomenon of natal females expressing a post-puberty rapid onset of gender dysphoria [14]. Some researchers have suggested that increased visibility of transgender people in the media, availability of information online, with a partial reduction of stigma may explain some of the increases in numbers of patients seeking care [27], but these factors would not explain the reversal of the sex ratio, disproportionate increase in adolescent natal females, and the new phenomenon of natal females experiencing gender dysphoria that begins during or after puberty. If there were cultural changes that made it more acceptable for natal females to seek transition [27], that would not explain why the reversal of the sex ratio reported for adolescents has not been reported for older adult populations [26]. There are many unanswered questions about potential causes for the recent demographic and clinical changes for gender dysphoric individuals.

Social and peer influences

Parental reports (on social media) of friend clusters exhibiting signs of gender dysphoria [1–4] and increased exposure to social media/internet preceding a child's announcement of a transgender identity [1–2, 9] raise the possibility of social and peer influences. In developmental psychology research, impacts of peers and other social influences on an individual's development are sometimes described using the terms peer contagion and social contagion, respectively. The use of "contagion" in this context is distinct from the term's use in the study of infectious disease, and furthermore its use as an established academic concept throughout this article is not meant in any way to characterize the developmental process, outcome, or behavior as a disease or disease-like state, or to convey any value judgement. Social contagion [29] is the spread of affect or behaviors through a population. Peer contagion, in particular, is the process where an individual and peer mutually influence each other in a way that promotes emotions and behaviors that can potentially have negative effects on their development [30]. Peer contagion has been associated with depressive symptoms, disordered eating, aggression, bullying, and drug use [30–31]. Internalizing symptoms such as depression can be spread via the mechanisms of co-rumination, which entails the repetitive discussion of problems, excessive reassurance seeking (ERS), and negative feedback [30, 32–34]. Deviancy training, which was first described for rule breaking, delinquency, and aggression, is the process whereby attitudes and behaviors associated with problem behaviors are promoted with positive reinforcement by peers [35, 36].

Peer contagion has been shown to be a factor in several aspects of eating disorders. There are examples in the eating disorder and anorexia nervosa literature of how both internalizing symptoms and behaviors have been shared and spread via peer influences [37–41] which may have relevance to considerations of a rapid onset of gender dysphoria occurring in AYAs. Friendship cliques can set the norms for preoccupation with one's body, one's body image,

and techniques for weight loss, and can predict an individual's body image concerns and eating behaviors [37–39]. Peer influence is intensified in inpatient and outpatient treatment settings for patients with anorexia and counter-therapeutic subcultures that actively promote the beliefs and behaviors of anorexia nervosa have been observed [39–41]. In these settings, there is a group dynamic where the "best" anorexics (those who are thinnest, most resistant to gaining weight, and who have experienced the most medical complications from their disease) are admired, validated, and seen as authentic while the patients who want to recover from anorexia and cooperate with medical treatment are maligned, ridiculed, and marginalized [39–41]. Additionally, behaviors associated with deceiving parents and doctors about eating and weight loss, referred to as the "anorexic tricks," are shared by patients in a manner akin to deviancy training [39–41]. Online environments provide ample opportunity for excessive reassurance seeking, co-rumination, positive and negative feedback, and deviancy training from peers who subscribe to unhealthy, self-harming behaviors. The pro-eating disorder sites provide motivation for extreme weight loss (sometimes calling the motivational content "thinspiration")[42–44]. Such sites promote validation of eating disorder as an identity, and offer "tips and tricks" for weight loss and for deceiving parents and doctors so that individuals may continue their weight-loss activities [42–44]. If similar mechanisms are at work in the context of gender dysphoria, this greatly complicates the evaluation and treatment of impacted AYAs.

In the past decade, there has been an increase in visibility, social media, and user-generated online content about transgender issues and transition [45], which may act as a double-edged sword. On the one hand, an increase in visibility has given a voice to individuals who would have been under-diagnosed and undertreated in the past [45]. On the other hand, it is plausible that online content may encourage vulnerable individuals to believe that nonspecific symptoms and vague feelings should be interpreted as gender dysphoria stemming from a transgender condition. Recently, leading international academic and clinical commentators have raised the question about the role of social media and online content in the development of gender dysphoria [46]. Concern has been raised that adolescents may come to believe that transition is the only solution to their individual situations, that exposure to internet content that is uncritically positive about transition may intensify these beliefs, and that those teens may pressure doctors for immediate medical treatment [25]. There are many examples on popular sites such as Reddit (www.reddit.com with subreddit ask/r/transgender) and Tumblr (www.tumblr.com) where online advice promotes the idea that nonspecific symptoms should be considered to be gender dysphoria, conveys an urgency to transition, and instructs individuals how to deceive parents, doctors, and therapists to obtain hormones quickly [47]. Fig 1 includes examples of online advice from Reddit and Tumblr.

Purpose

Rapid presentations of adolescent-onset gender dysphoria occurring in clusters of pre-existing friend groups are not consistent with current knowledge about gender dysphoria and have not been described in the scientific literature to date [1–8]. The purpose of this descriptive, exploratory research is to (1) collect data about parents' observations, experiences, and perspectives about their AYA children showing signs of a rapid onset of gender dysphoria that began during or after puberty, and (2) develop hypotheses about factors that may contribute to the onset and/or expression of gender dysphoria among this demographic group.

Materials and methods

The Icahn School of Medicine at Mount Sinai, Program for the Protection of Human Subjects provided approval of research for this project (HS#: 16–00744).

Instructions on lying	• "TL;DR find out what they want to hear if they're gonna give you T and then tell them just that. It's about getting treatment, not about being true to those around you. It's not their business and a lot of time doctors will screw stuff up for you."[a] • "…Get a story ready in your head, and as suggested keep the lie to a minimum. And only for stuff that can't be verified. Like how you were feeling, but was too afraid to tell anyone including your family."[b] • "I'd also look up the DSM for the diagnostic criteria for transgender and make sure your story fits it, assuming your psych follows it."[c]
Urgency to transition	• "…If you don't do it when you are young. You'll be miserable and unhappy with your body for the rest of your life."[d]
Vague and nonspecific symptoms called signs of GD	• "Signs of indirect gender dysphoria: 1. Continual difficulty with simply getting through the day. 2. A sense of misalignment, disconnect, or estrangement from your own emotions. 3. A feeling of just going through the motions in everyday life, as if you're always reading from a script. 4. A seeming pointlessness to your life, and no sense of any real meaning or ultimate purpose. 5. Knowing you're somehow different from everyone else, and wishing you could be normal like them…"[e]
	a. https://www.reddit.com/r/asktransgender/comments/2nt8gi/having_a_psych_eval_soon/#bottom-comments b. https://www.reddit.com/r/asktransgender/comments/4agf76/is_it_best_to_be_completely_honest_or_lie_a/ c. https://www.reddit.com/r/asktransgender/comments/4ihwar/what_things_should_i_never_tell_my_psychologist/ d. https://www.reddit.com/r/asktransgender/comments/3gpb94/at_the_final_stage_of_questioning_need_some/#bottom-comments e. https://transgenderteensurvivalguide.tumblr.com/post/62036014416/that-was-dysphoria-8-signs-and-symptoms-of

Fig 1. Example quotes of online advice from Reddit and Tumblr.

https://doi.org/10.1371/journal.pone.0202330.g001

Participants

During the recruitment period, 256 parents completed online surveys that met the study criteria. The sample of parents included more women (91.7%) than men (8.3%) and participants were predominantly between the ages of 45 and 60 (66.1%) (Table 1). Most respondents were White (91.4%), non-Hispanic (99.2%), and lived in the United States (71.7%). Most respondents had a Bachelor's degree (37.8%) or graduate degree (33.1%). The adolescents and young adults (AYAs) described by their parents were predominantly female sex at birth (82.8%) with an average current age of 16.4 years (range, 11–27 years). See Table 2.

Procedure

A 90-question survey instrument with multiple choice, Likert-type, and open-ended questions was created by the researcher. The survey was designed for parents (respondents) to complete about their adolescent and young adult children. The survey was uploaded onto Survey Monkey (SurveyMonkey, Palo Alto, CA, USA) via an account that was HIPPA-enabled. IRB approval for the study from the Icahn School of Medicine at Mount Sinai in New York, NY was received. Recruitment information with a link to the survey was placed on three websites where parents and professionals had been observed to describe what seemed to be a sudden or rapid onset of gender dysphoria (4thwavenow, transgender trend, and youthtranscriticalprofessionals), although the specific terminology "rapid onset gender dysphoria" did not appear on these websites until the recruitment information using that term was first posted on the sites. Website moderators and potential participants were encouraged to share the recruitment information and link to the survey with any individuals or communities that they thought might include eligible participants to expand the reach of the project through snowball sampling techniques. The survey was active from June 29, 2016 to October 12, 2016 (3.5 months)

Table 1. Demographic and other baseline characteristics of parent respondents.

Characteristics of Parent-respondents		n	%
Sex		254	
	Female	233	91.7
	Male	21	8.3
Age (y)		254	
	18–29	3	1.2
	30–44	74	29.1
	45–60	168	66.1
	>60	9	3.5
Race/Ethnicity*		255	
	White	233	91.4
	Other**	22	8.6
Country of Residence		254	
	US	182	71.7
	UK	39	15.4
	Canada	17	6.7
	Other	16	6.3
Education		254	
	Bachelor's degree	96	37.8
	Graduate degree	84	33.1
	Some college or Associates degree	63	24.8
	HS grad or GED	10	3.9
	<High School	1	0.4
Parent attitude on allowing gay and lesbian couples to marry legally		256	
	Favor	220	85.9
	Oppose	19	7.4
	Don't know	17	6.6
Parent belief that transgender people deserve the same rights and protections as others		255	
	Yes	225	88.2
	No	8	3.1
	Don't know	20	7.8
	Other	2	0.8

* may select more than one answer.

** declining order includes: Other, Multiracial, Asian, Hispanic.

https://doi.org/10.1371/journal.pone.0202330.t001

and took 30–60 minutes to complete. Participants completed the survey at a time and place of their own choosing. Data were collected anonymously and stored securely with Survey Monkey.

Participation in this study was voluntary and its purpose was clearly described in the recruitment information. Electronic consent was obtained. Participants had the option to withdraw consent at any time prior to submitting responses. Inclusion criteria were (1) completion of a survey with parental response that the child had a sudden or rapid onset of gender dysphoria; and (2) parental indication that the child's gender dysphoria began during or after puberty. There was logic embedded in the survey that disqualified surveys that answered "no" (or skipped the question) about whether the child had a sudden or rapid onset of gender dysphoria and 23 surveys were disqualified prior to completion (20 "no" answers and 3 skipped

Table 2. Demographic and other baseline characteristics of AYAs.

Characteristics of AYAs		n	%
AYA sex at birth (natal sex)		256	
	Female	212	82.8
	Male	44	17.2
AYA average current age (range of ages)	16.4 (11–27)	256	
Academic diagnoses		253	
	Gifted	120	47.4
	Learning Disability	11	4.3
	Both	27	10.7
	Neither	95	37.5
Natal female expressed sexual orientation before announcement*		212	
	Asexual	18	8.5
	Bisexual or Pansexual	78	36.8
	Gay or Lesbian	58	27.4
	Straight (Heterosexual)	75	35.4
	Did not express	57	26.9
Natal male expressed sexual orientation before announcement*		44	
	Asexual	4	9.1
	Bisexual or Pansexual	5	11.4
	Gay	5	11.4
	Straight (Heterosexual)	25	56.8
	Did not express	11	25.0
Gender dysphoria began		256	
	During puberty	125	48.8
	After puberty	131	51.2
Along with a rapid onset of GD, the AYA also:		256	
	Belonged to a friend group where one or multiple friends became transgender-identified during a similar timeframe	55	21.5
	Had an increase in social media/internet use	51	19.9
	Both of the above	116	45.3
	Neither	13	5.1
	Don't know	21	8.2

* may select more than one answer.

https://doi.org/10.1371/journal.pone.0202330.t002

answers). After cleaning the data for the 274 completed surveys, 8 surveys were excluded for not having a sudden or rapid onset of gender dysphoria and 10 surveys were excluded for not having gender dysphoria that began during or after puberty, which left 256 completed surveys for inclusion. As the survey was voluntary there was no refusal or dropout rate.

Recruitment sites

There were four sites known to post recruitment information about the research study. The first three were posted due to direct communication with the moderators of the sites. The fourth site posted recruitment information secondary to the snowball sampling technique. The following descriptions provide details about these sites.

4thwavenow

4thwavenow was created in 2015. The site, as seen in digitally archived screenshots from 2015 and 2016, stated that it is a "safe place for gender-skeptical parents and their allies", offered support for parents, and expressed concern about the rush to diagnose young people as transgender and the rush to proceed to medical treatment for them [2, 48]. By June 2016, the site had expanded to include the writing of several parents, "formerly trans-identified people, and people with professional expertise and experience with young people questioning their gender identity" [9]. The perspective of this site might be described as cautious about medical and surgical transition overall—specifically with a cautious or negative view of medical and surgical interventions for children, adolescents, and young adults and an accepting view that mature adults can make their own decisions about transition [2, 9].

Transgendertrend

Transgendertrend was founded in November 2015. The digitally archived screenshots from November 2015 and July 2016 "Who Are We?" section include the following description, "We are an international group of parents based mainly in the UK, US and Canada, who are concerned about the current trend to diagnose 'gender non-conforming' children as transgender. We reject current conservative, reactionary, religious-fundamentalist views about sexuality. We come from diverse backgrounds, some with expertise in child development and psychology, some who were themselves extreme gender non-conforming children and adolescents, some whose own children have self-diagnosed as 'trans' and some who know supportive trans adults who are also questioning recent theories of 'transgenderism'" [49]. In July of 2016, there was additional text added, expressing concern about legislation regarding public bathrooms and changing rooms [50].

Youth trans critical professionals

Youth Trans Critical Professionals was created in March 2016. The digitally archived screenshot from the April 2016 "About" section stated the following: "This website is a community of professionals "thinking critically about the youth transgender movement. We are psychologists, social workers, doctors, medical ethicists, and academics. We tend to be left-leaning, open-minded, and pro-gay rights. However, we are concerned about the current trend to quickly diagnose and affirm young people as transgender, often setting them down a path toward medical transition. Our concern is with medical transition for children and youth. We feel that unnecessary surgeries and/or hormonal treatments which have not been proven safe in the long-term represent significant risks for young people" [51].

Parents of transgender children

Parents of Transgender Children is a private Facebook group with more than 8,000 members [52]. The current "About" section states that requests to join the group "will be denied if you are not the parent (or immediate caregiver or family member) of a transgender, gender-fluid, gender-questioning, agender, or other gender-nonconforming child (of any age); or if you are uncooperative during screening" and that the "group is comprised of parents and parenting figures, as well as a select group of advocates INVITED by the admin[istrative] staff to assist & help us with understanding legal and other concerns" [52]. Although the parent discussions and comments are not viewable to non-members [52], this group is perceived to be pro -gender-affirming. The Parents of Transgender Children Facebook group is considered to be a site to find parents who are supportive of their child's gender identity [53], and it is listed as a

resource in a gender affirming parenting guide [54] and by gender affirming organizations [55–56].

Measures

Basic demographic and baseline characteristics

Basic demographic and baseline characteristic questions, including parental attitudes about LGBT rights, were included. Parents were asked about their children's mental health disorders and neurodevelopmental disabilities that were diagnosed before their child's onset of gender dysphoria as well as during and after. The question, "Has your child been formally identified as academically gifted, learning disabled, both, neither?" was used as a proxy to estimate rates of academic giftedness and learning disabilities. Questions about trauma and non-suicidal self-injury were also included as were questions about social difficulties described in a previous research study about gender dysphoric adolescents [13].

DSM-5 diagnostic criteria for gender dysphoria in children

The DSM 5 criteria for gender dysphoria in children consist of eight indicators of gender dysphoria [57]. To meet criteria for diagnosis, a child must manifest at least six out of eight indicators including the one designated A1, "A strong desire to be the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender)." Three of the indicators (A1, A7, and A8) refer to desires or dislikes of the child. Five of the indicators (A2-A6) are readily observable behaviors and preferences such as a strong preference or strong resistance to wearing certain kinds of clothing; a strong preference or strong rejection of specific toys, games and activities; and a strong preference for playmates of the other gender [57]. The eight indicators were simplified for language and parents were asked to note which, if any, their child had exhibited prior to puberty. The requirement of six-month duration of symptoms was not included.

DSM-5 diagnostic criteria for gender dysphoria in adolescents and adults

The DSM-5 criteria for gender dysphoria in adolescents and adults consist of six indicators of gender dysphoria [57]. To meet criteria for diagnosis, an adolescent or adult must manifest at least two of the six indicators. The six indicators were simplified for language, the first indicator was adjusted for a parent to answer about their child, and parents were asked to note which, if any, their child was expressing currently. The requirement of six-month duration of symptoms was not included.

Exposure to friend groups and social media/internet content

Survey questions were developed to describe AYA friend groups, including number of friends that became transgender-identified in a similar time period as the AYA, peer group dynamics and behaviors, and exposure to specific types of social media/internet content and messages that have been observed on sites popular with teens, such as Reddit and Tumblr.

Behaviors, outcomes, clinical interactions

Survey questions were developed to specifically quantify adolescent behaviors that had been described by parents in online discussions and observed elsewhere. Participants were asked to describe outcomes such as their child's mental well-being and parent-child relationship since becoming transgender-identified. Parents were also asked about experiences with clinicians and their children's disposition regarding steps taken for transition and duration of

transgender-identification both for children who were still transgender-identified and for children who were no longer transgender-identified.

Coping with strong or negative emotions

Two questions about the AYAs' ability to cope with negative and strong emotions were included. One question was "How does your child handle strong emotions? (please select the best answer)." Offered answers were "My child is overwhelmed by strong emotions and goes to great lengths to avoid feeling them," "My child is overwhelmed by strong emotions and tries to avoid feeling them," "My child neither avoids not seeks out strong emotions," "My child tries to seek out situations in order to feel strong emotions," "My child goes to great lengths to seek out situations in order to feel strong emotions," "None of the above," "I don't know." The other question was "How would you rate your child's ability to deal with their negative emotions and channel them into something productive?" An example was given regarding dealing with a low test grade by studying harder for the next test (excellent) or by ignoring it, throwing a tantrum, blaming the teacher or distracting themselves with computer games, alcohol, drugs, etc. (extremely poor). Offered answers were: excellent, good, fair, poor, extremely poor, and I don't know.

Data analysis

Statistical analyses of quantitative data were performed using Excel and custom shell scripts (Unix). Quantitative findings are presented as frequencies, percentages, ranges, means and/or medians. ANOVAs, chi-squared, and t-tests comparisons were used where appropriate using publicly available calculators and $p<0.05$ was considered significant. Qualitative data were obtained from open text answers to questions that allowed participants to provide additional information or comments. The types of comments and descriptions were categorized, tallied, and reported numerically. A grounded theory approach was selected as the analytic strategy of choice for handling the qualitative responses because it allowed the researcher to assemble the data in accordance with the salient points the respondents were making without forcing the data into a preconceived theoretical framework of the researcher's own choosing [58]. Illustrative respondent quotes and summaries from the qualitative data are used to illustrate the quantitative results and to provide relevant examples. Two questions were targeted for full qualitative analysis of themes (one question on friend group behaviors and one on clinician interactions). For these questions, a second reviewer with expertise in qualitative methods was engaged (MM). Both the author (LL) and reviewer (MM) independently analyzed the content of the open text answers and identified major themes. Discrepancies were resolved with collaborative discussion and themes were explored and refined until agreement was reached for the final lists of themes. Representative quotes for each theme were selected by LL, reviewed by MM, and agreement was reached.

Results

Baseline characteristics

Baseline characteristics (Table 1) included that the vast majority of parents favored gay and lesbian couples' right to legally marry (85.9%) and believed that transgender individuals deserve the same rights and protections as other individuals in their country (88.2%). Along with the sudden or rapid onset of gender dysphoria, the AYAs belonged to a friend group where one or multiple friends became gender dysphoric and came out as transgender during a similar time as they did (21.5%), exhibited an increase in their social media/internet use (19.9%), both

(45.3%), neither (5.1%), and don't know (8.2%) (Table 2). For comparisons, the first three categories will be combined and called "social influence" (86.7%) and the last two combined as "no social influence" (13.3%). Nearly half (47.4%) of the AYAs had been formally diagnosed as academically gifted, 4.3% had a learning disability, 10.7% were both gifted and learning disabled, and 37.5% were neither. Sexual orientation as expressed by the AYA prior to transgender-identification is listed separately for natal females and for natal males (Table 2). Overall, 41% of the AYAs expressed a non-heterosexual sexual orientation prior to disclosing a transgender-identification.

It is important to note that none of the AYAs described in this study would have met diagnostic criteria for gender dysphoria in childhood (Table 3). In fact, the vast majority (80.4%) had zero indicators from the DSM-5 diagnostic criteria for childhood gender dysphoria with 12.2% possessing one indicator, 3.5% with two indicators, and 2.4% with three indicators. Breaking down these results, for readily observable indicators (A2-6), 83.5% of AYAs had zero indicators, 10.2% had one indicator, 3.9% had two indicators, and 1.2% had three indicators. For the desire/dislike indicators (A1, A7, A8), which a parent would have knowledge of if the child expressed them verbally, but might be unaware if a child did not, 95.7% had zero indicators and 3.5% had one indicator. Parents responded to the question about which, if any, of the indicators of the DSM criteria for adolescent and adult gender dysphoria their child was

Table 3. DSM 5 Indicators for gender dysphoria.

Characteristics		n	%
AYAs who would have met diagnostic criteria for gender dysphoria in childhood		0	0
Number of DSM 5 indicators for gender dysphoria in children exhibited prior to puberty		255	
	Zero indicators	205	80.4
	One indicator	31	12.2
	Two indicators	9	3.5
	Three indicators	6	2.4
	Four indicators	3	1.2
Desire/Dislike Indicators (A1, A7, or A8)		255	
	Zero indicators	244	95.7
	One indicators	9	3.5
	Two indicators	0	0
	Three indicators	1	0.4
Readily observable indicators (A2-A6)		254	
	Zero indicators	212	83.5
	One indicator	26	10.2
	Two indicators	10	3.9
	Three indicators	3	1.2
	Four indicators	3	1.2
Average number of DSM 5 indicators for adolescent and adult gender dysphoria that the AYA is experiencing currently (range)			
	3.5 (range 0–6)	247	
AYAs currently experiencing two or more indicators of gender dysphoria for adolescents and adults		250	
	Yes	208	83.2
	No	40	16.0
	Don't know	2	0.8

https://doi.org/10.1371/journal.pone.0202330.t003

experiencing currently. The average number of positive current indicators was 3.5 (range 0–6) and 83.2% of the AYA sample was currently experiencing two or more indicators. Thus, while the focal AYAs did not experience childhood gender dysphoria, the majority of those who were the focus of this study were indeed gender dysphoric at the time of the survey completion.

The AYAs who were the focus of this study had many comorbidities and vulnerabilities predating the onset of their gender dysphoria, including psychiatric disorders, neurodevelopmental disabilities, trauma, non-suicidal self-injury (NSSI), and difficulties coping with strong or negative emotions (Table 4). The majority (62.5%) of AYAs had one or more diagnoses of a psychiatric disorder or neurodevelopmental disability preceding the onset of gender dysphoria (range of the number of pre-existing diagnoses 0–7). Many (48.4%) had experienced a traumatic or stressful event prior to the onset of their gender dysphoria. Open text descriptions of trauma were categorized as "family" (including parental divorce, death of a parent, mental disorder in a sibling or parent), "sex or gender related" (such as rape, attempted rape, sexual harassment, abusive dating relationship, break-up), "social" (such as bullying, social isolation), "moving" (family relocation or change of schools); "psychiatric" (such as psychiatric hospitalization), and medical (such as serious illness or medical hospitalization). Almost half (45.0%) of AYAs were engaging in non-suicidal self-injury (NSSI) behavior before the onset of gender dysphoria. Coping styles for these AYAs included having a poor or extremely poor ability to handle negative emotions productively (58.0%) and being overwhelmed by strong emotions and trying to avoid (or go to great lengths to avoid) experiencing them (61.4%) (Table 4). The majority of respondents (69.4%) answered that their child had social anxiety during adolescence; 44.3% that their child had difficulty interacting with their peers, and 43.1% that their child had a history of being isolated (not associating with their peers outside of school activities).

Announcing a transgender-identification

At the time the AYA announced they were transgender-identified ("came out"), most were living at home with one or both parents (88.3%) and a small number were living at college (6.2%). The average age of announcement of a transgender-identification was 15.2 years of age (range 10–21) (Table 5). Most of the parents (80.9%) answered affirmatively that their child's announcement of being transgender came "out of the blue without significant prior evidence of gender dysphoria." Respondents were asked to pinpoint a time when their child seemed not at all gender dysphoric and to estimate the length of time between that point and their child's announcement of a transgender-identity. Almost a third of respondents (32.4%) noted that their child did not seem gender dysphoric when they made their announcement and 26.0% said the length of time from not seeming gender dysphoric to announcing a transgender identity was between less than a week to three months. The most striking examples of "not seeming at all gender dysphoric" prior to making the announcement included a daughter who loved summers and seemed to love how she looked in a bikini, another daughter who happily wore bikinis and makeup, and another daughter who previously said, "I love my body!"

The majority of respondents (69.2%) believed that their child was using language that they found online when they "came out." A total of 130 participants provided optional open text responses to this question, and responses fell into the following categories: why they thought the child was using language they found online (51); description of what the child said but didn't provide a reason that they suspected the child was using language they found online (61); something else about the conversation (8) or the child (7) and don't know (3). Of the 51 responses describing reasons why respondents thought their child was reproducing language

Table 4. AYA baseline comorbidities and vulnerabilities predating the onset of gender dysphoria.

Characteristics		n	%
Mental disorder or neurodevelopmental disability diagnosed prior to the onset of gender dysphoria*		251	
	Anxiety	117	46.6
	Depression	99	39.4
	Attention Deficit Hyperactivity Disorder (ADHD)	29	11.6
	Obsessive Compulsive Disorder (OCD)	21	8.4
	Autism Spectrum Disorder (ASD)	20	8.0
	Eating Disorder	12	4.8
	Bipolar Disorder	8	3.2
	Psychosis	6	2.4
	None of above	94	37.5
	(Other) Borderline	3	1.2
	(Other) Oppositional Defiant Disorder	2	0.8
Traumatic or stressful experience prior to the onset of gender dysphoria		252	
	Yes	122	48.4
	No	91	36.1
	Don't know	38	15.1
	Other	1	0.4
Types of trauma*		113	
	Family	50	44.2
	Sex/Gender related	34	30.1
	Social	23	20.4
	Moving	20	17.7
	Psychiatric	9	8.0
	Medical	7	6.2
Non-suicidal self-injury (NSSI) before the onset of gender dysphoria		180	
		81	45.0
Ability to handle negative emotions productively		255	
	Excellent/Good	34	13.3
	Fair	70	27.5
	Poor/Extremely Poor	148	58.0
	Don't know	3	1.2
Coping style for dealing with strong emotions		254	
	Overwhelmed by strong emotions and tries to /goes to great lengths to avoid feeling them	156	61.4
	Neither avoids nor seeks out strong emotions	29	11.4
	Tries to/goes to great lengths to seeks out strong emotions	33	13.0
	Don't know	25	9.8
	None of the above	11	4.3
Social vulnerabilities		255	
	During adolescence child had social anxiety	177	69.4
	Child had difficulty interacting with their peers	113	44.3
	History of being isolated (not interacting with peers outside of school activities)	110	43.1
	Child felt excluded by peers throughout most of grade school	93	36.5
	Child had persistent experiences of being bullied before the onset of gender dysphoria	74	29.0

*may select more than one answer.

https://doi.org/10.1371/journal.pone.0202330.t004

Table 5. Announcing a transgender-identification.

Characteristics		n	%
Age of AYA when the AYA announced a transgender-identification (range)	15.2 average (10–21)	255	
Living arrangement at announcement		256	
	Living at home with one or both parents	226	88.3
	Living at college or university	16	6.2
	Other	14	5.5
AYA's announcement came from "out of the blue, without significant prior evidence of gender dysphoria"		256	
	Yes	207	80.9
	No	33	12.9
	Other	16	6.2
If a time was pinpointed when the child seemed not at all gender dysphoric, how long between that time and the child's announcement of a transgender-identity?		250	
	Did not seem at all gender dysphoric when they announced and transgender-identity	81	32.4
	Less than a week to 3 months	65	26.0
	4–6 months	31	12.4
	7–9 months	10	4.0
	10–12 months	29	11.6
	More than 12 months	20	8.0
	Don't know	14	5.6
Parent suspects that when the child first announced a transgender-identity, that the child used language that they found online		253	
	Yes	175	69.2
	No	53	20.9
	N/A	25	9.9
Parent thinks their child is correct in their child's belief of being transgender		255	
	Yes	6	2.4
	No	195	76.5
	Don't know	38	14.9
	Other	16	6.3
How soon after the announcement did the AYA ask for transition?		255	
	At the same time	86	33.7
	Between less than one week to one month	33	12.9
	2–5 months after announcement	26	10.2
	6 or more months after announcement	19	7.5
	Other	16	6.3
	N/A	75	29.4
Intention and request for transition*		189	
	AYA told the parent that they want cross-sex hormones	127	67.2
	AYA told the parent that they want to go to a gender therapist/gender clinic	111	58.7
	AYA told the parent that they want surgery	101	53.4
	AYA brought up the issue of suicides in transgender teens as a reason that their parent should agree to treatment	59	31.2

(*Continued*)

Table 5. (Continued)

Characteristics		n	%
AYA has very high expectation that transitioning will solve their problems in social, academic, occupational, or mental health areas		256	
	Yes	143	55.9
	No	13	5.1
	Don't know	100	39.1
AYA was willing to work on basic mental health before seeking gender treatments		253	
	Yes	111	43.9
	No	71	28.1
	Don't know	30	11.9
	N/A	41	16.2

*may select more than one answer.

https://doi.org/10.1371/journal.pone.0202330.t005

they found online, the top two reasons were that it didn't sound like their child's voice (19 respondents) and that the parent later looked online and recognized the same words and phrases that their child used when they announced a transgender identity (14 respondents). The observation that it didn't sound like their child's voice was also expressed as "sounding scripted," like their child was "reading from a script," "wooden," "like a form letter," and that it didn't sound like their child's words. Parents described finding the words their child said to them "verbatim," "word for word," "practically copy and paste," and "identical" in online and other sources. The following quotes capture these top two observations. One parent said, "It seemed different from the way she usually talked—I remember thinking it was like hearing someone who had memorized a lot of definitions for a vocabulary test." Another respondent said, "The email [my child sent to me] read like all of the narratives posted online almost word for word."

The following case summaries were selected to illustrate peer, trauma, and psychiatric contexts that might indicate more complicated clinical pictures.

- A 12-year-old natal female was bullied specifically for going through early puberty and the responding parent wrote "as a result she said she felt fat and hated her breasts." She learned online that hating your breasts is a sign of being transgender. She edited her diary (by crossing out existing text and writing in new text) to make it appear that she has always felt that she is transgender.
- A 14-year-old natal female and three of her natal female friends were taking group lessons together with a very popular coach. The coach came out as transgender, and, within one year, all four students announced they were also transgender.
- A natal female was traumatized by a rape when she was 16 years of age. Before the rape, she was described as a happy girl; after the rape, she became withdrawn and fearful. Several months after the rape, she announced that she was transgender and told her parents that she needed to transition.
- A 21-year-old natal male who had been academically successful at a prestigious university seemed depressed for about six months. Since concluding that he was transgender, he went on to have a marked decline in his social functioning and has become increasingly angry and

hostile to his family. He refuses to move out or look for a job. His entire family, including several members who are very supportive of the transgender community, believe that he is "suffering from a mental disorder which has nothing to do with gender."

- A 14-year-old natal female and three of her natal female friends are part of a larger friend group that spends much of their time talking about gender and sexuality. The three natal female friends all announced they were trans boys and chose similar masculine names. After spending time with these three friends, the 14-year-old natal female announced that she was also a trans boy.

The majority (76.5%) of the surveyed parents felt that their child was incorrect in their belief of being transgender (Table 5). More than a third (33.7%) of the AYAs asked for medical and/or surgical transition at the same time that they announced they were transgender-identified. Two thirds (67.2%) of the AYAs told their parent that they wanted to take cross-sex hormones; 58.7% that they wanted to see a gender therapist/gender clinic; and 53.4% that they wanted surgery for transition. Almost a third (31.2%) of AYAs brought up the issue of suicides in transgender teens as a reason that their parent should agree to treatment. More than half of the AYAs (55.9%) had very high expectations that transitioning would solve their problems in social, academic, occupational or mental health areas. While 43.9% of AYAs were willing to work on basic mental health before seeking gender treatments, a sizable minority (28.1%) were not willing to work on their basic mental health before seeking gender treatment. At least two parents relayed that their child discontinued psychiatric care and medications for pre-existing mental health conditions once they identified as transgender. One parent, in response to the question about if their child had very high expectations that transitioning would solve their problems elaborated, "Very much so. [She] discontinued anti-depressant quickly, stopped seeing psychiatrist, began seeing gender therapist, stopped healthy eating. [She] stated 'none of it' (minding what she ate and taking her Rx) 'mattered anymore.' This was her cure, in her opinion."

Friend-group exposure

The adolescent and young adult children were, on average, 14.4 years old when their first friend became transgender-identified (Table 6). Within friendship groups, the average number of individuals who became transgender-identified was 3.5 per group. In 36.8% of the friend groups described, the majority of individuals in the group became transgender-identified. The order that the focal AYA "came out" compared to the rest of their friendship group was calculated from the 119 participants who provided the number of friends coming out both before and after their child and 74.8% of the AYAs were first, second or third of their group. Parents described intense group dynamics where friend groups praised and supported people who were transgender-identified and ridiculed and maligned non-transgender people. Where popularity status and activities were known, 60.7% of the AYAs experienced an increased popularity within their friend group when they announced a transgender-identification and 60.0% of the friend groups were known to mock people who were not transgender or LGBTIA (lesbian, gay, bisexual, transgender, intersex, or asexual).

For the question about popularity changes when the child came out as having a transgender-identification, 79 participants provided optional open text responses which were categorized as: descriptions of the responses the child received (39); descriptions of the friends (14); description that the child did not "come out" to friends (8); not sure (9); speculation on how the child felt from the response (4), other (5). Of the 39 descriptions of responses, 19 of these responses referred to positive benefits the child received after coming out including positive attention, compliments, increased status, increased popularity, increased numbers of online

Table 6. Friend group exposure.

Characteristics		n	%
The AYA has been part of a friend group where one or more friends has come out as transgender around a similar timeframe as they did		254	
	Yes	176	69.3
	No	47	18.5
	Don't know	31	12.2
Age of AYA when their first friend became transgender-identified (range)	14.4 average (11–21)	174	
Number of friends from the friendship group who became gender dysphoric average (range)	3.5 average (2–10)	138	
Where numbers known, friend groups where the MAJORITY of the friends in the friendship group became transgender-identified		125	
	Yes	46	36.8
	No	79	63.2
Order of the AYAs "coming out" compared to the others in the friendship group		119	
	First in the friendship group	4	3.4
	Second in the friendship group	52	43.7
	Third in the friendship group	33	27.7
	Fourth in the friendship group	18	15.1
	Fifth in the friendship group	5	4.2
	Sixth or Seventh in the friendship group	6	5.0
Where popularity status known, change in popularity within friend group when AYA announced their transgender-identification		178	
	Increased popularity	108	60.7
	Decreased popularity	11	6.2
	Unchanged popularity	59	33.1
Where friend group activities known, friend group known to mock people who are not transgender/LGBT		145	
	Yes	87	60.0
	No	58	40.0

https://doi.org/10.1371/journal.pone.0202330.t006

followers, and improved protection from ongoing bullying. The following are quotes from parents about the perceived benefits of transgender-identification afforded to their child. One respondent said, "Great increase in popularity among the student body at large. Being trans is a gold star in the eyes of other teens." Another respondent explained, "not so much 'popularity' increasing as 'status'. . .also she became untouchable in terms of bullying in school as teachers who ignored homophobic bullying . . .are now all at pains to be hot on the heels of any trans bullying." Seven respondents described a mixed response where the child's popularity increased with some friends and decreased with others. Seven respondents described a neutral response such as "All of the friends seemed extremely accepting." Two described a temporary increase in their child's popularity: "There was an immediate rush of support when he came out. Those same friends have dwindled to nothing as he rarely speaks to any of them now." Another described the loss of friends. And two parents described that "coming out" prevented the loss of friends explained by one respondent as "to not be trans one would not have been included in his group."

Several AYAs expressed significant concern about the potential repercussions from their friend group when they concluded that they were not transgender after all. There were two unrelated cases with similar trajectories where the AYAs spent some significant time in a different setting, away from their usual friend group, without access to the internet. Parents described that these AYAs made new friendships, became romantically involved with another person, and during their time away concluded that they were not transgender. In both cases, the adolescents, rather than face their school friends, asked to move and transfer to different high schools. One parent said that their child, ". . .couldn't face the stigma of going back to school and being branded as a fake or phony. . . . Or worse, a traitor or some kind of betrayer. . .[and] asked us if we could move." In the other case, the parent relayed that their child thought none of the original friends would understand and expressed a strong desire to ". . .get out of the culture that 'if you are cis, then you are bad or oppressive or clueless.'" Both families were able to relocate and both respondents reported that their teens have thrived in their new environments and new schools. One respondent described that their child expressed relief that medical transition was never started and felt there would have been pressure to move forward had the family not moved away from the peer group.

Qualitative analysis

The open-ended responses from the question about whether the AYAs and friends mocked, teased, or made fun of individuals who weren't transgender or LGBTIA was selected for additional qualitative analysis. Seven major themes were identified from the comments provided by participants and are described, with representative supporting quotes.

Theme: Groups targeted. The groups targeted for mocking by the friend groups are often heterosexual (straight) people and non-transgender people (called "cis" or "cisgender"). Sometimes animosity was also directed towards males, white people, gay and lesbian (non-transgender) people, aromantic and asexual people, and "terfs". One participant explained, "They are constantly putting down straight, white people for being privileged, dumb and boring." Another participant elaborated, "In general, cis-gendered people are considered evil and unsupportive, regardless of their actual views on the topic. To be heterosexual, comfortable with the gender you were assigned at birth, and non-minority places you in the 'most evil' of categories with this group of friends. Statement of opinions by the evil cis-gendered population are consider phobic and discriminatory and are generally discounted as unenlightened."

Theme: Individuals targeted. In addition to targeting specific groups of people for mocking, the AYAs and their friend groups also directed mocking towards individuals in the AYAs' lives such as parents, grandparents, siblings, peers, allies, and teachers. The following quotes describe individuals targeted. One participant said, "They call kids who are not LGBT dumb and cis. And the mocking has been aimed at my transgender-identified child's [sibling]." Another parent said, "They definitely made fun of parents and teachers who did not agree with them." And a third participant said, ". . .they were asked to leave [a school-based LGBT club] because they were not queer enough [as straight and bisexual allies]. [One of them] was [then] bullied, harassed and denounced online."

Theme: Behaviors occurred both in person and in online settings. Parents observed the behaviors both in-person and in online settings, and specifically mentioned seeing posts and conversations on Tumblr, Twitter, Facebook, and Instagram. On participant said, "They speak with derision about how cis-gendered people do not understand them and are so close-minded." Another participant said, "I hear them disparaging heterosexuality, marriage and nuclear families." Another participant said, "On my daughter's Tumblr blog, she has liked or favorited or re-posted disparaging comments about those who aren't transgender or seem to

misunderstand the transgender identity." And another parent reported, "Her real life friends don't [mock non-LGBT people] but online they are always swapping jokes and comments about cisgender and about transphobia."

Theme: Examples of behaviors. Participants gave many examples of the observed behaviors that were mocking towards non-transgender people and non-LGB people. One participant said, "My daughter called me a 'breeder' and says things in a mocking 'straight person voice'. Her friends egg her on when she does this." Another parent offered, "If they aren't mocking 'cis' people, they are playing pronoun police and mocking people who can't get the pronouns correct." Another participant said, "New vocabulary includes 'cis-stupid' and 'cis-stupidity.'" And a fourth participant described, "They assume anyone that is critical about being transgender (even just asking questions) is either ignorant or filled with hate."

Theme: Emphasizing victimhood. Participants described that their children and friend group seemed to focus on feeling as though they were victims. One participant described, "They seem to wear any problems they may have, real or perceived like badges of honor. . .I feel like they want to believe they are oppressed & have really 'been through life', when they have little life experience." Another participant said, ". . .there is a lot of feeling like a victim [and being] part of a victimized club." Another parent said "But all talk is very 'victim' centered". And finally, another said, "They passionately decry 'Straight Privilege' and 'White Male Privilege'—while emphasizing their own 'Victimhood.'"

Theme: Consequences of behaviors. A few participants describe that because of their child's behavior, there were consequences, including making it difficult for one child to return to her school and the following description from another parent, "Most relatives have blocked her on [social media] over constant jokes regarding cis and straight people."

Theme: Fueling the behaviors. In some cases, parents describe a synergistic effect of kids encouraging other kids to persist in the behavior as was described in a previous quote, "Her friends egg her on when she does this" as well as the following, "Lots of discussion revolving around how their teachers 'discriminate' or are 'mean' to them based on their declared LGBTIA identity, and they get each other riled up convincing each other of their persecution by these perceived wrongs . . . privately they mock our intolerance, and in person act upon these false beliefs by treating us as people out to get them. . ."

Internet/social media exposure

In the time period just before announcing that they were transgender, 63.5% of AYAs exhibited an increase in their internet/social media (Table 7). To assess AYA exposure to existing online content, parents were asked what kind of advice their child received from someone/people online. AYAs had received online advice including how to tell if they were transgender (54.2%); the reasons that they should transition right away (34.7%); that if their parents did not agree for them to take hormones that the parents were "abusive" and "transphobic" (34.3%); that if they waited to transition they would regret it (29.1%); what to say and what not to say to a doctor or therapist in order to convince them to provide hormones (22.3%); that if their parents were reluctant to take them for hormones that they should use the "suicide narrative" (telling the parents that there is a high rate of suicide in transgender teens) to convince them (20.7%); and that it is acceptable to lie or withhold information about one's medical or psychological history from a doctor or therapist in order to get hormones/get hormones faster (17.5%). Two respondents, in answers to other questions, described that their children later told them what they learned from online discussion lists and sites. One parent reported, "He has told us recently that he was on a bunch of discussion lists and learned tips there. Places where teens and other trans people swap info. Like to use [certain, specific] words [with] the

Table 7. Internet/Social media exposures.

		n	%
AYAs internet/social media use just prior to announcement		255	
	Increased social media/internet use	162	63.5
	Decreased social media/internet use	3	1.2
	Unchanged social media/internet use	49	19.2
	Don't know	41	16.1
AYA exposure to internet content/advice*		251	
	How to tell if they are transgender	136	54.2
	The reasons that they should transition right away	87	34.7
	That if their parents did not agree to take them for hormones, that the parents are "abusive" and "transphobic"	86	34.3
	That if they waited to transition they would regret it	73	29.1
	That if they didn't transition immediately they would never be happy	72	28.7
	How to order physical items (binders, packers, etc) without parents finding out	67	26.7
	What to say and what NOT to say to a doctor or therapist in order to convince them to provide hormones	56	22.3
	That if their parents are reluctant to take them for hormones, that they should use the "suicide narrative" to convince them (telling the parents that there is a high rate of suicide in transgender teens.)	52	20.7
	Medical advice about the risks and benefits of hormones	55	21.9
	Medical advice about the risks and benefits of surgery	47	18.7
	That it is acceptable to lie to or withhold information about one's medical or psychological history from a doctor or therapist in order to get hormones/ get hormones faster	44	17.5
	How to hide physical items from parents	40	15.9
	How to hide or make excuses for physical changes	26	10.4
	How to get money from others online in order to pay for medications, etc	25	10.0
	How to get hormones from online sources	24	9.6
	How to hide hormones from parents	21	8.4
	I don't know if my child received online advice about these topics	127	50.6

*may select more than one answer.

https://doi.org/10.1371/journal.pone.0202330.t007

therapist when describing your GD, because [they are] code for potentially suicidal and will get you a diagnosis and Rx for hormones." Another parent disclosed, "The threat of suicide was huge leverage. What do you say to that? It's hard to have a steady hand and say no to medical transition when the other option is dead kid. She learned things to say that would push our buttons and get what she wanted and she has told us now that she learned that from trans discussion sites."

Parents identified the sources they thought were most influential for their child becoming gender dysphoric. The most frequently answered influences were: YouTube transition videos (63.6%); Tumblr (61.7%); a group of friends they know in person (44.5%); a community/group of people that they met online (42.9%); a person they know in-person (not online) 41.7%. In contrast to the majority of responses, two participants commented that they didn't think the

sources influenced their child to become gender dysphoric, rather they gave their child a name for their feelings or gave the child confidence to come out. The following quotes illustrate the dominant quantitative findings. One parent wrote, "We believe the biggest influence was the online pro-transition blogs and youtube videos. We feel she was highly influenced by the 'if you are even questioning your gender-you are probably transgender' philosophy. . .In the 'real world' her friends, other trans peers, and newfound popularity were additional areas of reinforcement." Another respondent described the online influence as part of a different question, "I believe my child experienced what many kids experience on the cusp of puberty—uncomfortableness!—but there was an online world at the ready to tell her that those very normal feelings meant she's in the wrong body."

Mental well-being, mental health, and behaviors

The trajectories of the AYAs were not consistent with the narrative of discovering one's authentic self and then thriving. Specifically, parents reported that, after "coming out," their children exhibited a worsening of their mental well-being. Additionally, parents noted worsening of the parent-child relationship and observed that their children had narrowed their interests (Table 8). Although small numbers of AYAs had improvement in mental well-being (12.6%), parent-child relationship (7.4%), grades/academic performance (6.4%), and had broadened their interests and hobbies (5.1%); the most common outcomes were worsened mental well-being (47.2%); worsened parent child relationship (57.3%); unchanged or mixed grades/academic performance (59.1%); and a narrowed range of interests and hobbies

Table 8. Outcomes and behaviors.

Characteristics		n	%
AYA mental well-being since announcement		254	
	Worse	120	47.2
	Better	32	12.6
	Unchanged or mixed	101	39.8
	Don't know	1	0.4
Parent-child relationship since announcement		253	
	Worse	145	57.3
	Better	18	7.4
	Unchanged or mixed	89	35.2
	Don't know	1	0.4
Grades/academic performance		220	
	Worse	76	34.5
	Better	14	6.4
	Unchanged/mixed	130	59.1
Range of interests and hobbies		255	
	Much broader	2	0.8
	Somewhat broader	11	4.3
	Unchanged	93	36.5
	Somewhat narrower	64	25.1
	Much narrower	56	22.0
	There are very few topics outside of transgender issues that my child is interested in	28	11.0
	Don/t know	1	0.4

https://doi.org/10.1371/journal.pone.0202330.t008

(58.1%). One parent describing her child's trajectory offered, "After announcing she was transgender, my daughter's depression increased significantly. She became more withdrawn. She stopped participating in activities which she previously enjoyed, stopped participating in family activities, and significantly decreased her interaction with friends. Her symptoms became so severe that she was placed on medication by her physician." Table 9 describes cumulative rates of mental illness and neurodevelopmental disability at the time of survey.

A total of 63.8% of the parents have been called "transphobic" or "bigoted" by their children for one or more reasons, the most common being for: disagreeing with the child about the child's self-assessment of being transgender (51.2%); recommending that the child take more time to figure out if their feelings of gender dysphoria persist or go away (44.6%); expressing concerns for the child's future if they take hormones and/or have surgery (40.4%); calling their child by the pronouns they used to use (37.9%); telling the child they thought that hormones or surgery would not help them (37.5%); recommending that their child work on other mental health issues first to determine if they are the cause of the dysphoria (33.3%); calling the child by their birth name (33.3%); or recommending a comprehensive mental health evaluation before starting hormones and/or surgery (20.8%) (Table 10). There were eight cases of estrangement. Estrangement was child-initiated in six cases where the child ran away, moved out, or otherwise refused contact with parent. There were two cases where the estrangement was initiated by the parent because the AYA's outbursts were affecting younger siblings or there was a threat of violence made by the AYA to the parent.

AYAs are reported to have exhibited one or more of the following behaviors: expressed distrust of information about gender dysphoria and transgenderism coming from mainstream doctors and psychologists (51.8%); tried to isolate themselves from their family (49.4%); expressed that they only trust information about gender dysphoria and transgenderism that comes from transgender websites and/or transgender people and sources (46.6%); lost interest in activities where participants aren't predominantly transgender or LGBTIA (32.3%); stopped spending time with friends who were not transgender (25.1%); expressed distrust of people who were not transgender (22.7%) (Table 10). Many AYAs have also: withdrawn from their family (45.0%); told other people or posted on social media that their parent is "transphobic," "abusive," or "toxic" because the parent does not agree with child's self-assessment of being transgender (43.0%); refused to speak to their parent (28.5%), defended the practice of lying to or withholding information from therapists or doctors in order to obtain hormones for transition more quickly (16.5%); tried to run away (6.8%). The behaviors and outcomes listed above

Table 9. AYA Cumulative mental disorder and neurodevelopmental disability diagnoses.

Characteristics		n	%
Mental disorder or neurodevelopmental disability		243	
	Anxiety	154	63.4
	Depression	143	58.8
	Attention Deficit Hyperactivity Disorder (ADHD)	36	14.8
	Obsessive Compulsive Disorder (OCD)	30	12.3
	Autism Spectrum Disorder (ASD)	30	12.3
	Eating Disorder	17	7.0
	Bipolar Disorder	17	7.0
	Psychosis	8	3.3
	None of above	52	21.4
	(Other) Borderline	7	2.9
	(Other) Oppositional Defiant Disorder	2	0.8

https://doi.org/10.1371/journal.pone.0202330.t009

Table 10. Additional behaviors.

		n	%
Parents have been called "transphobic" or "bigoted" by their child for the following reasons*		240	
	Disagreeing with their child about the child's assessment of being transgender	123	51.2
	Recommending that their child take more time to figure out if their feelings of gender dysphoria persist or go away	107	44.6
	Expressing concerns for their child's future if the child were to take hormones and/or have surgery	97	40.4
	Referring to their child by the pronouns that they used to use before announcement	91	37.9
	Telling their child that they thought hormones/surgery would not help them	90	37.5
	Calling their child by the child's birth name	80	33.3
	Recommending that their child work on other mental health issues first to determine if they are the cause of their dysphoria	80	33.3
	Recommending therapy for basic mental health issues (not related to gender)	74	30.8
	Recommending a comprehensive evaluation before starting hormones and/or surgery	50	20.8
	None of the above	87	36.2
Distrust and isolating behaviors exhibited by AYAs*		251	
	Expressed distrust of information about gender dysphoria and transgenderism coming from mainstream doctors and psychologists	130	51.8
	Tried to isolate themselves from their family	124	49.4
	Expressed that they ONLY trust information about gender dysphoria and transgenderism that comes from transgender websites and/or transgender people and sources	117	46.6
	Lost interest in activities where participants aren't predominantly transgender or LGBTIA	81	32.3
	Lost interest in activities that were not related to transgender or LGBTIA issues	65	25.9
	Stopped spending time with friends who are not transgender	63	25.1
	Expressed distrust of people who are not transgender	57	22.7
	Expressed hostility towards people who are not transgender	46	18.3
	None of the above	44	17.5
Other behavior and outcomes for AYAs*		249	
	Withdrawn from family	112	45.0
	Told other people or posted on social media that their parent is "transphobic", "abusive", or "toxic" because the parent does not agree with the child's assessment of being transgender	107	43.0
	Refused to speak to parent	71	28.5
	Defended the practice of lying to or withholding information from therapists or doctors in order to obtain hormones for transition more quickly	41	16.5
	Tried to run away	17	6.8
	Been unable to obtain a job	25	10.0
	Been unable to hold a job	18	7.2
	Dropped out of college	12	4.8
	Dropped out of high school	12	4.8
	Needed to take a leave of absence from college	12	4.8
	Been fired from a job	9	3.6
	Needed a leave of absence from high school	1	0.4
	None of the above	86	34.5
For any of the above, is this a significant change from the child's baseline behavior?		161	
	Yes	115	71.4
	No	46	28.6

*may select more than one answer.

https://doi.org/10.1371/journal.pone.0202330.t010

were considered significant changes from the child's baseline behaviors for 71.4% of respondents checking any of the items.

There was a subset of eight cases where parents described watching their child have declining mental well-being as they became gender dysphoric and transgender-identified and then had improving mental well-being as they dropped or backed away from a transgender-identification. One parent described a marked change in her daughter when she was out of school temporarily. "[Her] routine was disrupted. She spent all day on the internet, and lost her many school friends—her only friends were on-line and members of the trans community. In three months, my daughter announced she is trans, gender dysphoric, wants binders and top surgery, testosterone shots. . .she started self-harming. Now back at school. . .she tweeted that she's so young, isn't sure if she is trans, no longer wants to be referred to by the male name she had chosen. . .Since she has started back at school and is being exposed to a wide variety of people she is WAY happier." Another parent described, "My daughter's insight has improved considerably over the last few years, and she has also outgrown the belief that she is transgender. My daughter actually seemed to be looking for a reason for her depression which is now being successfully treated. . .My daughter is MUCH happier now that she is being treated for her genuine issues. Coming out as trans made her much worse for a while."

There was a subset of 30 cases where the AYAs' transgender-identification occurred in the context of a decline in their ability to function (such as dropping out of high school or college, needing a leave of absence from high school or college, and/or being unable to obtain or hold a job), which parents reported as a significant change from their child's baseline behavior. The declines were substantial as 43.3% of these AYAs had been identified as academically gifted students (some described as top of their class in high school, earning outstanding grades at prestigious universities) before they began to fail their classes, drop out of high school or college, and became unable to hold a job. In most of these cases (76.7%), there was one or more psychiatric diagnosis made at the same time or within the year (60.0%) or within two years (16.7%) of the AYA's new transgender-identification. Of the 23 individuals who had a psychiatric diagnosis made within two years of assuming a transgender-identification, 91.3% (21/23) were diagnosed with depression; 73.9% (17/23) with anxiety; 26.0% (6/23) with bipolar disorder; 17.4% (4/23) with borderline personality disorder; 8.7% (2/23) with psychosis/psychotic episode: and 8.7% (2/23) with an eating disorder.

Clinical encounters

Parents were asked if their child had seen a gender therapist, gone to a gender clinic, or seen a physician for the purpose of beginning transition and 92 respondents (36.2%) answered in the affirmative (Table 11). Many of the respondents clarified that their child had seen a clinician regarding their gender dysphoria for evaluation only. Although participants were not asked directly what kind of provider their child saw, specialties that were mentioned in answers included: general psychologists, pediatricians, family doctors, social workers, gender therapists, and endocrinologists. For parents who knew the content of their child's evaluation, 71.6% reported that the clinician did not explore issues of mental health, previous trauma, or any alternative causes of gender dysphoria before proceeding and 70.0% report that the clinician did not request any medical records before proceeding. Despite all of the AYAs in this study sample having an atypical presentation of gender dysphoria (no gender dysphoria prior to puberty), 23.8% of the parents who knew the content of their child's visit reported that the child was offered prescriptions for puberty blockers and/or cross-sex hormones at the first visit.

One participant described, "For the most part, I was extremely frustrated with providers NOT acknowledging the mental disorder, anxiety, depression, etc before recommending

Table 11. Interactions with clinicians.

		n	%
Did the AYA see a gender therapist, go to a gender clinic or see a physician for the purpose of transition?		254	
	No	151	59.4
	Yes	92	36.2
	Don't know	11	4.3
Did the therapist/physician/clinic staff explore issues of mental health, previous trauma, or any alternative causes of gender dysphoria before proceeding?		100	
	Yes	21	21.0
	No	53	53.0
	Don't know	26	26.0
Did the therapist/physician/clinic staff request any medical records before proceeding?		99	
	Yes	21	21.2
	No	49	49.5
	Don't know	29	29.3
Of parents who knew the content of the visit, did the AYA receive an Rx for puberty blockers and/or cross-sex hormones at their first visit?		80	
	AYA received an Rx for puberty blockers and/or cross-sex hormones at their first visit	17	21.2
	AYA was offered a Rx for puberty blockers and/or cross-sex hormones at their first visit, but AYA or parent declined	2	2.5
	Total number of AYAs who received or were offered an Rx at first visit	19	23.8
	AYAs who did not receive/were not offered an Rx at their first visit	61	76.2
Did AYA misrepresent their history to the doctor or relay their history accurately?		96	
	Parent is reasonably sure or positive that their child misrepresented or omitted parts of their history	64	66.7
	Parent is reasonable sure or positive that their child relayed their history completely and accurately	12	12.5
	Don't know	20	20.8

https://doi.org/10.1371/journal.pone.0202330.t011

hormone replacement therapy." And two participants described how the clinician treating their child's gender dysphoria refused to speak with the patients' primary care physicians. One participant said, "When we phoned the clinic, the doctor was hostile to us, told us to mind our own business. Our family doctor tried to reach our son's new doctor, but the trans doctor refused to speak with her." Another respondent shared "The pediatrician/'gender specialist' did not return calls or emails from the primary care physician who requested to talk with her about my son's medical history before she saw and treated him. . .she disregarded all historical information provided by the family and primary care physician. . .did not verify any information provided by my. . .son at his first visit even after being provided with multiple other historical sources which differed significantly from his story."

When asked about whether their child relayed their history completely and accurately to clinicians or whether they misrepresented or omitted parts of their history, of those who knew the content of their child's visit, 84.2% of the parent respondents were reasonably sure or positive that their child had misrepresented or omitted parts of their history. Twenty-eight participants provided optional open text responses to this question and the responses were categorized into: describing how the parent knew that the child misrepresented their history

(5); the content of what the child misrepresented (6 misrepresenting in general, 4 misrepresenting to the clinician for a total of 10 examples); don't know/not sure (4); expressing certainty (1); and not relevant (8). For the five participants describing how they knew, the reasons included: being present when it happened, reading the report from the gender specialist, being told by their child that the child had misrepresented the truth, and being informed by the child's psychiatrist. One respondent shared, "I have read the report from the gender specialist and it omits all the relevant context painting an almost unrecognizable picture of my son." A second parent simply responded, "I was present." Another respondent relayed about their (natal male) child, "My daughter told me and her mother that the first therapist she saw asked her stereotypical questions. . .She was afraid that if she didn't describe herself as a 'typical girl' she would not be believed." And finally, one respondent wrote, "He has said now that he did [misrepresent his history] and used key words he was advised to say." Ten participants provided 13 examples of the content of misrepresentations and of these, 6 examples could have been easily verified to be false (claiming to be under the care of a psychiatrist, claiming to be on medication to treat a psychiatric condition, how one was doing academically, and claiming a childhood history of having playmates of one sex when the opposite was observed, and claiming strong childhood preferences for specific toys and clothing that is the opposite of what multiple individuals observed). Three of the content examples would have been challenging to verify as false including: how one was feeling as a child, how one was feeling when a picture was taken, and whether one was from an abusive home. And four of the content examples did not provide enough information to determine if they would be easy or challenging to verify as false, such as "My child distorts her history and our family life on a regular basis," and "He has created an entire narrative that just isn't true."

In addition to the previously mentioned case where the child literally rewrote her history by editing her diary, there were seven respondents who conveyed a process where their child was constantly rewriting their personal history to make it consistent with the idea that they always were transgender and/or had created a childhood history that was not what others had observed. It is unclear whether this process was deliberate or if the individuals were unaware of their actions. The following are quotes describing this phenomenon. One parent said, ". . .she is actively rewriting her personal history to support the idea that she was always trans." Another respondent added,". . .my daughter denies events I recollect from her childhood and puberty that contradicts her narrative of 'always knowing she was a boy.'" Another respondent offered, "He is rewriting his personal history to suit his new narrative." And a fourth respondent described, "[Our] son has completely made up his childhood to include only girl friends and dressing up in girls clothes and playing with dolls, etc. This is not the same childhood we have seen as parents."

Qualitative analysis

The open-ended comments from the question about whether the clinician explored mental health, trauma or alternative causes of gender dysphoria before proceeding were selected for qualitative analysis. Nine major themes emerged from the data. Each theme is described in the following paragraphs with supporting quotes from participants.

Theme: Failure to explore mental health, trauma or alternative causes of GD. Parents described that clinicians failed to explore their child's mental health, trauma, or any alternative causes for the child's gender dysphoria. This failure to explore mental health and trauma occurred even when patients had a history of mental health disorder or trauma, were currently being treated for a mental health disorder, or were currently experiencing symptoms. One participant said, "Nothing other than gender dysphoria was considered to explain my daughter's

desire to transition." Another participant said, "My daughter saw a child therapist and the therapist was preparing to support transgendering and did not explore the depression and anxiety or previous trauma."

Theme: Insufficient evaluation. Another theme was insufficient evaluation where parents described evaluations that were too limited or too superficial to explore mental health, trauma or alternative causes of gender dysphoria. The following are three quotes by three different parents describing insufficient evaluations. One parent said, "The exploration was egregiously insufficient, very shallow, no effort to ask questions, engage in critical thinking about coexisting anxiety, or put on the brakes or even slow down." Another participant stated, "When we tried to give our son's trans doctor a medical history of our son, she refused to accept it. She said the half hour diagnosis in her office with him was sufficient, as she considers herself an expert in the field." And a third parent wrote, "We were STUNNED by the lack of information, medical history sought by therapist and radical treatment suggestion. [One]visit. The idea is, 'if they say they were born in the wrong body, they are. To question this will only hurt her and prolong her suffering.' [Our] daughter has had trauma in [the] past. [She] never was asked about it. [The] therapist did not ask parents a single question about our daughter."

Theme: Unwillingness or disinterest in exploring mental health, trauma or alternative causes of GD. Parents described that clinicians did not seem interested or willing to explore alternative causes. One parent described. "Her current therapist seems to accept her self diagnosis of gender dysphoria and follows what she says without seeming too much interested in exploring the sexual trauma in her past." Another parent wrote, "The Asperger psychiatrist did not seem to care whether our daughter's gender dysphoria stemmed from Asperger's. If our daughter wanted to be male, then that was enough." And a third parent said. "The therapist did ask about those issues but seemed to want to accept the idea wholeheartedly that my daughter was transgender first and foremost, all other factors aside."

Theme: Mental health was explored. A few parents had the experience where the clinician either made an appropriate referral for further evaluation or the issues had been addressed previously. One parent said, "[The] previous mental health issues [were] already explored by other therapists ([my] child was in therapy and medicated before coming out as transgender)."

Theme: Failure to communicate with patients' medical providers. Several participants described clinicians who were unwilling to communicate with primary care physicians and mental health professionals even those professionals who were currently treating the patient. One participant relayed, "She did not review the extensive psychiatric records that were available in a shared EMR [electronic medical record] and she did not consult with his outpatient psychiatrist prior to or after starting cross-sex hormonal therapy." Another parent said, "My child had been seen for mental health issues for several years before presenting this new identity, but the endocrinologist did not consult the mental health professionals for their opinions before offering hormones."

Theme: Misrepresentation of information by the patient. Several participants described how their child misrepresented their history to the clinician, thus, limiting the clinician's ability to adequately explore mental health, trauma and alternative causes. One participant wrote, "At [the] first visit, [my] daughter's dialogue was well-rehearsed, fabricated stories about her life told to get [the] outcome she desired. She parroted people from the internet." Another parent reported, "My son concealed the trauma and mental health issues that he and the family had experienced." And a third parent said, "I overheard my son boasting on the phone to his older brother that 'the doc swallowed everything I said hook, line and sinker. Easiest thing I ever did.'"

Theme: Transition steps were pushed by the clinician. Some parents described clinicians who seemed to push the process of transition before the patient asked for it. One parent described that the doctor gave her daughter a prescription that she didn't ask for, "The family

doctor who gave her the Androgel Rx [prescription] did NOT ask her many questions (she was surprised by this), nor did he await her assessment by a licensed psychiatrist before giving her this Rx. Nor did she ask him for this Rx." Another parent reported that she and her child were at the endocrinologist's office only to ask questions, and described, ". . .[he] didn't listen to a word we were saying. He was too eager to get us set up with a 'gender therapist' to get the legal form he needed to start hormones, all while making sure we set up our next appointment within 6 months to start the hormones. . ."

Theme: Parent views were discounted or ignored. Parents describe that the clinicians did not take their concerns seriously. One parent described, "I have to say I don't know, but it is hard to believe that they adequately examined the history of bullying and being ostracized for being different, and the autistic traits that would lend a person like my son to risk everything for identifying with a group. I know that in the few contacts I had with the providers, my concerns were discounted." And another said, "All of our emails went unanswered and were ignored. We are left out of everything because of our constant questioning of this being right for our daughter [because of her] trauma and current depression, anxiety and self-esteem problems."

Theme: Parent had concerns about the clinicians' competence, professionalism or experience. Parents expressed doubts about the clinicians regarding their experience, competence or professionalism. One parent said, "The clinic told me they explored these issues. I asked the risk manager at [redacted] if they'd considered a personality disorder. 'Oh, no,' she laughed. 'That's only with the older patients, not the teenagers.' I'm deeply suspicious of their competence." Another parent described, "What does concern me is that the people she talked to seemed to have no sense of professional duties, but only a mission to promote a specific social ideology."

Steps towards transition and current identification status

This section reports on the duration of AYA transgender-identification (time from the AYA's announcement of a transgender identity until the time the parent completed the survey) that covers, on average, 15.0 months (range 0.1–120 months) with a median of 11 months (Table 12). The steps taken towards transition during this timeframe are listed in Table 12. At the end of the timeframe, 83.2% of the AYAs were still transgender-identified, 5.5% were not still transgender-identified (desisted), 2.7% seemed to be backing away from transgender-identification, and 8.6% of the parents did not know if their child was still identifying as transgender. Descriptions of backing away or moving from transgender-identified to not transgender-identified include the following. One parent observed, "She identified as trans for six months . . . Now back at school, she is thinking maybe she's not trans." Another parent offered, "My daughter [identified] as trans from ages 13–16. She gradually desisted as she developed more insight into who she is." One parent described that after one year of identifying as transgender, "basically, she changed her mind once she stopped spending time with that particular group of friends." The duration of transgender-identification of the AYAs who were still transgender-identified at the time of survey was compared to the duration of those who were no longer transgender-identified and those who seemed to be backing away from a transgender-identification (combined) by t-test. The difference between these groups was statistically significant ($p = .025$), with a t-value of -2.25 showing that those who were no longer transgender-identified and backing away had a longer duration of identification (mean = 24.1 months) and those who were still transgender-identified had a shorter mean duration (mean = 14.4 months).

To explore the differences between the AYAs who had exposure to social influence (friend group, internet/social media, or both) and AYAs who did not have a clear exposure to social influence (neither and don't know), a series of chi-squared calculations were performed for

Table 12. Transition steps and disposition.

		n	%
Transition Steps*		256	
	Changed hairstyle	216	84.4
	Changed style of clothing	210	82.0
	Asks to be called a new name	188	73.4
	Asks for different pronouns	175	68.4
	Taken cross-sex hormones	29	11.3
	Legally changed name on government documents	19	7.4
	Taken anti-androgens	11	4.3
	Taken puberty blockers	7	2.7
	Had surgery	5	2.0
	None of the above	14	5.5
Disposition		256	
	Still transgender-identified	213	83.2
	Not transgender-identified any more (desisted)	14	5.5
	Seems to be backing away from transgender-identification	7	2.7
	Parent doesn't know if the child is still transgender-identified	22	8.6
	De-transitioned (also counted in desisted category)	3	1.2
Duration of transgender-identification overall	Median duration 11 months, Mean duration 15.0 months (range 0.1 months-120 months), median 11 months	225	
Duration of transgender-identification if still transgender-identified	Median duration 11 months, mean duration 14.4 months, ange (0.1 months-72 months)	204	
Duration of transgender-identification if no longer transgender-identified	Median duration 12 months, mean duration 24.2 months, range (.75 months to 120 months)	13	
Duration of transgender-identification if backing away	Median duration 12 months, mean duration 15 months, range (3 months-36 months)	8	

*may select more than one answer.

https://doi.org/10.1371/journal.pone.0202330.t012

selected variables. (See Table 13.) Statistically significant differences were revealed for AYAs with exposure to social influences having worse outcomes for mental well-being and parent-child relationships, and greater numbers exhibiting distrust, isolating and anti-social behaviors including: narrowed range of interests and hobbies, expressing that they only trusted information from transgender sources, trying to isolate themselves from their family, losing interest in activities that weren't predominantly with transgender or LGBTIA participants, and telling people or posting on social media that their parent is "transphobic," "abusive," or "toxic" because the parent doesn't agree with the child's assessment of being transgender. Although the differences in additional isolating and anti-social behaviors did not reach statistical significance, these behaviors trended towards higher rates in the AYAs who were exposed to social influence and may have not reached significant levels due to small numbers. No significant difference for age of AYA (at announcement or at time of survey completion) was detected between groups by a one-way ANOVA.

Discussion

This research describes parental reports about a sample of AYAs who would not have met diagnostic criteria for gender dysphoria during their childhood but developed signs of gender dysphoria during adolescence or young adulthood. The strongest support for considering that the gender dysphoria was new in adolescence or young adulthood is the parental answers for

Table 13. chi-squared comparisons for exposure to social influence (SI) vs not exposure to social influence (NSI).

		SI n (%)	NSI n (%)	p
Sex		222	34	.123
	Female	187 (84.2)	25 (73.5)	
	Male	35 (15.8)	9 (26.5)	
Indicators of childhood GD		221	33	**.004**
	0–2 indicators	**216 (97.7)**	**29 (87.9)**	
	3–4 indicators	**5 (2.3)**	**4 (12.1)**	
Currently have two or more GD indicators		214	34	.808
	Yes	179(83.6)	29 (85.3)	
	No	35(16.4)	5(14.7)	
No mental health or NDD diagnoses before onset of GD		222	34	**.036**
	Answered "None of the above"	**87(39.9)**	**7 (20.6)**	
Mental well-being since announcement		220	33	**.001**
	Worse	**114 (51.8)**	**6 (18.2)**	
	Better	**24 (10.9)**	**8 (24.2)**	
	Unchanged/Mixed	**82 (37.3)**	**19 (57.6)**	
Parent-child relationship since announcement		219	33	**.006**
	Worse	**134 (61.2)**	**11 (33.3)**	
	Better	**13 (5.9)**	**5 (15.2)**	
	Unchanged/Mixed	**72 (32.9)**	**17 (51.5)**	
Range of interests and hobbies		**220**	**34**	**<0.001**
	Broader range of interests and hobbies	**10 (4.5)**	**3 (8.8)**	
	Narrowed range of interest and hobbies	**139 (63.2)**	**9 (26.5)**	
	Unchanged range	**71 (32.3)**	**22 (64.7)**	
Distrust and Isolating Behaviors		222	34	
	Tried to isolate themselves from family	**114(51.4)**	**10 (29.4)**	**.017**
	Expressed that they ONLY trust information about GD and transgenderism that comes from transgender sources	**107 (48.2)**	**10 (29.4)**	**.041**
	Lost interest in activities where participants aren't predominantly transgender or LGBTIA	**76 (34.2)**	**5 (14.7)**	**.023**
	Stopped spending time with non-transgender friends	59 (26.6)	4 (11.8)	.062
	Expressed distrust of people who are not transgender	52 (23.4)	5 (14.7)	.255
	Told people or posted on social media that their parent is "transphobic," "abusive," or "toxic" because the parent doesn't agree with the child's assessment of being transgender	**102 (45.9)**	**5 (14.7)**	**<0.001**
	Defended the practice of lying to or withholding information from doctors/therapists to get hormones for transition more quickly	38 (17.1)	3 (8.8)	.219
	Brought up the issue of suicide in transgender teens as a reason parents should agree to treatment	55 (24.8)	4 (11.8)	.093
Did the AYA misrepresent their history to the doctor or relay it accurately?		68	8	.075
	Parent is reasonable sure or positive that their child misrepresented or omitted parts of their history	59 (86.8)	5 (62.5)	
	Parent is reasonable sure or positive that child relayed their history completely and accurately	9 (13.2)	3 (37.5)	

https://doi.org/10.1371/journal.pone.0202330.t013

DSM 5 criteria for childhood gender dysphoria. Not only would none of the sample have met threshold criteria, the vast majority had zero indicators. Although one might argue that three of the indicators could plausibly be missed by a parent (A1, A7, and A8 if the child had not

expressed these verbally), five of the indicators (A2-6) are readily observable behaviors and preferences that would be difficult for a parent to miss. Six indicators (including A1) are required for a threshold diagnosis. The nonexistent and low numbers of readily observable indicators reported in the majority of this sample does not support a scenario in which gender dysphoria was always present but was only recently disclosed to the parents.

Parents reported that before the onset of their gender dysphoria, many of the AYAs had been diagnosed with at least one mental health disorder or neurodevelopmental disability and many had experienced a traumatic or stressful event. Experiencing a sex or gender related trauma was not uncommon, nor was experiencing a family stressor (such as parental divorce, death of a parent, or a mental health disorder in a sibling or parent). Additionally, nearly half were described as having engaged in self-harm prior to the onset of their gender dysphoria. In other words, many of the AYAs and their families had been navigating multiple challenges and stressors before gender dysphoria and transgender-identification became part of their lives. This context could possibly contribute to friction between parent and child and these complex, overlapping difficulties as well as experiences of same-sex attraction may also be influential in the development of a transgender identification for some of these AYAs. Care should be taken not to overstate or understate the context of pre-existing diagnoses or trauma in this population as they were absent in approximately one third and present in approximately two thirds of the sample.

This research sample of AYAs also differs from the general population in that it is predominantly natal female, white, and has an over-representation of individuals who are academically gifted, non-heterosexual, and are offspring of parents with high educational attainment [59–61]. The sex ratio favoring natal females is consistent with recent changes in the population of individuals seeking care for gender dysphoria. Gender clinics have reported substantial increases in referrals for adolescents with a change in the sex ratio of patients moving from predominantly natal males seeking care for gender dysphoria to predominantly natal females [26–28, 62]. Although increased visibility of transgender individuals in the media and availability of information online, with a partial reduction of stigma might explain some of the rise in the numbers of adolescents presenting for care [27], it would not directly explain why the inversion of the sex ratio has occurred for adolescents but not adults or why there is a new phenomenon of natal females experiencing late-onset and adolescent-onset gender dysphoria. The unexpectedly high rate of academically gifted AYAs may be related to the high educational attainment of the parents and may be a reflection of parents who are online, able to complete online surveys and are able to question and challenge current narratives about gender dysphoria and transition. There may be other unknown variables that render academically gifted AYAs susceptible to adolescent-onset and late-onset gender dysphoria. The higher than expected rate of non-heterosexual orientations of the AYAs (prior to announcement of a transgender-identity) may suggest that the desire to be the opposite sex could stem from experiencing homophobia as a recent study showed that being the recipient of homophobic name calling from one's peers was associated with a change in gender identity for adolescents [63]. The potential relationship of experienced homophobia and the development of a rapid onset of gender dysphoria during adolescence or young adulthood as perceived by parents deserves further study.

This sample is distinctively different than what is described in previous research about gender dysphoria because of the distribution of cases occurring in friendship groups with multiple individuals identifying as transgender, the preponderance of adolescent (natal) females, the absence of childhood gender dysphoria, and the perceived suddenness of onset. In this study, parental reports of transgender identification duration in AYAs suggest that in some cases (~8% in this study) gender dysphoria and transgender-identification may be temporary, and

that longer observation periods may be needed to assess such changes. Further research is needed to verify these results. There have been anecdotal reports of adolescents who desisted approximately 9–36 months after showing signs of a rapid onset of gender dysphoria, but longitudinal research following AYAs with gender dysphoria would be necessary to study desistance trends. Although it is still unknown whether transition in gender dysphoric individuals decreases, increases, or fails to change the rates of attempted or completed suicides [64], this study documents AYAs using a suicide narrative as part of their arguments to parents and doctors towards receiving support and transition services. Despite the possibility that the AYAs are using a suicide narrative to manipulate others, it is critical that any suicide threat, ideation or concern is taken seriously and the individual should be evaluated immediately by a mental health professional.

The majority of parents were reasonably sure or certain that their child misrepresented or omitted key parts of their history to their therapists and physicians. In some cases, the misrepresentation of one's history may simply be a deliberate act by a person who is convinced that transition is the only way that they will feel better and who may have been coached that lying is the only way to get what they think they need. For others, the misrepresentation may not be a conscious act. The creation of an alternate version of one's childhood that conforms to a story of always knowing one was transgender and that is in sharp contrast to the childhood that was observed by third parties raises the question of whether there has been the creation of false childhood memories as part of, or outside of, the therapy process. Respondent accounts of clinicians who ignored or disregarded information (such as mental health symptoms and diagnoses, medical and trauma histories) that did not support the conclusion that the patient was transgender, suggests the possibility of motivated reasoning and confirmatory biases on the part of clinicians. In the 1990s, the beliefs and practices of many mental health professionals may have contributed to their patients' creation of false childhood memories consistent with a child sexual abuse narrative and research since then has shown that false childhood memories of mundane events can be implanted in laboratory settings [65–67]. It may be worthwhile to explore if, in today's culture, there might be beliefs and practices of some mental health professionals that are contributing to their patients' creation of false childhood memories consistent with an "always knew/always were transgender" narrative.

Emerging hypotheses

Hypothesis 1: Social influences can contribute to the development of gender dysphoria

It is unlikely that friends and the internet can make people transgender. However, it is plausible that the following can be initiated, magnified, spread, and maintained via the mechanisms of social and peer contagion: (1) the *belief* that non-specific symptoms (including the symptoms associated with trauma, symptoms of psychiatric problems, and symptoms that are part of normal puberty) should be perceived as gender dysphoria and their presence as proof of being transgender; 2) the *belief* that the only path to happiness is transition; and 3) the *belief* that anyone who disagrees with the self-assessment of being transgender or the plan for transition is transphobic, abusive, and should be cut out of one's life. The spread of these beliefs could allow vulnerable AYAs to misinterpret their emotions, incorrectly believe themselves to be transgender and in need of transition, and then inappropriately reject all information that is contrary to these beliefs. In other words, "gender dysphoria" may be used as a catch-all explanation for any kind of distress, psychological pain, and discomfort that an AYA is feeling while transition is being promoted as a cure-all solution.

One of the most compelling findings supporting a potential role of social and peer contagion in the development or expression of a rapid onset of gender dysphoria is the clusters of transgender-identification occurring within friendship groups. The expected prevalence of transgender young adult individuals is 0.7% [8]. Yet, according to the parental reports, more than a third of the friendship groups described in this study had 50% or more of the AYAs in the group becoming transgender-identified in a similar time frame. This suggests a localized increase to more than 70 times the expected prevalence rate. This is an observation that demands urgent further investigation. One might argue that high rates of transgender-identified individuals within friend groups may be secondary to the process of friend selection: choosing transgender-identified friends deliberately rather than the result of group dynamics and observed coping styles contributing to multiple individuals, in a similar timeframe, starting to interpret their feelings as consistent with being transgender. More research will be needed to finely delineate the timing of friend group formation and the timing and pattern of each new declaration of transgender-identification. Although friend selection may play a role in these high percentages of transgender-identifying members in friend groups, the described pattern of multiple friends (and often the majority of the friends in the friend group) *becoming* transgender-identified in a similar timeframe suggests that there may be more than just friend selection behind these elevated percentages.

There are many insights from our understanding of peer contagion in eating disorders and anorexia that may apply to the potential role(s) of peer contagion in the development of gender dysphoria. Just as friendship cliques can set the level of preoccupation with one's body, body image, weight, and techniques for weight loss [37–39], so too may friendship cliques set a level of preoccupation with one's body, body image, gender, and the techniques to transition. The descriptions of pro-anorexia subculture group dynamics where the thinnest anorexics are admired while the anorexics who try to recover from anorexia are ridiculed and maligned as outsiders [39–41] resemble the group dynamics in friend groups that validate those who identify as transgender and mock those who do not. And the pro-eating-disorder websites and online communities providing inspiration for weight loss and sharing tricks to help individuals deceive parents and doctors [42–44] may be analogous to the inspirational YouTube transition videos and the shared online advice about manipulating parents and doctors to obtain hormones.

Hypothesis 2: Parental conflict might provide alternative explanations for selected findings

Parents reported subjective declines in their AYAs' mental health and in parent-child relationships after the children disclosed a transgender identification. Additionally, per parent report, almost half of the AYAs withdrew from family, 28.5% refused to speak to a parent, and 6.8% tried to run away. It is possible that some of these findings might be secondary to parent-child conflict. Parent-child conflict could arise from disagreement over the child's self-assessment of being transgender. It is also possible that some parents might have had difficulty coping or could have been coping poorly or maladaptively with their child's disclosure. Other potential explanations for the above findings include worsening of AYAs' pre-existing (or onset of new) psychiatric conditions or the use of maladaptive coping mechanisms. To further evaluate these possibilities, future studies should incorporate information about family dynamics, parent-child interactions, parent coping, child coping, and psychiatric trajectories. This study did not collect data about the parents' baseline coping styles, how they were coping with their child's disclosure, and whether their coping seemed to be maladaptive or adaptive. Nor did it explore parents' mental well-being. Future studies should explore these issues as well.

Although most parents reported an absence of childhood indicators for gender dysphoria, it is possible that these indicators might have existed for some of the AYAs and that some parents either failed to notice or ignored these indicators when they occurred. Because the readily observable indicators could also have been observed by other people in the child's life, future studies should include input from parents, AYAs and from third party informants such as teachers, pediatricians, mental health professionals, babysitters, and other family members to verify the presence or absence of readily observable behaviors and preferences during childhood. Parental approaches to their child's gender dysphoria might contribute to specific outcomes. This study did not specifically explore parental approaches to gender dysphoria or parental views on medical or surgical interventions. Additional studies that explore whether parents support or don't support: gender exploration; gender nonconformity; non-heterosexual sexual identities; mental health evaluation and treatment; and exploration of potential underlying causes for dysphoria would be extremely valuable. It would also be worthwhile to explore whether parents favor affirming the child as a person or affirming the child's gender identity and whether parents hold liberal, cautious, or negative views about the use of medical and surgical interventions for gender dysphoria in AYAs.

Hypothesis 3: Maladaptive coping mechanisms may underlie the development of gender dysphoria for some AYAs

For some individuals, the drive to transition may represent an ego-syntonic but maladaptive coping mechanism to avoid feeling strong or negative emotions similar to how the drive to extreme weight loss can serve as an ego-syntonic but maladaptive coping mechanism in anorexia nervosa [68–69]. A maladaptive coping mechanism is a response to a stressor that might relieve the symptoms temporarily but does not address the cause of the problem and may cause additional negative outcomes. Examples of maladaptive coping mechanisms include the use of alcohol, drugs, or self-harm to distract oneself from experiencing painful emotions. One reason that the treatment of anorexia nervosa is so challenging is that the drive for extreme weight loss and weight loss activities can become a maladaptive coping mechanism that allows the patient to avoid feeling and dealing with strong emotions [69–70]. In this context, dieting is not felt as distressing to the patient, because it is considered by the patient to be the solution to her problems, and not part of the problems. In other words, the dieting and weight loss activities are ego-syntonic to the patient. However, distress is felt by the patient when external actors (doctors, parents, hospital staff) try to interfere with her weight loss activities thus curtailing her maladaptive coping mechanism.

Findings that may support a maladaptive coping mechanism hypothesis include that the most likely description of AYA ability to use negative emotions productively was poor/extremely poor and the majority of AYAs were described as "overwhelmed by strong emotions and tries to/goes to great lengths to avoid experiencing them." Although these are not validated questions, the findings suggest, at least, that there is a history of difficulty dealing with emotions. The high frequency of parents reporting AYA expectations that transition would solve their problems coupled with the sizable minority who reported AYA unwillingness to work on basic mental health issues before seeking treatment support the concept that the drive to transition might be used to avoid dealing with mental health issues and aversive emotions. Additional support for this hypothesis is that the sample of AYAs described in this study are predominantly female, were described by parents as beginning to express symptoms during adolescence and contained an overrepresentation of academically gifted students which bears a strong resemblance to populations of individuals diagnosed with anorexia nervosa [71–75]. The risk factors, mechanisms and meanings of anorexia nervosa [69–70, 76] may ultimately

prove to be a valuable template to understand the risk factors, mechanisms, and meanings for some cases of gender dysphoria.

Transition as a drive to escape one's gender/sex, emotions, or difficult realities might also be considered when the drive to transition arises after a sex or gender-related trauma or within the context of significant psychiatric symptoms and decline in ability to function. Although trauma and psychiatric disorders are not specific for the development of gender dysphoria, these experiences may leave a person in psychological pain and in search of a coping mechanism. The first coping mechanism that a vulnerable person adopts may be the result of their environment and which narratives for pain and coping are most prevalent in that environment—in some settings a gender dysphoria/drive to transition may be the dominant paradigm, in some settings a body dysphoria/drive for extreme weight loss is dominant, and in another the use of alcohol and drugs to cope with pain may be dominant. Because maladaptive coping mechanisms do not address the root cause of distress and may cause their own negative consequences, an outcome commonly reported for this sample, AYAs experiencing a decline in their mental well-being after transgender-identification, is consistent with this hypothesis. There was a subset of AYAs for whom parents reported improvement in their mental well-being as they desisted from their transgender-identification which would not be inconsistent with moving from a maladaptive coping mechanism to an adaptive coping mechanism.

If the above hypotheses are correct, rapid onset of gender dysphoria that is socially mediated and/or used as a maladaptive coping mechanism may be harmful to AYAs in the following ways: (1) non-treatment or delayed treatment for trauma and mental health problems that might be the root of (or at least an inherent part of) the AYAs' issues; (2) alienation of the AYAs from their parents and other crucial social support systems; (3) isolation from mainstream, non-transgender society, which may curtail educational and vocational potential; and (4) the assumption of the medical and surgical risks of transition without benefit. In addition to these indirect harms, there is also the possibility that this type of gender dysphoria, with the subsequent drive to transition, may represent a form of intentional self-harm. Promoting the affirmation of a declared gender and recommending transition (social, medical, surgical) without evaluation may add to the harm for these individuals as it can reinforce the maladaptive coping mechanism, prolong the length of time before the AYA accepts treatment for trauma or mental health issues, and interfere with the development of healthy, adaptive coping mechanisms. It is especially critical to differentiate individuals who would benefit from transition from those who would be harmed by transition before proceeding with treatment.

Reflections

Clinicians need to be aware of the myriad of barriers that may stand in the way of making accurate diagnoses when an AYA presents with a desire to transition including: the developmental stage of adolescence; the presence of subcultures coaching AYAs to mislead their doctors; and the exclusion of parents from the evaluation. In this study, 22.3% of AYAs were reported as having been exposed to online advice about what to say to doctors to get hormones, and 17.5% to the advice that it is acceptable to lie to physicians; and the vast majority of parents were reasonably sure or positive that their child misrepresented their history to their doctor or therapist. Furthermore, although parents may be knowledgeable informants on matters of their own child's developmental, medical, social, behavioral, and mental health history- and quite possibly *because* they are knowledgeable- they are often excluded from the clinical discussion by the AYAs, themselves. An AYA telling their clinician that their parents are transphobic and abusive may indeed mean that the parents are transphobic and abusive. However, the findings of this research indicate that it is also possible that the AYA calls the parent

transphobic and abusive because the parent disagrees with the child's self-diagnosis, has expressed concern for the child's future, or has requested that the child be evaluated for mental health issues before proceeding with treatment.

The findings of this study suggest that clinicians need to be cautious before relying solely on self-report when AYAs seek social, medical or surgical transition. Adolescents and young adults are not trained medical professionals. When AYAs diagnose their own symptoms based on what they read on the internet and hear from their friends, it is quite possible for them to reach incorrect conclusions. It is the duty of the clinician, when seeing a new AYA patient seeking transition, to perform their own evaluation and differential diagnosis to determine if the patient is correct or incorrect in their self-assessment of their symptoms and their conviction that they would benefit from transition. This is not to say that the convictions of the patient should be dismissed or ignored, some may ultimately benefit from transition. However, careful clinical exploration should not be neglected, either. The patient's history being significantly different than their parents' account of the child's history should serve as a red flag that a more thorough evaluation is needed and that as much as possible about the patient's history should be verified by other sources. The findings that the majority of clinicians described in this study did not explore trauma or mental health disorders as possible causes of gender dysphoria or request medical records in patients with atypical presentations of gender dysphoria is alarming. The reported behavior of clinicians refusing to communicate with their patients' parents, primary care physicians, and psychiatrists betrays a resistance to triangulation of evidence which puts AYAs at considerable risk.

It is possible that some teens and young adults may have requested that their discussions with the clinicians addressing gender issues be kept confidential from their parents, as is their right (except for information that would put themselves or others at harm). However, maintaining confidentiality of the patient does not prevent the clinician from listening to the medical and social history of the patient provided by the parent. Nor does it prevent a clinician from accepting information provided by the patient's primary care physicians and psychiatrists. Because adolescents may not be reliable historians and may have limited awareness and insight about their own emotions and behaviors, the inclusion of information from multiple informants is often recommended when working with or evaluating minors. One would expect that if a patient refuses the inclusion of information from parents and physicians (prior and current), that the clinician would explore this with the patient and encourage them to reconsider. At the very least, if a patient asks that all information from parents and medical sources be disregarded, it should raise the suspicion that what the patient is presenting may be less than forthcoming and the clinician should proceed with caution.

The argument to surface from this study is not that the insider perspectives of AYAs presenting with signs of a rapid onset of gender dysphoria should be set aside by clinicians, but that the insights of parents are a pre-requisite for robust triangulation of evidence and fully informed diagnosis. All parents know their growing children are not always right, particularly in the almost universally tumultuous period of adolescence. Most parents have the awareness and humility to know that even as adults they are not always right themselves. When an AYA presents with signs of a rapid onset of gender dysphoria it is incumbent upon all professionals to fully respect the young person's insider perspective but also, in the interests of safe diagnosis and avoidance of clinical harm, to have the awareness and humility themselves to engage with parental perspectives and triangulate evidence in the interest of validity and reliability.

The strengths of this study include that it is the first empirical description of a specific phenomenon that has been observed by parents and clinicians [14] and that it explores parent observations of the psychosocial context of youth who have recently identified as transgender with a focus on vulnerabilities, co-morbidities, peer group interactions, and social media use.

Additionally, the qualitative analysis of responses about peer group dynamics provides a rich illustration of AYA intra-group and inter-group behaviors as observed and reported by parents. This research also provides a glimpse into parent perceptions of clinician interactions in the evaluation and treatment of AYAs with an adolescent-onset (or young adult-onset) of gender dysphoria symptoms.

The limitations of this study include that it is a descriptive study and thus has the known limitations inherent in all descriptive studies. This is not a prevalence study and does not attempt to evaluate the prevalence of gender dysphoria in adolescents and young adults who had not exhibited childhood symptoms. Likewise, this study's findings did not demonstrate the degree to which the onset of gender dysphoria symptoms may be socially mediated or associated with a maladaptive coping mechanism, although these hypotheses were discussed here. Gathering more data on the topics introduced is a key recommendation for further study. It is not uncommon for first, descriptive studies, especially when studying a population or phenomenon where the prevalence is unknown, to use targeted recruiting. To maximize the possibility of finding cases meeting eligibility criteria, recruitment is directed towards communities that are likely to have eligible participants. For example, in the first descriptive study about children who had been socially transitioned, the authors recruited potential subjects from gender expansive camps and gender conferences where parents who supported social transition for young children might be present and the authors did not seek out communities where parents might be less inclined to find social transition for young children appropriate [77]. In the same way, for the current study, recruitment was targeted primarily to sites where parents had described the phenomenon of a rapid onset of gender dysphoria because those might be communities where such cases could be found. The generalizability of the study must be carefully delineated based on the recruitment methods, and, like all first descriptive studies, additional studies will be needed to replicate the findings.

Three of the sites that posted recruitment information expressed cautious or negative views about medical and surgical interventions for gender dysphoric adolescents and young adults and cautious or negative views about categorizing gender dysphoric youth as transgender. One of the sites that posted recruitment information is perceived to be pro-gender-affirming. Hence, the populations viewing these websites might hold different views or beliefs from each other. And both populations may differ from a broader general population in their attitudes about transgender-identified individuals. This study did not explore specific participant views about medical and surgical interventions for gender dysphoric youth or whether participants support or don't support: exploration of gender identity, exploration of potential underlying causes for gender dysphoria, affirmation of children as valued individuals or affirmation of children's gender identity. Future studies should explore all these issues. This study cannot speak to those details about the participants.

Respondents were asked, "Do you believe that transgender people deserve the same rights and protections as others in your country?" which is a question that was adapted from a question used for a US national poll [78]. Although this question cannot elicit specific details about a persons' beliefs about medical interventions, beliefs about transgender identification, or their beliefs about their own child, it can be used to assess if the participants in this study are similar in their basic beliefs about the rights of transgender people to the participants in the US national poll. The majority (88.2%) of the study participants gave affirmative answers to the question which is consistent with the 89% affirmative response reported in a US national poll [78]. All self-reported results have the potential limitation of social desirability bias. However, comparing this self-report sample to the national self-report sample [78], the results show similar rates of support. Therefore, there is no evidence that the study sample is appreciably different in their support of the rights of transgender people than the general American population.

It is also important to note that recruitment was not limited to the websites where the information about the study was first posted. Snowball sampling was also used so that any person viewing the recruitment information was encouraged to share the information with any person or community where they thought there could be potentially eligible participants, thus substantially widening the reach of potential respondents. In follow up studies on this topic, an even wider variety of recruitment sources should be attempted.

Another limitation of this study is that it included only parental perspective. Ideally, data would be obtained from both the parent and the child and the absence of either perspective paints an incomplete account of events. Input from the youth would have yielded additional information. Further research that includes data collection from both parent and child is required to fully understand this condition. However, because this research has been produced in a climate where the input from parents is often neglected in the evaluation and treatment of gender dysphoric AYAs, this research supplies a valuable, previously missing piece to the jigsaw puzzle. If Hypothesis 3 is correct that for some AYAs gender dysphoria represents an egosyntonic maladaptive coping mechanism, data from parents are especially important because affected AYAs may be so committed to the maladaptive coping mechanism that their ability to assess their own situation may be impaired. Furthermore, parents uniquely can provide details of their child's early development and the presence or absence of readily observable childhood indicators of gender dysphoria are especially relevant to the diagnosis. There are, however, obvious limitations to relying solely on parent report. It is possible that some of the participating parents may not have noticed symptoms of gender dysphoria before their AYA's disclosure of a transgender identity; could have been experiencing shock, grief, or difficulty coping from the disclosure; or even could have chosen to deny or obscure knowledge of long term gender dysphoria. Readers should hold this possibility in mind. Overall, the 200 plus responses appear to have been prepared carefully and were rich in detail, suggesting they were written in good faith and that parents were attentive observers of their children's lives. Although this research adds the necessary component of parent observation to our understanding of gender dysphoric adolescents and young adults, future study in this area should include both parent and child input.

This research does not imply that no AYAs who become transgender-identified during their adolescent or young adult years had earlier symptoms nor does it imply that no AYAs would ultimately benefit from transition. Rather, the findings suggest that *not all* AYAs presenting at these vulnerable ages are correct in their self-assessment of the cause of their symptoms and *some* AYAs may be employing a drive to transition as a maladaptive coping mechanism. It may be difficult to distinguish if an AYA's declining mental health is occurring due to the use of a maladaptive coping mechanism, due to the worsening of a pre-existing (or onset of a new) psychiatric condition, or due to conflict with parents. Clinicians should carefully explore these options and try to clarify areas of disagreement with confirmation from outside sources such as medical records, psychiatrists, psychologists, primary care physicians, and other third party informants where possible. Further study of maladaptive coping mechanisms, psychiatric conditions and family dynamics in the context of gender dysphoria and mental health would be an especially valuable contribution to better understand how to treat youth with gender dysphoria.

More research is needed to determine the incidence, prevalence, persistence and desistence rates, and the duration of gender dysphoria for adolescent-onset gender dysphoria and to examine whether rapid-onset gender dysphoria is a distinct and/or clinically valid subcategory of gender dysphoria. Adolescent-onset gender dysphoria is sufficiently different from early-onset of gender dysphoria that persists or worsens at puberty and therefore, the research results from early-onset gender dysphoria should not be considered generalizable to

adolescent-onset gender dysphoria. It is currently unknown whether the gender dysphorias of adolescent-onset gender dysphoria and of late-onset gender dysphoria occurring in young adults are transient, temporary or likely to be long-term. Without the knowledge of whether the gender dysphoria is likely to be temporary, extreme caution should be applied before considering the use of treatments that have permanent effects such as cross-sex hormones and surgery. Research needs to be done to determine if affirming a newly declared gender identity, social transition, puberty suppression and cross-sex hormones can cause an iatrogenic persistence of gender dysphoria in individuals who would have had their gender dysphoria resolve on its own and whether these interventions prolong the duration of time that an individual feels gender dysphoric before desisting. There is also a need to discover how to diagnose these conditions, how to treat the AYAs affected, and how best to support AYAs and their families. Additionally, analyses of online content for pro-transition sites and social media should be conducted in the same way that content analysis has been performed for pro-eating disorder websites and social media content [44]. Finally, further exploration is needed for potential contributors to recent demographic changes including the substantial increase in the number of adolescent natal females with gender dysphoria and the new phenomenon of natal females experiencing late-onset or adolescent-onset gender dysphoria.

Conclusion

Collecting data from parents in this descriptive exploratory study has provided valuable, detailed information that allows for the generation of hypotheses about potential factors contributing to the onset and expression of gender dysphoria among AYAs. Emerging hypotheses include the possibility of a potential new subcategory of gender dysphoria (referred to as rapid-onset gender dysphoria) that has not yet been clinically validated and the possibility of social influences and maladaptive coping mechanisms contributing to the development of gender dysphoria. Parent-child conflict may also contribute to the course of the dysphoria. More research that includes data collection from AYAs, parents, clinicians and third party informants is needed to further explore the roles of social influence, maladaptive coping mechanisms, parental approaches, and family dynamics in the development and duration of gender dysphoria in adolescents and young adults.

Supporting information

S1 Appendix. Survey instrument.
(PDF)

S2 Appendix. COREQ checklist.
(PDF)

Acknowledgments

I would like to acknowledge Michael L. Littman, PhD, for his assistance in the statistical analysis of quantitative data, Michele Moore, PhD, for her assistance in qualitative data analysis and feedback on an earlier version of the manuscript, Lisa Marchiano, LCSW, for feedback on earlier versions of the manuscript, and four external peer-reviewers, three PLOS ONE staff editors and two Academic Editors for their attention to this research.

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Archives of Sexual Behavior (2021) 50:3353–3369
https://doi.org/10.1007/s10508-021-02163-w

ORIGINAL PAPER

Individuals Treated for Gender Dysphoria with Medical and/or Surgical Transition Who Subsequently Detransitioned: A Survey of 100 Detransitioners

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Received: 5 October 2020 / Revised: 17 September 2021 / Accepted: 20 September 2021 / Published online: 19 October 2021

Abstract
The study's purpose was to describe a population of individuals who experienced gender dysphoria, chose to undergo medical and/or surgical transition and then detransitioned by discontinuing medications, having surgery to reverse the effects of transition, or both. Recruitment information with a link to an anonymous survey was shared on social media, professional listservs, and via snowball sampling. Sixty-nine percent of the 100 participants were natal female and 31.0% were natal male. Reasons for detransitioning were varied and included: experiencing discrimination (23.0%); becoming more comfortable identifying as their natal sex (60.0%); having concerns about potential medical complications from transitioning (49.0%); and coming to the view that their gender dysphoria was caused by something specific such as trauma, abuse, or a mental health condition (38.0%). Homophobia or difficulty accepting themselves as lesbian, gay, or bisexual was expressed by 23.0% as a reason for transition and subsequent detransition. The majority (55.0%) felt that they did not receive an adequate evaluation from a doctor or mental health professional before starting transition and only 24.0% of respondents informed their clinicians that they had detransitioned. There are many different reasons and experiences leading to detransition. More research is needed to understand this population, determine the prevalence of detransition as an outcome of transition, meet the medical and psychological needs of this population, and better inform the process of evaluation and counseling prior to transition.

Keywords Gender dysphoria · Detransition · Transgender

Introduction

Detransition is the act of stopping or reversing a gender transition. The visibility of individuals who have detransitioned is new and may be rapidly growing. As recently as 2014, it was challenging for an individual who detransitioned to find another person who similarly detransitioned (Callahan, 2018). Between 2015 and 2017, a handful of blogs written by individual detransitioners started to appear online, private support groups for detransitioners formed, and interviews with detransitioners began to appear in news articles, magazines, and blogs (Anonymous, 2017; 4thwavenow, 2016; Herzog, 2017; McCann, 2017). Although few YouTube videos about detransition existed prior to 2016, multiple detransitioners started to post videos documenting their experiences in 2016 and the numbers of these videos continues to increase.[1] In late 2017, the subreddit r/detrans (r/detrans, 2020) was revitalized and in four years has grown from 100 members to more than 21,000 members. A member poll of r/detrans conducted in 2019 estimated that approximately one-third of the members responding to the survey were desisters or detransitioners (r/detrans, 2019). The Pique Resilience Project, a group of four detransitioned or desisted young women, was founded in 2018 as a way to share the experiences of detransitioners with the public (Pique Resilience Project, 2019). In late 2019, the Detransition Advocacy Network, a nonprofit organization to "improve the well-being of detransitioned people everywhere" was launched (The

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10508-021-02163-w.

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[1] A search of the word "detransition" in YouTube can be filtered by date of upload. https://www.youtube.com/results?search_query=%22detransition%22&sp=CAI%253D22.

Detransition Advocacy Network, 2020) and the first formal, in-person conference for detransitioned people was held (Bridge, 2020). In the face of this massive change, clinicians have called for more research into the experiences of detransitioners (Butler & Hutchinson, 2020; Entwistle, 2021; Marchiano, 2020).

Although there were rare published reports about detransitioners prior to 2016, most of the published literature about detransition is recent (Callahan, 2018; D'Angelo, 2018; Djordjevic et al., 2016; Kuiper & Cohen-Kettenis, 1998; Levine, 2018; Marchiano, 2017; Pazos Guerra et al., 2020; Stella, 2016; Turban & Keuroghlian, 2018; Turban et al., 2021; Vandenbussche, 2021). The prevailing cultural narratives about detransition are that most individuals who detransition will retransition and that the reasons for detransition are discrimination, pressures from others, and nonbinary identification (Turban et al., 2021). However, case reports are shedding light on a broader and more complex range of experiences that include trauma, worsened mental health with transition, re-identification with natal sex, and difficulty separating sexual orientation from gender identity (D'Angelo, 2018; Levine, 2018; Pazos Guerra et al., 2020).[2] Detransitioners and desisters, in their own words, have provided additional depth to the discussion, describing that:

(1) Trauma (including sexual trauma) and mental health conditions contributed to their transgender identification and transition (Callahan, 2018; Herzog, 2017; twitter.com/ftmdetransed & twitter.com/radfemjourney, 2019)
(2) Their dysphoria and transition were due to homophobia and difficulty accepting themselves as homosexual (Bridge, 2020; Callahan, 2018; upperhandMARS, 2020)
(3) Peers, social media, and online communities were influential in the development of transgender identification and desire to transition (Pique Resilience Project, 2019; Tracey, 2020; upperhandMARS, 2020)
(4) Their dysphoria was rooted in misogyny (Herzog, 2017)

Two recently published convenience sample reports provide additional context about the topic of detransition. First, Turban et al. (2021) analyzed data from the United States Trans Survey (USTS) (James et al., 2016). The USTS contains data from 27,715 transgender and gender diverse adults from the U.S. who were recruited through lesbian, gay, bisexual, transgender, queer (LGBTQ), and allied organization outreach. The USTS included the question, "Have you ever detransitioned? In other words, have you ever gone back to living as your sex assigned at birth, at least for a while?" with the multiple choice options of "yes," "no," and "I have never transitioned." For the 2,242 participants who answered "yes," Turban et al. analyzed the responses to the multiple choice question, "Why did you detransition? In other words, why did you go back to living as your sex assigned at birth? (Mark all that apply)." Although most of the offered answer options were about external pressures to detransition (pressure from spouse or partner, pressure from family, pressure from friends, pressure from employer, discrimination, etc.), participants could write in additional reasons that were not listed. Turban et al.'s sample included more natal males (55.1%) than natal females (44.9%). Roughly half (50.2%) had taken cross-sex hormones and 16.5% had obtained surgery. The findings revealed that most (82.5%) of the sample expressed at least one external factor for detransitioning and 15.9% expressed at least one internal factor (factors originating from self).

The second study by Vandenbussche (2021) recruited detransitioners from online communities of detransitioners and analyzed data for the participants who answered affirmatively to the question, "Did you transition medically and/or socially and then stopped?" The sample of 237 participants was predominantly natal female (92%), and from the U.S. (51%) and Europe (32%). Most (65%) had transitioned both medically and socially. Participants selected from multiple choice options to indicate why they detransitioned with options covering a range of experiences. Respondents also had the option to write in additional reasons. Frequently endorsed reasons for detransition included realizing that their gender dysphoria was related to other issues (70%); health concerns (62%); observing that transition did not help their dysphoria (50%); and that they found alternatives to deal with their dysphoria (45%). In contrast to Turban et al. (2021), external factors such as lack of support, financial concerns, and discrimination were less common (13%, 12%, and 10%, respectively). Many in the sample described that when they detransitioned they lost support or were ostracized from lesbian, gay, bisexual, and transgender (LGBT) communities, suggesting that many of the participants in Vandenbussche (2021) would not have been reached by the recruitment efforts of the USTS (James et al., 2016).

The objective of the current study was to describe a population of individuals who experienced gender dysphoria, chose to undergo medical and/or surgical transition and then detransitioned by discontinuing medications, having surgery to reverse the effects of transition, or both. In contrast to Turban et al. (2021) and Vandenbussche (2021), this study focused only on

[2] The debate about the terminologies used to describe an individual's sex (including "assigned sex at birth," "biological sex," "natal sex," "birth sex," "sex," etc.) is far from settled. Although some professionals have argued for the use of "assigned sex at birth," others argue that this terminology is misleading and not consistent with the events that occur at birth and prior to birth (Bouman et al., 2017; Byng et al., 2018; Dahlen, 2020; Griffin et al., 2020). Supporting the unsettled nature of the discussion, I received conflicting comments from the reviewers of this manuscript about my selection of natal sex terms–one reviewer asked that I justify my preference for natal sex over the other terminologies; another reviewer expressed support for my use of natal sex. I prefer to use "natal sex" and "birth sex" because they are accurate and objective. Further, I propose that "natal sex" and "birth sex" might be seen as reasonable, polite compromise terms between "biological sex" and "assigned sex at birth."

individuals who transitioned and detransitioned medically, surgically, or both. For the purpose of this study, medical transition refers to the use of puberty blockers, cross-sex hormones, or anti-androgens and surgical transition refers to any of a variety of surgical procedures (common surgical procedures include mastectomy, genital surgery, and breast augmentation). This study does not describe the population of individuals who undergo medical or surgical transition without issue nor is it designed to assess the prevalence of detransition as an outcome of transition. Instead, the goal was to identify detransition reasons and narratives in order to inform clinical care and future research.

Method

Participants and Procedure

During the recruitment period, 101 individuals who met the study criteria completed online surveys. Inclusion criteria were (1) completion of a survey via Survey Monkey; (2) answering that they had taken or had one or more of the following for the purpose of gender transition: cross-sex hormones, anti-androgens, puberty blockers, breast surgery, genital surgery, other surgery; and (3) answering that they had done any of the following for the purpose of detransitioning: stopped taking cross-sex hormones, stopped taking anti-androgens, stopped taking puberty blockers, had any surgery to reverse transition. One survey was excluded for nonsense answers leaving 100 surveys for analysis. The sample included more natal females (69.0%) than natal males (31.0%) with respondents who were predominantly White (90.0%), non-Hispanic (98.0%), resided in the U.S. (66.0%); had no religious affiliation (63.0%), and support the rights of gay and lesbian couples to marry legally (92.9%) (see Table 1). At the time of survey completion, the mean age of respondents was 29.2 years (SD = 9.1) though natal females were significantly younger ($M = 25.8$; SD = 5.0) than natal males ($M = 36.7$; SD = 11.4), $t(98) = -6.56$, $p < .001$. Prior to transitioning, natal females were more likely to report an exclusively homosexual sexual orientation and natal males were more likely to report an exclusively heterosexual sexual orientation.

A 115-question survey instrument with multiple choice, Likert-type, and open-ended questions was created by the author and two individuals who had personally detransitioned. The author had met both detransitioners by way of introductions from colleagues. The author and both individuals who had detransitioned created questions for the survey, provided feedback, and revised the survey questions collaboratively with a focus on content, clarity, and relevance to a variety of transition and detransition experiences. The survey instrument included two questions that were adapted from an online survey of female detransitioners (Stella, 2016). Once completed, the survey was uploaded onto Survey Monkey (SurveyMonkey, Palo Alto, CA) via an account that was HIPAA-enabled.

Recruitment information with a link to the survey was posted on blogs that covered detransition topics and shared in a private online detransition forum, in a closed detransition Facebook group, and on Tumblr, Twitter, and Reddit. Recruitment information was also shared on the professional listservs for the World Professional Association for Transgender Health, the American Psychological Association Section 44, and the SEXNET listserv (which is a listserv of sex researchers and clinicians) and the professionals on the listservs were asked to share recruitment information with anyone they knew who might be eligible. Efforts were made to reach out to communities with varied views about the use of medical and surgical transition and recruitment information stated that participation was sought from individuals regardless of whether their transition experiences were positive, negative or neutral. Potential participants were invited to share recruitment information with any potentially eligible person or community with potentially eligible people. The survey was active from December 15, 2016 to April 30, 2017 (4.5 months). The median time to complete a survey was 49 min; 50% of the surveys were completed between 32 and 71 min. There were no incentives offered for participating. Data were collected anonymously, without IP addresses, and stored securely with Survey Monkey.

Participation in this study was voluntary. Electronic consent was obtained from all participants in the following manner. The first page of the online survey informed respondents about the research purpose, potential risks and benefits, that participation was voluntary, and provided contact information for the researcher. Survey questions were only displayed if the participant clicked "agree" which indicated that they read the information, voluntarily agreed to participate and were at least 18 years of age.

Measures

Demographic and Baseline Characteristics

Information was collected about participant age, natal sex, race/ethnicity, country of residence, educational attainment, socioeconomic status, religion, attitudes about legal marriage for gay and lesbian couples, and where they first heard about the study. The term sexual orientation in this article is intended to refer to the natal sex of the participant and the natal sex of the individuals with whom they are sexually attracted. Participants were asked to select one or more labels for how they identified their sexual orientation prior to transition with options inclusive of participant sex (e.g., asexual female, bisexual female, heterosexual female, etc.). These responses were coded to be consistent with participant natal sex and were categorized into homosexual, heterosexual, bisexual, pansexual, asexual, and multiple. The multiple category included respondents who

Table 1 Demographic and baseline characteristics

	Natal female *N* (%) *N* = 69	Natal male *N* (%) *N* = 31
*Race/ethnicity**		
White	62 (89.9%)	28 (90.3%)
Multiracial	6 (8.7%)	3 (9.7%)
Other	4 (5.8%)	0 (0%)
Asian	1 (1.4%)	1 (3.2%)
Hispanic	1 (1.4%)	1 (3.2%)
Black	0 (0%)	0 (0%)
Country of residence		
USA	46 (66.7%)	20 (64.5%)
UK	8 (11.6%)	1 (3.2%)
Canada	5 (7.2%)	4 (12.9%)
Australia	2 (2.9%)	2 (6.5%)
Other	8 (11.6%)	4 (12.9%)
Education		
Bachelor's or graduate degree	29 (42.0%)	18 (58.1%)
Associates degree	3 (4.3%)	1 (3.2%)
Some college but no degree	28 (40.6%)	9 (29.0%)
High school graduate or GED	8 (11.6%)	2 (6.5%)
< High school	1 (1.4%)	0 (0%)
Other	0 (0%)	1 (3.2%)
Socioeconomic status compared to others in country of residence		
Above average (somewhat or very much)	19 (27.5%)	12 (38.7%)
About average	20 (29.0%)	7 (22.6%)
Below average (somewhat or very much)	27 (39.1%)	12 (38.7%)
Prefer not to say	3 (4.3%)	0 (0%)
Categorized sexual orientation (by natal sex) prior to transition[a]		
Homosexual	18 (26.1%)	2 (6.5%)
Heterosexual	6 (8.7%)	12 (38.7%)
Bisexual	15 (21.7%)	8 (25.8%)
Pansexual	4 (5.8%)	1 (3.2%)
Multiple	20 (29.0%)	5 (16.1%)
Asexual	6 (8.7%)	3 (9.7%)
Religious affiliation		
No religious affiliation	41 (59.4%)	22 (73.3%)
Liberal Christian	5 (7.2%)	3 (10.0%)
Liberal Jewish	5 (7.2%)	0 (0%)
Conservative Christian	1 (1.4%)	2 (6.7%)
Liberal Muslim	1 (1.4%)	0 (0%)
Conservative Jewish	0 (0%)	0 (0%)
Conservative Muslim	0 (0%)	0 (0%)
Other	16 (23.2%)	3 (10.0%)
Legal marriage for gay and lesbian couples		
Favor	65 (97.0%)	26 (83.9%)
Oppose	1 (1.5%)	5 (16.1%)
Don't know	1 (1.5%)	0 (0%)
Source where participant first heard about study		
Detransition blogs	26 (37.7%)	15 (48.4%)
Other social media	37 (53.6%)	11 (35.5%)
A person they know	3 (4.3%)	3 (9.7%)
Other	3 (4.3%)	2 (6.5%)

*May select more than one answer

[a]Natal females were more likely to express an exclusively homosexual sexual orientation prior to transition ($\chi^2 = 5.15$. The *p*-value is .023). Natal males were more likely to express an exclusively heterosexual sexual

Table 1 (continued)

orientation prior to transition ($\chi^2 = 13.05$. The p value is $< .001$). Natal sex differences were not significant for individuals expressing pre-transition sexual orientations of bisexual, pansexual, multiple, and asexual. For bisexual sexual orientation, $\chi^2 = 0.20$. For pansexual sexual orientation, $\chi^2 = 0.29$. For multiple sexual orientations reported, $\chi^2 = 1.88$. For asexual sexual orientation, $\chi^2 = 0.02$

selected more than one response where responses indicated more than one pattern of sexual attraction (e.g., lesbian female and heterosexual female). Other questions about baseline characteristics included questions about diagnosed psychiatric disorders and neurodevelopmental disabilities, trauma, and non-suicidal self-injury (NSSI) before the onset of gender dysphoria.

Gender Dysphoria Onset and Typologies

Participants were asked how old they were when they first experienced gender dysphoria and whether this was during childhood, at the onset of puberty, during puberty, or later. Respondents were categorized as having early-onset gender dysphoria if they indicated that their gender dysphoria began "during childhood" and late-onset gender dysphoria if their gender dysphoria began "at the onset of puberty" or later. To evaluate typologies, participants were characterized by Blanchard's (1985, 1989) typology as homosexual (if the sexual orientations listed prior to transition were exclusively homosexual) or non-homosexual which includes heterosexual, asexual, bisexual, pansexual, and multiple responses.

Transition

Participants were asked for their age and the year that they first sought care to transition, sources that encouraged them to believe that transition would be helpful to them, and whether they felt pressured to transition. The friendship group dynamics that were identified in previous work were assessed by asking respondents whether their friendship group mocked people who were not transgender, whether people in their pre-existing friend group transitioned before the participant decided to transition, and how participant popularity changed after announcing that they would transition (Littman, 2018). Questions were asked about participant experiences with clinicians, the social, medical, and surgical steps they took to transition, and the duration of time spent taking each medication.

Detransition

Participants were asked for their age and the year that they decided to detransition, how long they were transitioned before deciding to detransition, their reasons for wanting to detransition, what sources encouraged them to believe that detransition would be helpful to them, and whether they felt pressured to detransition. Participants were also asked which social, medical, and surgical steps they took to detransition and whether they contacted the doctor or clinic that they used for their transition to tell them that they detransitioned.

Transition and Detransition Narratives

In this article, "narratives" denote participant interpretations of their experiences and rationales surrounding their decisions to transition and detransition. To associate each participant survey with a set of relevant narratives, the data were reviewed with horizontal (beginning to end) passes and vertical passes for selected questions (these questions are listed in the supplemental materials). Surveys were coded as belonging to zero or more of the following narrative categories: discrimination, nonbinary, retransition, trauma and mental health, internalized homophobia, social influence, and misogyny. Each narrative and the responses that were associated with them are detailed below. Example quotes were selected with care taken to avoid quoting a participant more than once per narrative. Narratives are ordered and reported with the more commonly accepted narratives first and the newer narratives next.

The *discrimination* narrative was defined as when someone detransitioned due to experiencing discrimination or external social pressures. The *nonbinary* narrative consisted of answering that their current identification was "nonbinary/genderqueer" or providing open-text responses that described aspects of discovering or maintaining a nonbinary identification. Although there were no questions in the survey specifically asking about retransition, the *retransition* narrative was identified if participants expressed that they had retransitioned or resumed transition in any of the open-text responses in the survey. The *gender dysphoria was caused by trauma or a mental health condition* narrative was identified by selection for the answers, "what I thought were feelings of being transgender were actually the result of trauma," "what I thought were feelings of being transgender were actually the result of a mental health condition," "I discovered that my gender dysphoria was caused by something specific (ex. trauma, abuse, mental health condition)" or open-text responses consistent with these reasons. The *internalized homophobia/difficulty accepting oneself as a lesbian female, gay male, or bisexual person* narrative consisted of descriptions that the respondents' discomfort and distress about being lesbian, gay, or bisexual was related to their gender dysphoria, transition, or detransition, or that they assumed they were transgender because they did not yet understand themselves to be lesbian, gay or bisexual. The *social pressure to transition* narrative was identified with an affirmative

answer to whether they felt pressured to transition with an open-text response indicating that the pressure came from a person or group of people. The *misogyny* narrative was identified for natal female respondents with open-text responses using the word "misogyny" or expressing a hatred of femaleness.

Gender Identification at Start of Transition and at Survey Completion

Participants were asked how they identified their gender when they started their transition and at the time of survey completion. They were given options of female, male, nonbinary/genderqueer, trans man/FTM, trans woman/MTF, none of the above, and other. Responses were coded by natal sex and categorized as transgender, birth sex, nonbinary, and other. Answers that were combinations of the above categories were reported as combinations such as "birth sex and nonbinary."

Self-Appraisal of Transition and Detransition

One question asked if participants believe they were helped and another if they were harmed by their transition with options of "very much," "a little," or "not at all." These results were categorized into exclusively helped, exclusively harmed, and both helped and harmed. Participants were asked which of the following reflected their feelings about their transition: "I am glad that I transitioned," "I wish I had never transitioned," "Transitioning distracted me from what I should have been doing," "Transition was a necessary part of my journey." Participants were asked to rate their regret about their transition ("no regrets," "mild regrets," "strong regrets," and "very strong regrets") and were asked to indicate their satisfaction with their decisions to transition and detransition ("extremely satisfied," "very satisfied," "somewhat satisfied," "somewhat dissatisfied," "very dissatisfied," and "extremely dissatisfied"). Satisfaction options were collapsed into "satisfied" and "dissatisfied." In addition, participants were asked if they knew then what they know now, would they have chosen to transition.

Data Analysis

After data were cleaned, statistical analyses were performed using google sheets. Results are presented as frequencies, percentages, medians, means and standard deviations. *t* tests and chi-square tests were performed for selected variables and were considered significant for $p < .05$. Qualitative data were obtained from the open-text answers to questions that allowed participants to provide additional information. Selected open-text responses were categorized, tallied, and reported numerically. Salient respondent quotes and summaries from the qualitative data were selected to illustrate the quantitative results and to provide relevant examples.

Results

Before Transition

Mental health diagnoses and traumatic experiences before the onset of gender dysphoria. Table 2 shows data about psychiatric disorders, neurodevelopmental disabilities, NSSI, and trauma that were reported as occurring prior to the onset of gender dysphoria. Because these conditions and events occurred before participants began to feel gender dysphoric, they cannot be considered to be secondary to gender incongruence or transphobia.

Gender dysphoria onset and typology. Most participants (82.0%) were living with one or both parents when they first experienced gender dysphoria at a mean age of 11.2 years (SD = 5.6). The mean age of gender dysphoria onset was not statistically different between natal females ($M = 11.3$; SD = 5.4) and natal males ($M = 11.0$; SD = 5.9), $t(96) = 0.25$. By Blanchard typologies, 26.1% of natal females were exclusively homosexual and 73.9% non-homosexual while 6.5% of natal males were exclusively homosexual and 93.5% non-homosexual (Blanchard, 1985, 1989). Slightly more than half of the respondents (56.0%) experienced early-onset gender dysphoria and slightly less than half (44.0%) experienced late-onset gender dysphoria. Although late-onset gender dysphoria in natal females was largely absent from the scientific literature prior to 2012 (Steensma et al., 2013; Zucker & Bradley, 1995; Zucker et al., 2012a), 55.1% of the natal female participants reported that their gender dysphoria began with puberty or later. Because the information about the timing of gender dysphoria onset was obtained from participants reporting on their own experiences, it can be assumed that these cases were indeed late-onset rather than early-onset gender dysphoria that was concealed from parents and other people.

Transition reasons. Table 3 shows data about the reasons that individuals wanted to transition and the most frequently endorsed were: wanting to be perceived as the target gender (77.0%); believing that transitioning was their only option to feel better (71.0%); the sensation that their body felt wrong the way it was (71.0%), and not wanting to be associated with their natal sex (70.0%). Most participants believed that transitioning would eliminate (65.0%) or decrease (63.0%) their gender dysphoria and that with transitioning they would become their true selves (64.0%).

Sources of transition encouragement and friend group dynamics. Participants identified sources that encouraged them to believe transitioning would help them. Social media and online communities were the most frequently reported, including YouTube transition videos (48.0%), blogs (46.0%), Tumblr (45.0%), and online communities (43.0%) (see supplemental materials). Also common were people who the respondents knew offline such as therapists (37.0%); someone (28.0%) or a group of friends (27.0%) that they knew in-person. A subset of

Table 2 Mental health diagnoses and traumatic experiences prior to the onset of gender dysphoria

	Natal female *N* (%) *N* = 69	Natal male *N* (%) *N* = 31
*Diagnosed with a mental illness or neurodevelopmental disability**[a]		
Depression	27 (39.1%)	5 (16.1%)
Anxiety	22 (31.9%)	5 (16.1%)
Attention deficit hyperactivity disorder (ADHD)	10 (14.5%)	2 (6.5%)
Post-traumatic stress disorder (PTSD)	10 (14.5%)	1 (3.2%)
Eating disorders	10 (14.5%)	0 (0%)
Autism spectrum disorders	9 (13.0%)	1 (3.2%)
Bipolar disorder	9 (13.0%)	0 (0%)
Obsessive compulsive disorder	6 (8.7%)	3 (9.7%)
Borderline personality disorder	5 (7.2%)	0 (0%)
Schizophrenia or other psychotic disorders	1 (1.4%)	0 (0%)
None of the above	28 (40.6%)	17 (54.8%)
Other	7 (10.1%)	2 (6.5%)
Non-suicidal self-injury (NSSI)[b]		
Engaged in NSSI before the onset of gender dysphoria	19 (27.5%)	5 (16.1%)
Trauma[c]		
Experienced a trauma less than one year before the start of gender dysphoria	33 (47.8%)	4 (12.9%)

*May select more than one answer

[a]Natal sex difference for one or more pre-existing diagnoses (100-none of the above) was not significant [$\chi^2(1, 100) = 1.76$]

[b]Natal sex differences for NSSI before the onset of gender dysphoria was not significant ($\chi^2 = 1.52$)

[c]Experiencing a trauma less than one year before the start of gender dysphoria was statistically different [$\chi^2(1, 100) = 11.19$, $p < .001$] with natal females > natal males

Table 3 Transition reasons

	Natal female *N* (%) *N* = 69	Natal male *N* (%) *N* = 31
*Reasons for transition**		
I wanted others to perceive me as the target gender	53 (76.8%)	24 (77.4%)
I thought transitioning was my only option to feel better	50 (72.5%)	21 (67.7%)
My body felt wrong to me the way it was	50 (72.5%)	21 (67.7%)
I didn't want to be associated with my natal sex/natal gender	51 (73.9%)	19 (61.3%)
It made me uncomfortable to be perceived romantically/sexually as a member of my natal sex/natal gender	49 (71.0%)	18 (58.1%)
I thought transitioning would eliminate my gender dysphoria	43 (62.3%)	22 (71.0%)
I felt I would become my true self	42 (60.9%)	22 (71.0%)
I identified with the target gender	40 (58.0%)	24 (77.4%)
I thought transitioning would lessen my gender dysphoria	45 (65.2%)	18 (58.1%)
I felt I would fit in better with the target gender	36 (56.5%)	20 (64.5%)
I felt I would be more socially acceptable as a member of the target gender	38 (55.1%)	11 (35.5%)
I felt I would be treated better if I was perceived as the target gender	35 (50.7%)	14 (45.2%)
I saw myself as a member of the target gender	31 (44.9%)	18 (58.1%)
I thought transitioning would reduce gender-related harassment or trauma I was experiencing	35 (50.7%)	5 (16.1%)
I had erotic reasons for wanting to transition	9 (13.0)	12 (38.7%)
Other	9 (13.0%)	3 (9.7%)

*May select more than one answer

participants experienced the friendship group dynamics identified in previous work, including belonging to a friendship group that mocked people who were not transgender (22.2%), having one or more friend from the pre-existing friend group transition before the participant decided to transition (36.4%), and experiencing an increase in popularity after announcing plans to transition (19.6%) (Littman, 2018). Most did not have this experience (68.7%, 61.6%, and 62.9%, respectively).

Pressure to transition. More than a third of the participants (37.4%) felt pressured to transition. Natal sex differences in feeling pressured to transition were significant by chi-square test with natal females > natal males $\chi^2(1, 99) = 4.22$, $p = .04$. Twenty-eight participants provided open-text responses of which 24 described sources of pressure (17 described social pressures and 7 described sources that were not associated with other people). Clinicians, partners, friends, and society were named as sources that applied pressure to transition, as seen in the following quotes: "My gender therapist acted like it [transition] was a panacea for everything;" "[My] [d]octor pushed drugs and surgery at every visit;" "I was dating a trans woman and she framed our relationship in a way that was contingent on my being trans;" "A couple of later trans friends kept insisting that I needed to stop delaying things;" "[My] best friend told me repeatedly that it [transition] was best for me;" "The forums and communities and internet friends;" "By the whole of society telling me I was wrong as a lesbian;" and "Everyone says that if you feel like a different gender…then you just are that gender and you should transition." Participants also felt pressure to transition that did not involve other people as illustrated by the following: "I felt pressured by my inability to function with dysphoria" and "Not by people. By my life circumstances."

Experiences with clinicians. When participants first sought care for their gender dysphoria or desire to transition, more than half of the participants (53.0%) saw a psychiatrist or psychologist; about a third saw a primary care doctor (34.0%) or a counselor (including licensed clinician social worker, licensed professional counselor, or marriage and family therapist) (32.0%); and 17.0% saw an endocrinologist. For transition, 45.0% of participants went to a gender clinic (44.4% of those attending a gender clinic specified that the gender clinic used the informed consent model of care); 28.0% went to a private doctor's office; 26.0% went to a group practice; and 13.0% went to a mental health clinic (see supplemental materials).

The majority (56.7%) of participants felt that the evaluation they received by a doctor or mental health professional prior to transition was not adequate and 65.3% reported that their clinicians did not evaluate whether their desire to transition was secondary to trauma or a mental health condition. Although 27.0% believed that the counseling and information they received prior to transition was accurate about benefits and risks, nearly half reported that the counseling was overly positive about the benefits of transition (46.0%) and not negative enough about the risks (26.0%). In contrast, only a small minority found the counseling not positive enough about benefits (5.0%) or too negative about risks (6.0%) suggesting a bias toward encouraging transition.

Transition

Participants were on average 21.9 years old (SD = 6.1) when they sought medical care to transition with natal females seeking care at younger ages ($M = 20.0$; SD = 4.2) than natal males ($M = 26.0$; SD = 7.5), $t(97) = -5.07$, $p < .001$. Given that the majority of natal males were categorized as Blanchard typology non-homosexual, the finding that natal males sought medical care to transition at older ages than natal females is concordant with previous research (Blanchard et al., 1987). The average year for seeking care was more recent for natal females ($M = 2011$; SD = 3.8) than natal males ($M = 2007$; SD = 6.9), $t(96) = 2.78$, $p = .007$, and thus, there may have been differences in the care they received due to differences in the culture surrounding transition and the prevailing medical approaches to gender dysphoria for the time.

At the start of transitioning, nearly all (98.0%) of the participants identified as either transgender (80.0%), nonbinary (15.0%), or both transgender and nonbinary (3.0%). Participants identified which social, medical, and surgical steps they had taken to transition. Table 4 shows these steps, separated by natal sex where appropriate. Most respondents adopted new pronouns (91.0%) and names (88.0%), and the vast majority (97.1%) of natal females wore a binder. Most participants took cross-sex hormones (96.0%) and most natal males took anti-androgens (87.1%). The most frequent transition surgery was breast or chest surgery for natal females (33.3%). Genital surgery was less common (1.4% of natal females and 16.1% of natal males). Natal females took testosterone for a mean duration of 2.0 years (SD = 1.6). Natal males took estrogen for a mean duration of 5.1 years (SD = 5.9) and anti-androgens for 2.8 years (SD = 2.6). The minority of patients who took puberty blockers took them for a mean duration of less than a year ($M = 0.9$ years; SD = 0.6).

Detransition

Before deciding to detransition, participants remained transitioned for a mean duration of 3.9 years (SD = 4.1) with natal females remaining transitioned for a shorter period of time ($M = 3.2$ years; SD = 2.7) than natal males ($M = 5.4$ years; SD = 6.1), $t(96) = -2.40$, $p = .018$. When participants decided to detransition they were a mean age of 26.4 years old (SD = 7.4) though natal females were significantly younger ($M = 23.6$; SD = 4.5) than natal males ($M = 32.7$; SD = 8.8), $t(97) = -6.75$, $p < .001$. The mean calendar year when participants decided to detransition was 2014 ($M = 2014$; SD = 3.3), but the difference

Table 4 Steps taken for social, medical, and surgical transition

	N (%)
*Social transition**	
Pronouns	91 (91.0%)
Different name	88 (88.0%)
Clothes/hair/makeup	90 (90.0%)
Legal name change	49 (49.0%)
Gender/sex changed on government documents	36 (36.0%)
Voice training	20 (20.0%)
Natal female	
Wore a binder	67 (97.1%)
*Medical transition**	
Cross-sex hormones	96 (96.0%)
Puberty blockers	7 (7.0%)
Natal male	
Anti-androgens	27 (87.1%)
*Surgical transition**	
Face/neck surgery	5 (5.0%)
Natal female	
Breast/chest surgery	23 (33.3%)
Genital surgery (to create a penis)	1 (1.4%)
Natal male	
Breast implants	5 (16.1%)
Genital surgery (to create a vagina)	5 (16.1%)

*May select more than one answer

between natal females and natal males was not significant ($M = 2014$, SD = 3.3; $M = 2014$, SD = 3.5), $t(95) = 0.52$.

Respondents detransitioned for a variety of reasons and most (87.0%) selected more than one reason. The most frequently endorsed reason for detransitioning was that the respondent's personal definition of male and female changed and they became comfortable identifying with their natal sex (60.0%) (see Table 5). Other commonly endorsed reasons were concerns about potential medical complications (49.0%); transition did not improve their mental health (42.0%); dissatisfaction with the physical results of transition (40.0%); and discovering that something specific like trauma or a mental health condition caused their gender dysphoria (38.0%). External pressures to detransition such as experiencing discrimination (23.0%) or worrying about paying for treatments (17.0%) were less common.

Encouragement and pressure to detransition. Participants were asked to select sources that encouraged them to believe that detransitioning would help them. These included blogs (37.0%), Tumblr (35.0%), and YouTube detransition videos (23.0%) (see supplemental materials). At some point in their process, 23.2% felt pressured to detransition. There was no significant difference between natal females and natal males for feeling pressured to detransition, $\chi^2(1, 99) = 1.11$. Of the 21 open-text responses provided, 14 respondents expressed social pressure to detransition; three expressed internal pressure to detransition and four provided responses that were neither

Table 5 Reasons for detransitioning

	Natal female *N* (%) $N = 69$	Natal male *N* (%) $N = 31$
*Reasons for detransitioning**		
My personal definition of female or male changed and I became more comfortable identifying as my natal sex	45 (65.2%)	15 (48.4%)
I was concerned about potential medical complications from transitioning	40 (58.0%)	9 (29.0%)
My mental health did not improve while transitioning	31 (44.9%)	11 (35.5%)
I was dissatisfied by the physical results of the transition/felt the change was too much	35 (50.7%)	5 (16.1%)
I discovered that my gender dysphoria was caused by something specific (ex, trauma, abuse, mental health condition)	28 (40.6%)	10 (32.3%)
My mental health was worse while transitioning	27 (39.1%)	9 (29.0%)
I was dissatisfied by the physical results of the transition/felt the change was not enough	22 (31.9%)	11 (35.5%)
I found more effective ways to help my gender dysphoria	25 (36.2%)	7 (22.6%)
My physical health was worse while transitioning	21 (30.4%)	11 (35.5%)
I felt discriminated against	12 (17.4%)	11 (35.5%)
I had medical complications from transitioning	12 (17.4%)	7 (22.6%)
Financial concerns about paying for transition care	11 (15.9%)	6 (19.4%)
My gender dysphoria resolved	10 (14.5%)	5 (16.1%)
My physical health did not improve while transitioning	9 (13.0%)	2 (6.5%)
I resolved the specific issue that was the cause of my gender dysphoria	6 (8.7%)	4 (12.9%)
I realized that my desire to transition was erotically motivated	1 (1.4%)	5(16.1%)
Other	19 (27.5%)	6 (19.4%)

*May select more than one answer

or unclear. Regarding social pressure to detransition, seven participants expressed that the pressure came from partners, parents, or other family members as shown in the following example quotes: "I was threatened that if I did not immediately detransition I would NEVER see my […] children again," "My father very much wanted me to desist," and "Parents constantly encouraging me to detransition." Five participants expressed societal pressure to detransition as expressed in the following quotes: "I did not pass, I was mocked in public, I could not get a job. It was not ok to be trans" and "Well, I mean basically the entire world was against me transitioning, so yeah." One participant felt pressured by doctors and another one from a blog.

Detransition steps. Table 6 shows data about the social, medical, and surgical steps participants took to detransition. Nearly all participants medically detransitioned by ceasing cross-sex hormones (95.0%). Social detransition steps were also common and included returning to the use of previously used pronouns (63.0%) and birth names (33.0%) and changing one's clothes and hair presentations (48.0%). Surgical detransition steps were less common (9.0%).

Finding better ways of coping with gender dysphoria**.** Participants were asked to select responses that that they considered to have been better ways for them to cope with their gender dysphoria. Responses included community (44.0%), mindfulness/meditation (41.0%), exercise (39.0%), therapy (24.0%), trauma work (24.0%), medication to treat a mental health condition (18.0%), and yoga (14.0%).

Table 6 Social, medical, and surgical detransition steps

	N (%)
*Social detransition**	
Previous pronouns	63 (63.0%)
Clothes/hair/makeup	48 (48.0%)
Birth name	33 (33.0%)
New name (not birth name)	24 (24.0%)
None of the above	2 (2.0%)
*Medical detransition**	
Stopped cross-sex hormones	95 (95.0%)
Stopped puberty blockers	4 (4.0%)
Started hormones consistent with natal sex	14 (14.0%)
Natal male	
Stopped anti-androgens	17 (54.8%)
*Surgical detransition**	
Surgery to reverse changes from transition	9 (9.0%)

*May select more than one answer

Transition and Detransition Narratives

Several transition and detransition narratives emerged from the data. A sizable minority of participants (41.0%) expressed more than one narrative in their responses.

The *discrimination and external pressures to detransition* narrative was described by 29.0% of participants. Examples include: "I had to detransition in order to get a job"; "I was afraid of being homeless and unable to support myself"; "I felt much happier with myself but I couldn't go anywhere without being afraid. I passed okay but not perfectly. I was stared down and sneered at in the women's clothes section, I wouldn't dare use a public toilet because I'd find either violent men or women who wished an encounter with a violent man on me."

A *nonbinary* narrative was expressed by 16.0% of participants. Some described that they discovered their nonbinary gender identity during their transition, as in the following quotes: "I still was uncomfortable with my body and figured I should stop and make sure I really wanted to keep going. I didn't and I decided I must be nonbinary, not FTM"; "Transitioning didn't do what I thought I wanted it to. I had transitioned to the wrong gender. I still felt wrong. Then, I realized I was not male, but genderqueer. I detransitioned to suit my true identity." And others described a consistent nonbinary identification, as in the following quote, "I identified the same way that I did before. I had gotten what I wanted out of HRT and was ready to stop taking it." (Cross-sex hormones are sometimes referred to as "hormone replacement therapy" and abbreviated as HRT).

Three participants (3.0%) expressed the *retransition* narrative in open-text answers indicating that they had retransitioned, including the following quotes: "I am now transitioning for a second time"; I retransitioned after 5 years of detransitioning"; and "Anyway, I retransitioned over 10 years after detransitioning."

Most participants (58.0%) expressed the *gender dysphoria was caused by trauma or a mental health condition* narrative which included endorsing the response options indicating that their gender dysphoria was caused by something specific, such as a trauma or a mental health condition. More than half of the participants (51.2%) responded that they believe that the process of transitioning delayed or prevented them from dealing with or being treated for trauma or a mental health condition. The following are example quotes that were in response to why participants chose to detransition: "I slowly began addressing the mental health conditions and traumatic experiences that caused such a severe disconnect between myself and my body…"; "I was starting to become critical of transition because I felt that many people were doing it out of self-hatred and started to realize that applied to me as well"; "I was deeply uncomfortable with my secondary sex characteristics, which I now understand was a result of childhood trauma and associating my secondary sex characteristics with those events."

Despite the absence of any questions about this topic in the survey, nearly a quarter (23.0%) of the participants expressed the *internalized homophobia and difficulty accepting oneself as lesbian, gay, or bisexual* narrative by spontaneously describing that these experiences were instrumental to their gender dysphoria, their desire to transition, and their detransition. All

of the participants in this category indicated that they were either same-sex attracted exclusively or were same-sex attracted in combination with opposite-sex attraction (such as bisexual, pansexual, etc.). The following responses were written in as "other" for the question about why participants transitioned: "Transitioning to male would mean my attraction to girls would be 'normal'"; "being a 'gay trans man' (female dating other females) felt better than being a lesbian, less shameful"; "I felt being the opposite gender would make my repressed same-sex attraction less scary"; "I didn't want to be a gay man." Some participants described that it took time for them to gain an understanding of themselves as lesbian, gay, or bisexual as seen in the following: "At the time I was trying to figure out my identity and felt very male and thought I was transgender. I later discovered that I was a lesbian…"; and "Well, after deep discovery, I realized I was a gay man and realized that a sexual trauma after puberty might [have] confused my thought. I wanted to live as a gay man again." Several natal female respondents expressed that seeing other butch lesbians would have been helpful to them as shown by the following: "What would have helped me is being able to access women's community, specifically lesbian community. I needed access to diverse female role-models and mentors, especially other butch women."

The *social influence* narrative was identified where participants added information to the question about if they had felt pressured to transition and the response described pressure from a person or people. One-fifth (20.0%) of participants expressed that they felt pressured by a person or people to transition. Example quotes for social influence were described in a previous section.

Of the natal females, 7.2% expressed the *misogyny* narrative. Example quotes include: "…I realized how much of it [dysphoria] may have been caused by internalized misogyny and homophobia"; "Finally realizing there's nothing wrong or disgusting or weak about being female"; and "My transition was a desperate attempt to distance myself from womanhood and femaleness due to internalized lesbophobia and misogyny combined with a history of sexual trauma."

After Detransition

Disposition. At the time of survey completion, most participants had returned to identifying solely as their birth sex (61.0%) with an additional 10.0% identifying as their birth sex plus another identification. Fourteen percent of the participants identified solely as nonbinary with an additional 11.0% identifying as nonbinary plus a second identification. Eight percent of the participants identified solely as transgender with an additional 5.0% identifying as transgender plus another identification. Four percent of the responses did not fit into the above categories and were coded as "other." Figure 1 illustrates the distribution of participants' current gender identification (post-detransition). Only 24.0% of participants had informed

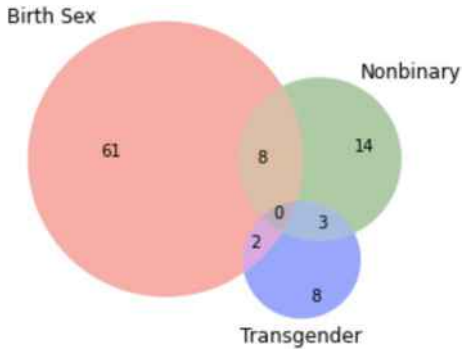

Fig. 1 Distribution of participants' current gender identification (after detransition) (n = 100). *Notes*: The sum of the numbers appearing in the "Birth Sex" circle indicates the number of participants who returned to identifying with their birth sex (71)—either as birth sex alone (61) or birth sex in addition to a second identification (10) represented in the overlap between two circles. For example, eight participants identify as their birth sex and as nonbinary. The sum of the numbers appearing in the "Nonbinary" circle indicates the number of participants who identify as nonbinary (25)—either as nonbinary alone (14) or nonbinary in addition to a second identification (11). The sum of the numbers appearing in the "Transgender" circle indicates the number of participants who identify as transgender (13)—either as transgender alone (8) or transgender in addition to a second identification (5). Four participants had responses that did not fit the categories above and were coded as "other"

the doctor or clinic that facilitated their transitions that they had detransitioned.

Self-appraisal of past transgender identification. Table 7 presents the data for responses endorsed by participants to reflect how they feel currently about having identified as transgender in the past. The statements most frequently selected included: "I thought gender dysphoria was the best explanation for what I was feeling" (57.0%), "My gender dysphoria was similar to the gender dysphoria of those who remain transitioned" (42.0%), "What I thought were feelings of being transgender actually were the result of trauma" (36.0%), "What I thought were feelings of being transgender actually were the result of a mental health condition" (36.0%).

Self-appraisal of transition and detransition. When asked to select which statement best reflects their feelings about their transition, nearly a third (30.0%) indicated that they wish they had never transitioned while 11.0% indicated they were glad they transitioned. Some (34.0%) selected the statement that transition "was a necessary part of [their] journey" but others (21.0%) indicated that the process of transitioning distracted them from what they should have been doing. Responses about whether transition helped or harmed them were also complicated. While 50.5% selected answers consistent with being both helped and harmed, 32.3% indicated that they were only harmed and 17.2% indicated that they were only helped. The majority of respondents were dissatisfied with their decision to transition (69.7%) and satisfied with their decision to detransition (84.7%). At least some amount of transition regret was

Table 7 Self-appraisal of past transgender identification

	Natal female *N* (%) *N* = 69	Natal male *N* (%) *N* = 31
*Self-appraisal about identifying as transgender in the past**		
I thought gender dysphoria was the best explanation for what I was feeling	39 (56.5%)	18 (58.1%)
My gender dysphoria was similar to the gender dysphoria of those who remain transitioned	32 (46.4%)	10 (32.3%)
What I thought were feelings of being transgender actually were the result of trauma	31 (44.9%)	5 (16.1%)
What I thought were feelings of being transgender actually were the result of a mental health condition	28 (40.6%)	8 (25.8%)
Someone else told me that the feelings I was having meant that I was transgender and I believed them	25 (36.2%)	10 (32.3%)
I still identify as transgender	20 (29.0%)	10 (32.3%)
I believed I was transgender then, but I was mistaken	16 (23.2%)	6 (19.4%)
I was transgender then but I am not transgender now	15 (21.7%)	7 (22.6%)
I formerly identified as transgender and now identify as genderqueer/nonbinary	12 (17.4%)	5 (16.1)
My gender dysphoria was different from the gender dysphoria of those who remain transitioned	11 (15.9%)	4 (12.9%)
I was never transgender	8 (11.6%)	3 (9.7%)
I thought I had gender dysphoria but I was mistaken	4 (5.8%)	4 (12.9%)
I never had gender dysphoria	1 (1.4)	2 (6.5%)
N/A as I did not identify as transgender in the past	0 (0%)	1 (3.2%)
Other	18 (26.1%)	5 (16.1%)

*May select more than one answer

common (79.8%) and nearly half (49.5%) reported strong or very strong regret. Most respondents (64.6%) indicated that if they knew then what they know now, they would not have chosen to transition.

Discussion

This study was designed to explore the experiences of individuals who obtained medical and surgical treatment for gender dysphoria and then detransitioned by discontinuing the medications or having surgery to reverse the changes from transition. The findings of this study, however, should not be assumed to be representative of all individuals who detransition. Although this study further documents that detransitioners exist, the prevalence of detransition as an outcome of transition is unknown. Only a small percentage of detransitioners (24.0%) informed the clinicians and clinics that facilitated their transitions that they had detransitioned. Therefore, clinic rates of detransition are likely to be underestimated and gender transition specialists may be unaware of how many of their own patients have detransitioned, particularly for patients who are no longer under their care.

This research demonstrates that the experiences of individuals who detransition are varied and the reasons for detransition are complex. Nearly all participants identified as transgender or nonbinary at the start of their transition and most sought transition because they did not want to be associated with their natal sex, their bodies felt wrong the way they were, and they believed that transition was the only option to relieve their distress. Some were helped by transition and only detransitioned because they were pressured to do so by people in their lives, society, or because they had medical complications. Some were harmed by transition and detransitioned because they concluded that their gender dysphoria was caused by trauma, a mental health condition, internalized homophobia, or misogyny—conditions that are not likely to be resolved with transition. These findings highlight the complexity of gender dysphoria and suggest that, in some cases, failure to explore co-morbidities and the context in which the gender dysphoria emerged can lead to misdiagnosis, missed diagnoses, and inappropriate gender transition. Some individuals detransitioned because their gender dysphoria resolved, because they found better ways to address their symptoms, or because their personal definitions of male and female changed and they became comfortable identifying as their natal sex.

The study sample was predominantly young natal females, many of whom experienced late-onset gender dysphoria which mirrors the recent, striking changes in the demographics of gender dysphoric youth seeking care as well as the youth described by their parents in Littman (2018) (see also Aitken et al., 2015; de Graaf et al., 2018; Zucker, 2019). Concerns have been raised that this new cohort of gender dysphoric individuals is unlike previous cohorts. Professionals have started to call for caution before treating this cohort with interventions with permanent effects because the etiologies, desistance and persistence rates,

expected duration of symptoms, and whether this new population is helped or harmed by gender transition is still unknown (D'Angelo et al., 2021; Kaltiala-Heino et al., 2018). The natal females and natal males in this sample differed on several dimensions, including that natal females were younger than natal males when they sought transition, when they decided to detransition, and at the time of survey completion. Natal females were more likely than natal males to have experienced a trauma less than one year before the onset of their gender dysphoria and were more likely to have felt pressured to transition. Compared to natal males, natal females remained transitioned for a shorter duration of time before deciding to detransition. Additionally, natal females transitioned more recently than natal males, so their experiences may vary due to changing trends in the clinical management of gender dysphoria and the cultural settings in which they became gender dysphoric.

The study findings covered a wide range of detransition experiences that are consistent with the diversity of experiences described in previously published clinical case reports and case series. Overlap of findings include: transition regret; absence of transition regret; re-identification with birth sex; continued identification as transgender; improvement or worsening of well-being with transition; retransitioning; detransitioning due to external social pressures; nonbinary identification; and recognizing and accepting oneself as homosexual or bisexual (D'Angelo, 2018; Djordjevic et al., 2016; Levine, 2018; Pazos Guerra et al., 2020; Turban & Keuroghlian, 2018; Turban et al., 2021; Vandenbussche, 2021). The population in this study is similar to the population in Vandenbussche in that both were predominantly natal females in their mid-20s. Because the current study recruited in 2016–2017 and Vandenbussche recruited in 2019, the similar mean age of participants may reflect the age of individuals who can be reached in online detransitioner communities. Several findings in this study were consistent with Vandenbussche's findings, including similar reasons for detransition (realizing that their gender dysphoria was related to other issues, finding alternatives to address gender dysphoria, gender dysphoria resolved, etc.). Although these two studies were recruited in different years, had different eligibility criteria, and included participants from several countries, it is possible that there may be some overlap of study populations.

The current study findings provide additional insight into the complex relationships between internalized homophobia, gender dysphoria, and desire to transition. Contrary to arguments against the potential role of homophobia in gender transitions (Ashley, 2020), participants reported that their own gender dysphoria and desire to transition stemmed from the discomfort they felt about being same-sex attracted, their desire to not be gay, and the difficulties that they had accepting themselves as lesbian, gay or bisexual. For these individuals, exploring their distress and discomfort around sexual orientation issues may have been more helpful to them than medical and surgical transition or at least an important part of exploration before making the decision to transition. This research adds to the existing evidence that gender dysphoria can be temporary (Ristori & Steensma, 2016; Singh et al., 2021; Zucker, 2018). It has been established that the most likely outcome for prepubertal youth with gender dysphoria is to develop into lesbian, gay, bisexual (LGB) (non-transgender) adults (Ristori & Steensma, 2016; Singh et al., 2021; Wallien & Cohen-Kettenis, 2008; Zucker, 2018). And, temporary gender dysphoria may be a common part of LGB identity development (Korte et al., 2008; Patterson, 2018). Therefore, intervening too soon to medicalize gender dysphoric youth risks iatrogenically derailing the development of youth who would otherwise grow up to be LGB non-transgender adults. Participants who detransitioned because they became comfortable identifying as their natal sex and because their gender dysphoria resolved further support that gender dysphoria is not always permanent.

The data in this study strengthen, with first-hand accounts, the rapid-onset gender dysphoria (ROGD) hypotheses which, briefly stated, are that psychosocial factors (such as trauma, mental health conditions, maladaptive coping mechanisms, internalized homophobia, and social influence) can cause or contribute to the development of gender dysphoria in some individuals (Littman, 2018). Littman also postulated that certain beliefs could be spread by peer contagion, including the belief that a wide range of symptoms should be interpreted as gender dysphoria (and proof of being transgender) and the belief that transition is the only solution to relieve distress. The current study supports the potential role of psychosocial factors in the development of gender dysphoria and further suggests, by participant responses that transitioning prevented or delayed them from addressing their underlying conditions, that maladaptive coping mechanisms may be relevant for some individuals. The potential role of social influence is demonstrated as well. First, when respondents were asked to describe how they currently feel about having identified as transgender in the past, more than a third endorsed the option, "Someone told me that the feelings I was having meant that I was transgender, and I believed them." Second, a subset of participants experienced the unique friendship group dynamics reported in Littman where peer groups mocked people who were not transgender and popularity within the friend group increased when respondents announced their plan to transition. Additionally, respondents identified several social sources that encouraged them to believe that transitioning would help them including: YouTube transition videos, blogs, Tumblr, and online communities. And finally, 20.0% of participants felt pressured to transition by social sources that included friends, partners, and society. More research is needed to further explore these hypotheses.

The current study and the Turban et al. (2021) analysis of the USTS data share some similarities and differences. Similarities include the use of convenience samples, targeted recruitment, and anonymous data collection. The findings of Turban et al. (including external pressures to detransition and transgender

identification after detransition) are a subset of the array of experiences described in the current study. The current study differed from James et al. (2016) and Turban et al. in that it enrolled participants based on the criterion of detransition after medical or surgical transition regardless of how they currently identified, recruited from communities with diverse perspectives about transition and detransition, used a precise definition for detransition that specifies the use of medication or surgery, and included answer options that were relevant to many different types of detransition experiences. In contrast, the USTS only enrolled transgender-identifying individuals regardless of whether they medically or surgically transitioned, recruited from communities likely to have similar perspectives about transition and detransition, and provided multiple choice answer options that were relevant to a narrower range of detransition experiences (James et al., 2016). Further, the definition used by the USTS for "detransitioned" (having "gone back to living as [their] sex assigned as birth, at least for a while") is quite vague. Although Turban et al. provide valuable information about the subset of transgender-identifying people who may have detransitioned, the current study provides a more comprehensive view of individuals who detransition after medical or surgical transition.

Over the past 15 years, there have been substantial changes in the clinical approach to gender dysphoric patients notable for a shift from approaches that employ thorough evaluations and judicious use of medical and surgical transition (the watchful waiting or Dutch approach, the developmentally informed approach, and the medical model of care) to approaches with minimized or eliminated evaluation and liberal use of transition interventions (the affirmative approach and the informed consent model of care) (Cavanaugh et al., 2016; de Vries & Cohen-Kettenis, 2012; Meyer et al., 2002; Rafferty et al., 2018; Schulz, 2018; Zucker et al., 2012b). This trend is prominent in the U.S. where the American Academy of Pediatrics endorsed the affirmative approach in 2018 and Planned Parenthood currently uses the informed consent model to provide medical transition in more than 200 clinics in 35 states (Planned Parenthood, 2021; Rafferty et al., 2018). It is plausible that an unintended consequence of these clinical shifts may be an increase in people who detransition. Many participants in this study believe that they did not receive an adequate evaluation by a clinician before transition. The definition of "adequate evaluation" was not provided in the survey and may be open to respondent interpretation. But given the complexities of the gender dysphoria described in the current study, one might consider a low bar of "adequate" to be the exploration of factors that could be misinterpreted as non-temporary gender dysphoria as well as factors that could be underlying causes for gender dysphoria. The most recently emerging approach to gender dysphoria is called the "exploratory approach" which is a neutral psychotherapeutic approach to help individuals gain a deeper understanding of their gender distress and the factors contributing to their dysphoria (Churcher Clarke & Spiliadis, 2019; Spiliadis, 2019). The study's findings suggest that an exploratory type of approach may have been beneficial to some of the respondents. Future research is needed to determine which patients are best treated by which approaches long term.

Patients considering medical and surgical interventions deserve accurate information about the risks, benefits, and alternatives to that treatment. In this sample, nearly half of the participants reported that the counseling they received about transition was overly positive about the benefits of transition and more than a quarter reported that the counseling was not negative enough about the risks. Several participants felt pressured to transition by their doctors and therapists. If these types of clinical interactions are verified, exploration is needed to determine the extent to which this situation occurs and what measures might be taken to ensure that clinicians provide patients with their options accurately and dispassionately.

There are several obstacles to obtaining accurate rates of detransition and desistance, including stigma and the low numbers of detransitioners who inform their clinicians that they detransitioned. One approach to bypass some of these barriers would be to incorporate non-judgmental questions about detransition and desistance into nationally representative surveys that collect health data. For example, the Behavioral Risk Factor Surveillance System contains an optional module about sexual orientation and gender identity that includes two questions to explore gender issues (Downing & Przedworski, 2018). By changing one existing question, "Do you consider yourself to be transgender?" into two questions, "Have you ever, at any point in your life, considered yourself to be transgender?" and "Do you currently consider yourself to be transgender?" and by adding a follow-up question if answers indicate past but not current transgender identification, "Did you ever take puberty blockers, cross-sex hormones, anti-androgens, or have any surgery as part of your transition?", valuable information about desistance, detransition, and current transgender identification could be obtained. These types of questions may also be of use in clinical practice and electronic medical records. The information gained about rates of detransition and desistance would enhance transgender healthcare by aiding informed consent processes at the start of any medical or surgical transition.

One of the strengths of this study is that it is one of the largest samples of detransitioners to date. Other strengths include the use of a precise definition for detransition, enrollment of detransitioners regardless of their post-detransition gender identification, recruitment from communities with likely divergent views about transition and detransition, and collaboration with two individuals who had detransitioned which helped to create a survey instrument with questions relevant to a variety of detransition experiences and enhanced the recruitment efforts.

There are several limitations to this study that should be considered when interpreting the findings. Like Vandenbussche (2021), James et al. (2016), and Turban et al. (2021), this study

used a cross-sectional design, anonymous surveying, and a convenience sample and therefore shares the same limitations that are inherent to these methodologies. These limitations include that conclusions about causation cannot be determined, identities of participants cannot be verified, and the findings of this study may not be generalizable to the entire population of people who detransition or to people outside of the countries where participants were from. Although this study reached out to communities with differing perspectives about transition and detransition, targeted recruitment and convenience samples always introduce the limitations associated with selection biases which should be addressed in future research. Finally, many of the participants in this study had less than ideal outcomes to their medical and surgical transitions, and it is possible that these experiences may have colored some of the responses.

Additional research is needed to determine the prevalence of detransition as an outcome of transition and to identify and meet the psychological and medical needs of the emerging detransitioned population. Because many individuals who detransition re-identify with their birth sex, are no longer connected to LGBT communities, and don't return to gender clinics, future research about detransition needs to expand recruitment efforts beyond gender clinics and transgender communities. The development and testing of non-medical interventions for gender dysphoria could provide valuable options to be used as alternatives or in conjunction with medical and surgical treatments. Because of the potential for some to experience trauma, mental health conditions, internalized homophobia, and misogyny as gender dysphoria, research needs to be conducted on the evaluation process before transition to find approaches that respectfully and collaboratively explore factors that might contribute to gender-related distress. There continues to be an absence of long-term outcomes evidence for youth treated with medical and surgical transition and a lack of information about the trajectories of youth experiencing late-onset gender dysphoria–research is needed to address these gaps. Continued work is needed to reduce rigid gender roles, increase representation of gender stereotype nonconformity, and to address discrimination and social pressures exerted against people who are transgender, lesbian, gay, bisexual, and gender stereotype non-conforming.

Conclusion

This study described individuals who, after transitioning with medications or surgery, have detransitioned. The prevalence of detransitioning after transition is unknown but is likely underestimated because most of the participants did not inform the doctors who facilitated their transitions that they had detransitioned. There is no single narrative to explain the experiences of all individuals who detransition and we should take care to avoid painting this population with a broad brush. Some detransitioners return to identifying with their birth sex, some assume (or maintain) a nonbinary identification, and some continue to identify as transgender. Some detransitioners regret transitioning and some do not. Some of the detransitioners reported experiences that support the ROGD hypotheses, including that their gender dysphoria began during or after puberty and that mental health issues, trauma, peers, social media, online communities, and difficulty accepting themselves as lesbian, gay, or bisexual were related to their gender dysphoria and desire to transition. Natal female and natal male detransitioners appear to have differences in their baseline characteristics and experiences and these differences should be further delineated. Future research about gender dysphoria and the outcomes of transition should consider the diversity of experiences and trajectories. More research is needed to determine how best to provide support and treatment for the long-term medical and psychological well-being of individuals who detransition. Findings about detransition should be used to improve our understanding of gender dysphoria and to better inform the processes of evaluation, counseling, and informed consent for individuals who are contemplating transition.

Acknowledgements I would like to thank the two individuals with personal experience of detransitioning who helped to create the survey instrument and assisted with recruitment; and Dr. Anna Hutchinson, Dr. Roberto D'Angelo, and the peer-reviewers for providing feedback on earlier versions of this manuscript

Funding No funding was received for conducting this study. Open access fees were provided by the Institute for Comprehensive Gender Dysphoria Research.

Declarations

Conflict of interest The author has no relevant financial or non-financial conflicts of interest to disclose.

Consent to Participate Electronic consent was obtained from all participants included in the study. On the first page of the online survey, participants were informed of the research purpose and potential risks and benefits of participating, that their participation was voluntary, and were presented with a way to contact the researcher. The research survey questions were displayed only if the participant clicked "agree" which indicated that the participant read the information, voluntarily agreed to participate, and were at least 18 years of age.

Ethical Approval The research was determined to be Exempt Human Research by the Program for the Protection of Human Subjects of the Icahn School of Medicine at Mount Sinai in New York, NY. All procedures were performed in accordance with the ethical standards of the Program for the Protection of Human Subjects at the Icahn School of Medicine at Mount Sinai and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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Journal of Homosexuality

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/wjhm20

Detransition-Related Needs and Support: A Cross-Sectional Online Survey

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To cite this article: Elie Vandenbussche (2021): Detransition-Related Needs and Support: A Cross-Sectional Online Survey, Journal of Homosexuality, DOI: 10.1080/00918369.2021.1919479

To link to this article: https://doi.org/10.1080/00918369.2021.1919479

JOURNAL OF HOMOSEXUALITY
https://doi.org/10.1080/00918369.2021.1919479

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Detransition-Related Needs and Support: A Cross-Sectional Online Survey

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ABSTRACT

The aim of this study is to analyze the specific needs of detransitioners from online detrans communities and discover to what extent they are being met. For this purpose, a cross-sectional online survey was conducted and gathered a sample of 237 male and female detransitioners. The results showed important psychological needs in relation to gender dysphoria, comorbid conditions, feelings of regret and internalized homophobic and sexist prejudices. It was also found that many detransitioners need medical support notably in relation to stopping/changing hormone therapy, surgery/treatment complications and reversal interventions. Additionally, the results indicated the need for hearing about other detransitioners' experiences and meeting each other. A major lack of support was reported by the respondents overall, with a lot of negative experiences coming from medical and mental health systems and from the LGBT+ community. The study highlights the importance of increasing awareness and support given to detransitioners.

KEYWORDS

Detransition; gender dysphoria; gender identity; cross-sex hormones; detransitioners; transgender; transition; support

Introduction

In recent years, there has been an increasing interest in the phenomenon of detransition. Many testimonies have been shared by self-identified detransitioners online and detrans communities have formed on social media. This phenomenon started to attract the attention of scholars, who have emphasized the need for research into the specific needs of this group (e.g., Butler & Hutchinson, 2020; Entwistle, 2020; Hildebrand-Chupp, 2020). A few case studies have been conducted in order to explore individual experiences of detransition (Pazos-Guerra et al., 2020; Turban & Keuroghlian, 2018). The latter studies highlighted the complexity of detransition experiences but did not provide sufficient data to assess the general needs and characteristics of detransitioners. The current study aims to explore this issue in more depth and to serve as a basis for future research on the phenomenon of detransition.

To date there has been little agreement on a definition of the word "detransition." As explained by Expósito-Campos (2021), this term has been used interchangeably to refer to what he perceives to be two distinctive situations: in

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the first, the detransitioning individual stops identifying as transgender; in the second, they do not. It is therefore necessary here to clarify exactly what is meant when writing about detransition.

In this paper, I will be using the following concepts: "medical detransition," "social detransition" and (male or female) "detransitioner." Medical detransition refers to the process of ceasing/reversing the medical aspects of one's medical transition. This might include stopping or changing hormone therapy and undergoing reversal surgeries, among others. Likewise, social detransition refers to the process of changing/undoing the social aspects of one's social transition. For example, it might include presenting oneself as one's birth sex again, changing one's post-transition name or going back to using the pronouns associated with one's birth sex.

The term "detransitioner" will be used here to refer to someone who possibly underwent some of these medical and/or social detransition steps and, more importantly, who identifies as a detransitioner. It is important to add this dimension, because the act of medical/social detransition can be performed by individuals who did not cease to identify as transgender and who do not identify as detransitioners or as members of the detrans community. Furthermore, some individuals might identify as detransitioners after having ceased to identify as trans, while not being in a position to medically or socially detransition due to medical or social concerns. As Hildebrand-Chupp (2020) puts it: "[B]ecoming a detransitioner involves a fundamental shift in one's subjective understanding of oneself, an understanding that is constructed within these communities." (p.802). More qualitative research should be conducted in order to better understand how members of the detrans community define themselves and make sense of their own detransition process. However, this goes beyond the scope of this study.

The creation of support and advocacy groups for detransitioners in recent years (e.g., DetransCanada, n.d., Detrans Voices, n.d., The Detransition Advocacy Network, n.d., Post Trans, n.d.) testifies to the formation of a detrans community whose members have specific needs. Scholars and clinicians have recently started raising concerns around the topic (e.g., Butler & Hutchinson, 2020; Entwistle, 2020; Hildebrand-Chupp, 2020; Marchiano, 2020). However, little research has been done specifically into the characteristics of this seemingly growing community.

Two informal surveys conducted by detransitioners (Hailey, 2017; Stella, 2016) have explored the demographics and (de)transition experiences of members of online female detrans communities. These will constitute interesting points of comparison in the discussion section of the current research.

The purpose of this exploratory study is to offer an overview of the current needs of detransitioners from online detrans communities, which will hopefully serve as a useful basis for further experimental studies around the topic of detransition. The current research primarily seeks to address the following

questions: What are the current needs of detransitioners? What support is given to detransitioners in order to fulfil these needs?

Methods

Procedure

A cross-sectional survey was conducted, using online social media to recruit detransitioners. Access to the questionnaire was open from the 16th of November until the 22nd of December 2019. Any detransitioner of any age or nationality was invited to take part in the study. The survey was shared by Post Trans (www.post-trans.com)—a platform for female detransitioners—via public posts on Facebook, Instagram and Twitter. Participants were also recruited through private Facebook groups and a Reddit forum for detransitioners (r/detrans). Some of the latter platforms were addressed exclusively to female detransitioners. The purpose of the study was presented as gaining a better understanding of detransitioners' current needs. Potential participants were asked to fill out the form and share it to fellow detransitioners. All participants have been fully anonymized.

Everyone who answered "yes" to the question "Did you transition medically and/or socially and then stopped?" was selected in the study. The individual questionnaires of the 9 respondents who answered "no" to this question were looked at closely, in order to assess whether they should be included in the study. Eight of them were added to the final sample, as their other answers indicated that their experiences lead them to identify as detransitioners.

This research was approved by the Ethics Committee for Noninvasive Research on Humans in the Faculty of Society and Economics of the Rhine-Waal University of Applied Sciences

Questionnaire design

The questionnaire consisted of 24 questions (see Appendix). The first series of questions was aimed at defining the profile of the respondent (age, sex, country, etc.), the second was asking about relevant aspects of transition and detransition experiences (transition type, gender dysphoria, therapy, medical interventions, reasons for detransitioning etc.), and the third focused on the needs encountered as well as the support (or lack of) received during the process of detransition (medical, psychological, legal and social needs and support).

Most of the items were multiple-choice questions. The conception of the multiple choices was based on observations drawn from several detransition online resources and forums. An open "other" category was available when relevant for the respondents to write in possibly lacking options. The survey

was designed to leave a lot of free space to add answers, since the detransition population is still very much under-researched and there is a lot to learn from each of its members. This is why a more qualitative approach was taken for the last question notably, leaving an open field for adding comments about the support—or lack of—received while detransitioning. This qualitative data was analyzed through the identification of recurrent themes, which will be presented in the results section.

Participants

A total of 237 participants were included in the final sample. The large majority was female; 217 female (92%) for 20 male respondents (8%). This was determined based on the answers to the question: "What sex were you assigned at birth?" The average age was 25.02 years (SD = 7.72), ranging from 13 to 64. The mean age of female detransitioners (M = 24.38; SD = 6.86) was lower than that of male detransitioners (M = 31.95; SD = 12.26).

Around half of the sample (51%) reported coming from the United States and close to a third from Europe (32%). Fifteen respondents are from Canada (6%), twelve from Australia (5%), and one from each of the following countries: Brazil, Kazakhstan, Mexico, Russia and South Africa.

Close to two thirds (65%) transitioned both socially and medically; 31% only socially. A few respondents rightly criticized the fact that the option of medically transitioning only was not available in the questionnaire. The absence of this option needs to be kept in mind when looking at the results.

Around half (51%) of the respondents started socially transitioning before the age of 18, and a quarter (25%) started medically transitioning before that age as well. The average age of social transition was 17.96 years (17.42 for females; 23,63 for males) (SD = 5.03) and that of medical transition was 20.70 years (20.09 for females; 26.19 for males) (SD = 5.36). Fourteen percent of the participants detransitioned before turning 18. The average age of detransition was 22.88 years (22.22 for females; 30.00 for males) (SD = 6.46). The average duration of transition of the respondents (including both social and medical transition) was 4.71 years (4.55 for females; 6.37 for males) (SD = 3.55).

Eighty percent of the male detransitioners underwent hormone therapy, compared to 62% for female detransitioners. Out of the respondents who medically transitioned, 46% underwent gender affirming surgeries.

Results

For sake of clarity, the results will be presented based on the three categories mentioned above in the methods section: profile of the respondents, relevant aspects of transition and detransition and, finally, detransition-related needs and support. The qualitative results will be displayed at the end of this section.

Profile of the respondents

Most of the information related to the profile of the respondents can be found in the methods section. The sample showed a high prevalence of comorbidities, considering that over half of the participants (54%) reported having had at least 3 diagnosed comorbid conditions (out of the 11 conditions listed in the survey—see Table 1). The most prevalent diagnosed comorbid conditions are depressive disorders (69%) and anxiety disorders (63%), including PTSD (33%) (see Table 1).

Relevant aspects of transition and detransition

A great majority of the sample (84%) reported having experienced both social and body dysphoria. (Social dysphoria being defined as a strong desire to be seen and treated as being of a different gender, and body dysphoria as a strong desire to have sex characteristics of the opposite sex/rejection of your own sex). Eight percent reported having experienced only body dysphoria, 6% only social dysphoria and 2% neither of them.

Forty-five percent of the whole sample reported not feeling properly informed about the health implications of the accessed treatments and interventions before undergoing them. A third (33%) answered that they felt partly informed, 18% reported feeling properly informed and 5% were not sure.

The most common reported reason for detransitioning was realized that my gender dysphoria was related to other issues (70%). The second one was health concerns (62%), followed by transition did not help my dysphoria (50%), found alternatives to deal with my dysphoria (45%), unhappy with the social changes (44%), and change in political views (43%). At the very bottom of the list are: lack of support from social surroundings (13%), financial concerns (12%) and discrimination (10%) (see Figure 1).

34 participants (14%) added a variety of other reasons such as absence or desistance of gender dysphoria, fear of surgery, mental health concerns related

Table 1. Number of participants with comorbid conditions.

Comorbid condition	Diagnosed	Suspected
Depressive disorder	163 (70%)	32 (14%)
Anxiety disorder	149 (63%)	43 (18%)
Post-traumatic stress disorder	79 (33%)	63 (27%)
Attention deficit disorder	57 (24%)	50 (21%)
Autism spectrum condition	47 (20%)	61 (26%)
Eating disorder	46 (19%)	58 (25%)
Personality disorder	40 (17%)	26 (11%)
Obsessive compulsive disorder	35 (15%)	44 (19%)
Polycystic ovary syndrome (only females)	22 (10%)	13 (6%)
Dissociative identity disorder	14 (6%)	23 (10%)
Schizo-spectrum disorder	5 (2%)	9 (4%)

"Diagnosed" and "Suspected" were mutually exclusive categories.

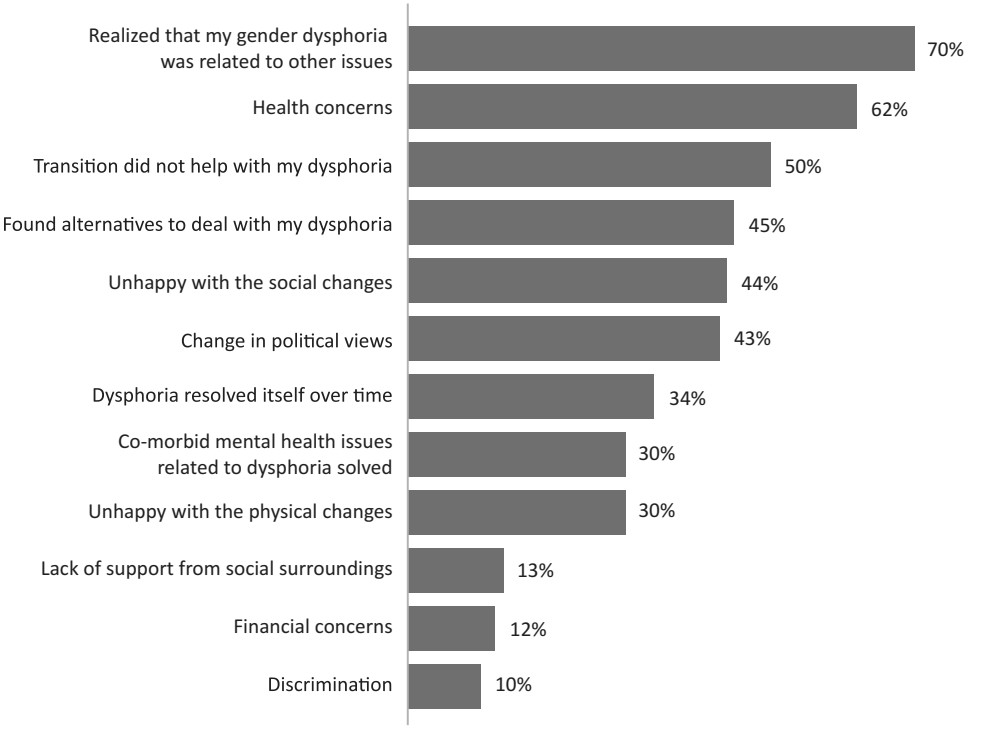

Figure 1. Reasons for detransitioning.

to treatment, shift in gender identity, lack of medical support, dangerosity of being trans, acceptance of homosexuality and gender non-conformity, realization of being pressured to transition by social surroundings, fear of surgery complications, worsening of gender dysphoria, discovery of radical feminism, changes in religious beliefs, need to reassess one's decision to transition, and realization of the impossibility of changing sex.

Detransition-related needs and support

The different types of needs were divided into four categories in the questionnaire: medical, psychological, legal and social needs.

Medical needs

The most commonly chosen answer was the need for receiving accurate information on stopping/changing hormonal treatment (49%), followed by receiving help for complications related to surgeries or hormonal treatment (24%) and receiving information and access to reversal surgeries/procedures (15%). Forty-six percent of the participants reported not having any detransition-related medical need. Sixteen respondents (7%) added another non-listed answer, such as tests to determine current reproductive health, information

about long-term effects of hormone therapy, about the health consequences of having had a full hysterectomy and about pain related to chest binding.

Psychological needs

Psychological needs appeared to be the most prevalent of all, with only 4% of the respondents reporting not having any. The answers working on comorbid mental issues related to gender dysphoria and learning to cope with gender dysphoria; finding alternatives to medical transition are at the top of the list, both with 65%. Below that, learning to cope with feelings of regret (60%), followed by learning to cope with the new physical and/or social changes related to detransitioning (53%) and learning to cope with internalized homophobia (52%). Thirty-four respondents (14%) added another non-listed answer, such as trauma therapy, learning how to deal with shame and internalized misogyny, how to cope with rejection from the LGBT and trans communities and how to deal with the aftermath of leaving a manipulative group. Other answers disclosed the need for help recovering from addictive sexual behavior related to gender dysphoria, psychosexual counseling and peer support.

Legal needs

More than half of the sample (55%) reported not having any detransition-related legal need. The main legal need expressed was changing back legal gender/sex marker and/or name (40%), followed by legal advice and support to take legal action over medical malpractice (13%). Five respondents (2%) added another non-listed answer, such as employment legal aid and support to take legal action for having been forced to go through a sterilization.

Social needs

The big majority of the respondents reported a need for hearing about other detransition stories (87%). The second most common answer was getting in contact with other detransitioners (76%), followed by receiving support to come out and deal with negative reactions (57%). Thirty-three respondents (14%) added another non-listed answer such as being accepted as female while looking male, help navigating social changes at the workplace, building a new social network, more representation of butch lesbians, real life support and finding a community.

When looking at from whom the respondents received support while transitioning and detransitioning, it appears that the biggest source of help comes from online groups/forums/social media for both transition and detransition (65%). The support received from friends, partner(s) and family is a little higher for detransition (64%) than for transition (56%).

Only 8% of the respondents reported having received help from an LGBT+ organization while detransitioning, compared to 35% while transitioning.

Similarly, 5% reported having received help from a trans-specific organization while detransitioning, compared to 17% while transitioning.

A total of 29% reported having received support for their detransition from the medical professionals that helped them during their transition. In contrast, 38% sought support from a new therapist/doctor. A part of the sample reported not receiving help from anybody for transitioning (8%) and for detransitioning (11%) (see Figure 2).

Around half of the respondents (51%) reported having the feeling of not having been supported enough throughout their detransition, 31% said they did not know and 18% answered that they had received enough support.

Qualitative results

Two open-ended questions allowed participants to write more extensively about their needs and support in the questionnaire. The first one enabled the respondents to write about any additional need that they encountered while detransitioning, while the second asked about the support—or lack of—that they had received.

Additional comments about needs

Thirty-seven participants (16%) left various comments about specific needs that they experienced during their transition and detransition.

Several respondents expressed the need for different types of therapy and counseling for dealing with issues of dissociation, childhood sexual trauma, anorexia, relationship issues and body issues caused by irreversible gender affirming surgeries. A participant also mentioned the importance of help revolving around suicide prevention for those who need it.

Additionally, someone emphasized the need for therapists to validate the feelings of being harmed by transition that some detransitioners experience, rather than dismissing or opposing them. Similarly, another respondent expressed the need for non-judgmental medical practitioners. Someone else described the need for as much medical autonomy as possible and a total freedom from psychology and psychiatry. A participant also explained that she would have needed to know the health risks of chest binding before experiencing them.

Furthermore, two respondents highlighted the need to look into individual experiences and needs without forcing them into a rigid model of transition. Others wrote about the need for more information about detransition and a better general understanding of this phenomenon.

Lastly, a few female detransitioners expressed the need for being valued as a woman, for learning about feminist theories and for more gender-nonconforming role models.

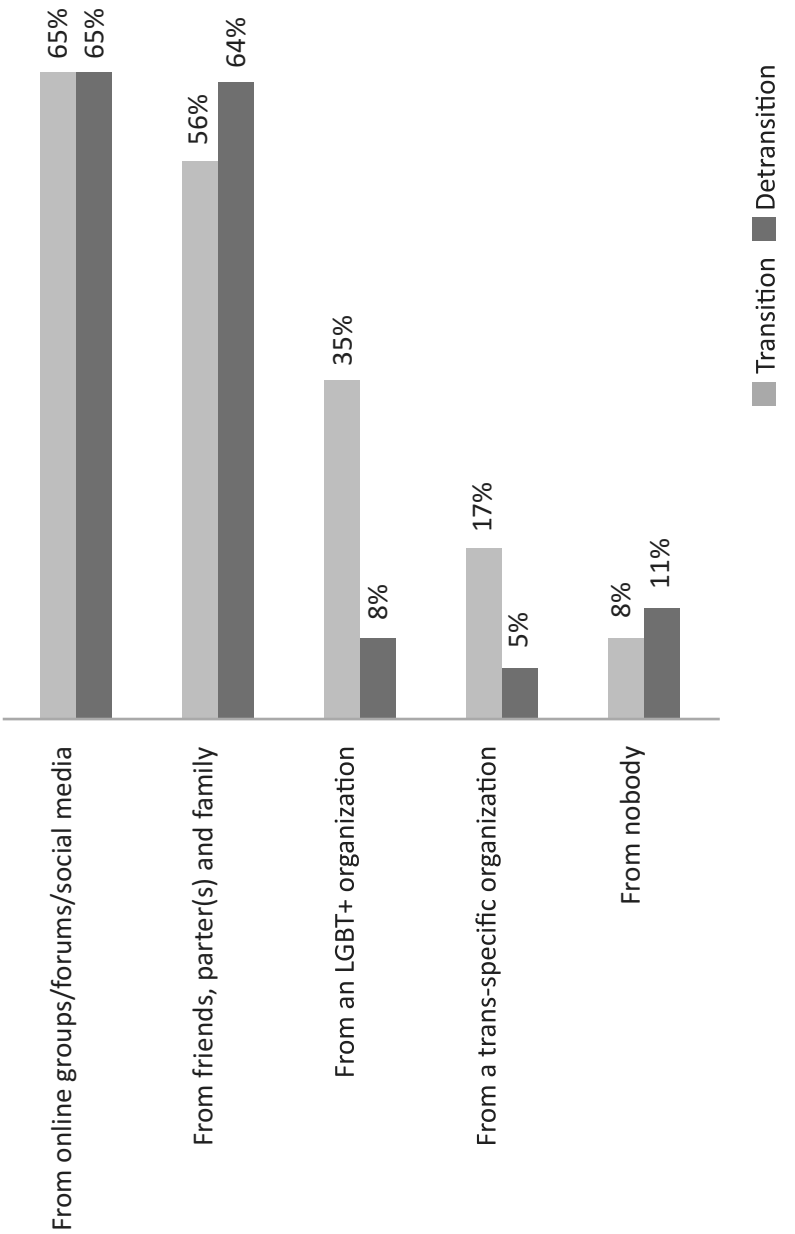

Figure 2. Comparison between transition and detransition support.

Additional comments about support

At the end of the questionnaire, a second open-ended question invited the participants to give further comments about the support—or lack of—that they had received during their detransition process.

A third of the participants (34%) answered this question, often with long and detailed accounts of their personal experiences with regard to this aspect. The most common themes identified were: loss of support from the LGBT community and friends (see Table 2), negative experiences with medical professionals (see Table 3), difficulty to find a detrans-friendly therapist and lack of offered alternatives to transitioning (see Table 4), as well as isolation and lack of overall support. Some gave more positive accounts of the support that they had received from their family, partners and friends and emphasized their important role.

A recurrent theme in the answers was a sense amongst respondents that it was very difficult to talk about detransition within LGBT+ spaces and with trans friends. Many expressed a feeling of rejection and loss of support in relation to their decision to detransition, which lead them to step away from LGBT+ groups and communities (see Table 2).

Whilst a minority reported positive experiences with medical professionals during their detransition, most participants expressed strong difficulties finding the help that they needed during their detransition process. Participants' own descriptions of the nature of these difficulties can be found in Table 3.

Another reported issue was the difficulty of finding a therapist willing and able to look at the factors behind gender dysphoria and to offer alternatives to transitioning. Some respondents highlighted the fact that they were

Table 2. Extracts about experiences of exclusion from LGBT+ communities.

"The LGBT+ community doesn't support detransitioners and I lost all LGBT+ friends I had because they deemed me transphobic/terfy, only non-LGBT+ friends supported me."
"Where I live detransitioners are seen bad for most of the LGBT community, so it's hard to talk about it with freedom."
"It is unacceptable that, at least in my experience, detransition is not something allowed to be talked about in LGBT spaces."
"Only lesbians and feminists helped me. The trans and queer community demonized me and ostracized me for my reidentification."
"I lost a lot of support and attracted a lot of hostility from trans people when I detransitioned socially. I also deal with a lot of people assuming that my dysphoria is gone entirely/cured because I have detransitioned socially, and decided not to go through with medical transition."
"Lgbt organizations don't want to talk about detransition. I did not feel welcome at lgbt events after I detransitioned."
"Telling my trans friends that I'm desisting is nearly impossible. The community is too toxic to allow any kind of discussion about alternatives to transition, sources of dysphoria beyond 'that's just who you are', or stories about detransitioners."
"I've been shunned by most of my trans identifying friends. I had to leave my old doctor, therapist and LGBT group out of shame and embarrassment."
"I have several de-trans friends whom had permanent body alterations they regretted that led to more dysphoria and eventually their suicides. Biggest factors were a lack of medical support and outright rejection from LGBT organisations/communities."
"I still have transgender friends who don't want me to talk about detransition. They're okay with me being detransitioned, but they don't want me to criticize transition or discuss the negative side effects of HRT."

Table 3. Extracts about negative medical experiences during detransition.

"I needed gender and transition experienced providers to assist with my medical detransition, but none of them seemed to understand or provide the type of care I needed, despite my self-advocacy. I got better care from providers outside of the LGBT and transgender specialty clinics."
"I still struggle to find a doctor who has knowledge of detransition and the effects HRT had on me/my best course of action since stopping."
"When I first brought up wanting to stop T to my doctor, they were very dismissive and condescending about it."
"My experience with transition left me with greatly diminished faith in medicine and zero faith in the mental health profession. I now avoid all doctors most of the time (unless I am convinced they are the only way to access a strongly evidence-based treatment or diagnostic tool for a condition which causes more suffering than doctors themselves- many do not) and totally avoid any contact with mental health professionals, and am much better off for it."
"As soon as I 'detransed' I was discharged from all gender services, despite asking for help in dealing with sex dysphoria should it arise again."
"I had no medical help from the doctor who prescribed me T, she wanted nothing to do with me."
"The team that transitioned you is not willing to help you detransition. You need new doctors."
"The medical team that helped me transition is helpful, but they are also causing a lot of hassle, which is very frustrating for me. Like for example they keep me stuck with my male sex marker for I don't know how long, and they don't believe I'm sure enough that I want to detransition, because they think I should have consistent 'reverse dysphoria' and mine kinda isn't so consistent."
"My hormone blocker implant is several years old and is only barely still functioning but they will not remove it. It's in my arm and I have no contact with the doctor because he shut down his business apparently."

Table 4. Extracts about the difficulty of finding a detrans-friendly therapist.

"It is very hard to find a therapist who won't tell you it's 'internalized transphobia' or that dealing with dysphoria in other ways is 'conversion therapy'."
"The only thing that comes to mind is one of the therapists I had, who pushed me not to detransition."
"Therapists are unprepared to handle the detrans narrative and some that I have seen since detransitioning have pushed the trans narrative. Some therapists couldn't tell the difference between being transgender and having internalized misogyny and homophobia."
"I could have benefitted from counseling but don't trust psychologists ideological bias."
"I struggled to find a therapist who supported questioning my trans identity and considering alternatives to transitioning; most only knew how to encourage transitioning and reinforced the harmful ideas that led to my wrongly identifying as FtM in the first place."
"I was doubtful that transition would help my dysphoria before beginning and was assured by multiple professionals that transition was The Solution and proven to work for everyone with dysphoria. A 'gender specialist' therapist flat-out told me that transitioning was the only method of reducing dysphoria that worked when I expressed my desperation for an alternate solution."
"The gender clinic I went to basically told me that the only way to deal with gender dysphoria was transitioning even when I told them I wanted to detransition."
"I struggled to find a therapist who supported questioning my trans identity and considering alternatives to transitioning; most only knew how to encourage transitioning and reinforced the harmful ideas that led to my wrongly identifying as FtM in the first place."
"The biggest issue for me was that when I did try to get support from a therapist or psychologist on entangling the actual reasons behind my dysphoria and how to deal with it, and deal with detransitioning, nobody had any clue or any experience, so they couldn't help me. Which made me even feel more lonely, and made detransitioning so much harder mentally than transitioning was."

cautious regarding the possible ideological bias or lack of knowledge of therapists.

Overall, most respondents explained that their detransition was a very isolating experience, during which they did not receive enough support. However, some participants emphasized the fact that the support that they received from their family, partners and friends, as well as online detrans groups and lesbian and feminist communities was extremely important and valuable to them.

Discussion

The present study was designed to better understand the needs of detransitioners, as well as the support—or lack of—that they are currently receiving. In order to do so, members of online detrans communities were recruited to answer a survey, in which questions were asked about their demographics, their transition and detransition experiences and the needs that they faced as well as the support that they received while detransitioning. In this section, I will discuss the results in relation to the main research question of the current study: What are the needs of detransitioners?

The sample surveyed appeared to be mostly female, young, from Western countries, with an experience of both social and medical transition and a high prevalence of certain comorbid conditions. The current study found that most detransitioners stopped transitioning before their mid-twenties, after an average of 4 years of transition. This observation is consistent with that made by Stella (2016) in her informal study on female detransitioners. The average transition age of the 203 respondents of her survey was 17.09 years, compared to 17.42 years in female detransitioners of the current study. The average detransition age of her sample was 21.09 years, compared to 22.22 years here.

Another finding of the current study was that a majority of the sample underwent hormone therapy (62% for females; 80% for males) and 45% of those who medically transitioned underwent gender affirming surgeries. This is likely to have implications in terms of the medical needs faced by this population. Close to half of the sample (49%) reported a need for receiving accurate information on stopping or changing hormone therapy, and almost a quarter (24%) reported the need for receiving help for complications related to surgeries or hormone therapy. The latter finding is concerning when looking at the negative medical experiences described by respondents in Table 3. Participants recounted situations in which their doctors either did not believe them, did not listen to them, refused them services, or simply did not have the required knowledge to help them during their detransition process. These experiences had a negative impact on some of the participants' trust in healthcare providers.

Similarly, the current study suggested that detransitioners have important psychological needs. This was made visible on the one hand through the fact that a majority of respondents (65%) reported the need for help in working on comorbid mental conditions related to gender dysphoria and in finding alternatives to medical transition. Other needs were reported by a majority of participants, such as learning to cope with feelings of regret (60%), learning to cope with the new physical and/or social changes related to detransitioning (53%) and learning to cope with internalized homophobia (52%). On the other hand, the high prevalence of comorbid conditions described in Table 1 might also be an indicator of important psychological needs. These results are similar

to that found by Hailey (2017) in her informal survey of comorbid mental health in detransitioned females. In her study, 77% reported a diagnosis of a depressive disorder (compared to 70% here), 74% of the sample reported a diagnosis of an anxiety disorder (compared to 63% here), 32% reported a diagnosis of PTSD (compared to 33% here) and 22% reported a diagnosis of an eating disorder (compared to 19% here). This is also very concerning information considering the descriptions made by detransitioners about the difficulty of finding a therapist willing or able to help them, and of finding alternative ways to deal with gender dysphoria after detransitioning (see Table 4).

The majority (84%) of the respondents reported having experienced both body and social gender dysphoria. Half of the sample (50%) later reported having decided to detransition due to the fact that their transition did not alleviate their gender dysphoria. Others (45%) reported having found alternative ways to deal with their gender dysphoria (see Figure 1). These results highlight the necessity to start looking into alternative solutions for treating gender dysphoria, in order to help those who did not find medical and/or social transition fulfilling.

In addition to that, 70% of the sample reported having realized that their gender dysphoria was related to other issues. Further research should be conducted in order to identify the ways in which other issues such as comorbid mental health conditions, trauma or internalized misogyny and homophobia possibly interact with gender dysphoria, and what can be done to alleviate them.

Furthermore, the high prevalence of autism spectrum condition (ASC) (20%) found in detransitioners in the current study, which is supported by Hailey (2017) findings (15%), also constitutes an interesting avenue for future research. Previous studies have provided evidence suggesting a co-occurrence of gender dysphoria and ASC (e.g., De Vries, Noens, Cohen-Kettenis, Van Berckelaer- Onnes, & Doreleijers, 2010; Glidden, Bouman, Jones, & Arcelus, 2016; VanderLaan et al., 2014; Van Der Miesen, Hurley, & De Vries, 2016; Zucker et al., 2017), which might explain the high number of detransitioners with an ASC diagnosis found in the current study.

In general, support given to detransitioners seems to be very poor at the moment, considering the fact that only 18% of the participants in the current study reported having received enough support during their detransition.

Based on the results of the current study, it appears that detransitioning is often accompanied by a break with LGBT+ communities. Only 13% of the participants reported having received support from an LGBT+ or trans-specific organization while detransitioning, compared to 51% while transitioning (see Figure 2). In addition to that, many respondents described experiences of outright rejection from LGBT+ spaces due to their decision to detransition (see Table 2). Looking at studies showing the positive role

of peer support and trans community connectedness on the mental health of its members (Johnson & Rogers, 2019; Pflum, Testa, Balsam, Goldblum, & Bongar, 2015; Sherman, Clark, Robinson, Noorani, & Poteat, 2020), it seems reasonable to suspect that this loss of support experienced by detransitioners must have serious implications on their psychological well-being.

Fortunately, the current study shows that detransitioners have access to other sources of support, online (groups, forums, social media) and in their social surroundings (family, partners and friends) (see Figure 2). Online groups and websites for detransitioners seem to be particularly important in light of the social needs expressed by the respondents of the current study. An overwhelming majority of respondents reported the need for hearing about other detransition stories (87%) and for getting in contact with other detransitioners (76%). Detransitioners need platforms and spaces where they can connect with each other and build a community. This point is best illustrated by the following account of one participant: "I found the peer support I received through other detransitioned women to be totally adequate and feel I benefited substantially from learning how to exist without institutional validation."

Conclusion

The aim of the present research was to examine detransitioners' needs and support. The four categories of needs (psychological, medical, legal and social) that were created for sake of clarity in the survey were a simplification of the real complexity of the experiences made by detransitioners and they have their limitations. Nonetheless, these categories enabled the current study to uncover the fact that most detransitioners could benefit from some form of counseling and in particular when it comes to psychological support on matters such as gender dysphoria, comorbid conditions, feelings of regret, social/physical changes and internalized homophobic or sexist prejudices. Medical support was also found to be needed by many, in order to address concerns related to stopping/changing hormone therapy, surgery/treatment complications and access to reversal interventions. Furthermore, the current study has shown that detransitioners need spaces to hear about other detransition stories and to exchange with each other.

Unfortunately, the support that detransitioners are receiving in order to fulfill these needs appears to be very poor at the moment. Participants described strong difficulties with medical and mental health systems, as well as experiences of outright rejection from the LGBT+ community. Many respondents have expressed the wish to find alternative treatments to deal with their gender dysphoria but reported that it was impossible to talk about it within LGBT+ spaces and in the medical sphere.

These accounts are concerning and they show the urgency to increase awareness and reduce hostility around the topic of detransition among healthcare providers and members of the LGBT+ community in order to address the specific needs of detransitioners.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Appendix.

Full Questionnaire

(1) How old are you?
(2) What country are you living in?
(3) What sex were you assigned at birth?
- Female
- Male
- Other:

(4) How do you see yourself now? (Tick all that apply)
- Woman
- Man
- Trans man
- Trans woman
- Female detransitioner
- Male detransitioner
- Non binary
- Other:

(5) Did you transition socially and/or medically and then stopped?
- Yes, both
- Only socially
- No

(6) Did you experience body dysphoria and/or social dysphoria? (Body dysphoria = strong desire to have sex characteristics of the opposite sex/rejection of your own sex; Social dysphoria = strong desire to be seen and treated as being of a different gender)
- Yes, both
- Only body dysphoria
- Only social dysphoria
- No

(7) Who helped you starting your social/medical transition? (Tick all that apply)
- A medical team specialized in transition
- An LGBT+ organization
- A trans-specific organization
- A therapist/doctor
- Online groups/forums/social media
- Friends, partner(s) and family
- Nobody
- Other:

(8) If you transitioned medically, how long were you in therapy before getting any hormones or surgeries? (in months; write 0 if none)

(9) During your transition, did you undergo some of the following interventions/treatments? (Tick all that apply)
- Hormone blockers
- Feminizing hormone treatment
- Masculinizing hormone treatment
- Gender affirming surgery(ies)
- No

(10) Do you feel like you were properly informed about the health implications of these treatments/interventions before undergoing them?
- Yes
- Partly
- No
- I am not sure

(11) What were the reasons that made you stop transitioning/detransition? (Tick all that apply)
- Health concerns
- Change in political views
- Transition did not help with my dysphoria
- Lack of support from social surroundings
- Discrimination
- Financial concerns
- Dysphoria resolved itself over time
- Unhappy with the physical changes
- Unhappy with the social changes
- Comorbid mental health issues related to dysphoria solved
- Realized that my gender dysphoria was related to other issues
- Found alternatives to deal with dysphoria
- Other:

(12) Were you diagnosed with or do you suspect having any of the following conditions?

	Diagnosed	Suspected	No
Attention Deficit (Hyperactive) Disorder			
Autism Spectrum Condition			
Anxiety Disorders			
Depressive Disorders			
Dissociative Identity Disorder			
Eating Disorders			
Obsessive Compulsive Disorder			
Polycystic Ovary Syndrome			
Post Traumatic Stress Disorder			
Personality Disorders			
Schyzo-spectrum Disorder			

(13) If you transitioned socially, at what age did you start?
(14) If you transitioned medically, at what age did you start?
(15) At what age did you start detransitioning/stop transitioning?
(16) What are the medical needs that you had while detransitioning/stopping your transition? (Tick all that apply)
- Receiving accurate information on stopping/changing hormonal treatment
- Receiving information and access to reversal surgeries/procedures
- Receiving help for complications related to surgeries or hormonal treatment
- None
- Other:

(17) What are the psychological needs that you had while detransitioning/stopping your transition? (Tick all that apply)
- Learning to cope with gender dysphoria; finding alternatives to medical transition
- Learning to cope with the new physical and/or social changes related to detransitioning
- Learning to cope with feelings of regret
- Learning to cope with internalized homophobia
- Working on comorbid mental issues related to gender dysphoria
- None
- Other:

(18) What are the legal needs that you had while detransitioning/stopping your transition? (Tick all that apply)
- Changing back legal gender/sex marker and/or name
- Legal advice and support to take legal action over medical malpractice
- None
- Other:

(19) What are the social needs that you had while detransitioning/stopping your transition? (Tick all that apply)
- Getting in contact with other detransitioners
- Receiving support to come out and deal with negative reactions
- Hearing about other detransition stories
- None
- Other:

(20) Is there any other need that you would like to mention?

(21) Which of these needs did you get support for?

	Full support	Partly	Not at all	Not needed
Medical needs				
Psychological needs				
Legal needs				
Social needs				

(22) From whom? (Tick all that apply)
- The medical team that helped me transition
- An LGBT+ organization
- A trans specific organization
- The therapist/doctor who supported me through my transition
- A new therapist/doctor
- Online groups/forums/social media
- Friends, partner(s) and family
- Nobody
- Other:

(23) Do you feel like you have received enough support throughout your detransition process overall?
- Yes
- No
- I don't know

(24) If you have any comment concerning the support/lack of support you received during your detransition, you can write it here.

Young Adult Psychological Outcome After Puberty Suppression and Gender Reassignment

WHAT'S KNOWN ON THIS SUBJECT: Puberty suppression has rapidly become part of the standard clinical management protocols for transgender adolescents. To date, there is only limited evidence for the long-term effectiveness of this approach after gender reassignment (cross-sex hormones and surgery).

WHAT THIS STUDY ADDS: In young adulthood, gender dysphoria had resolved, psychological functioning had steadily improved, and well-being was comparable to same-age peers. The clinical protocol including puberty suppression had provided these formerly gender-dysphoric youth the opportunity to develop into well-functioning young adults.

abstract

BACKGROUND: In recent years, puberty suppression by means of gonadotropin-releasing hormone analogs has become accepted in clinical management of adolescents who have gender dysphoria (GD). The current study is the first longer-term longitudinal evaluation of the effectiveness of this approach.

METHODS: A total of 55 young transgender adults (22 transwomen and 33 transmen) who had received puberty suppression during adolescence were assessed 3 times: before the start of puberty suppression (mean age, 13.6 years), when cross-sex hormones were introduced (mean age, 16.7 years), and at least 1 year after gender reassignment surgery (mean age, 20.7 years). Psychological functioning (GD, body image, global functioning, depression, anxiety, emotional and behavioral problems) and objective (social and educational/professional functioning) and subjective (quality of life, satisfaction with life and happiness) well-being were investigated.

RESULTS: After gender reassignment, in young adulthood, the GD was alleviated and psychological functioning had steadily improved. Well-being was similar to or better than same-age young adults from the general population. Improvements in psychological functioning were positively correlated with postsurgical subjective well-being.

CONCLUSIONS: A clinical protocol of a multidisciplinary team with mental health professionals, physicians, and surgeons, including puberty suppression, followed by cross-sex hormones and gender reassignment surgery, provides gender dysphoric youth who seek gender reassignment from early puberty on, the opportunity to develop into well-functioning young adults. *Pediatrics* 2014;134:696–704

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KEY WORDS

gender dysphoria, transgenderism, adolescents, psychological functioning, puberty suppression, longitudinal outcomes

ABBREVIATIONS

ABCL—Adult Behavior Checklist
ASR—Adult Self-Report
BDI—Beck Depression Inventory
BIS—Body Image Scale
CBCL—Child Behavior Checklist
CGAS—Children's Global Assessment Scale
CSH—cross-sex hormones
GD—gender dysphoria
GnRHa—gonadotropin-releasing hormone analogs
GRS—gender reassignment surgery
SHS—Subjective Happiness Scale
STAI—Spielberger's Trait Anxiety Scale
SWLS—Satisfaction With Life Scale
TPI—Spielberger's Trait Anger Scale
UGDS—Utrecht Gender Dysphoria Scale
YSR—Youth Self-Report

Dr de Vries conceptualized the study, clinically assessed the participants, drafted the initial manuscript, and reviewed and revised the manuscript; Dr McGuire conceptualized the study, planned and carried out the analyses, assisted in drafting the initial manuscript, and reviewed and revised the manuscript; Dr Steensma conceptualized the study, coordinated and supervised data collection, and reviewed and revised the manuscript; Dr Wagenaar coordinated and invited participants for assessments and reviewed and revised the manuscript; Drs Doreleijers and Cohen-Kettenis conceptualized the study and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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www.pediatrics.org/cgi/doi/10.1542/peds.2013-2958

doi:10.1542/peds.2013-2958

Accepted for publication Jul 7, 2014

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(Continued on last page)

Transgender adolescents experience an incongruence between their assigned gender and their experienced gender and may meet the Diagnostic and Statistical Manual of Mental Disorders 5 criteria for gender dysphoria (GD).[1] Fifteen years ago, pubertal delay was introduced as an aid in the treatment of a gender dysphoric adolescent.[2] Although not without debate, blocking pubertal development has rapidly become more widely available[3–7] and is now part of the clinical management guidelines for GD.[8–12]

Gonadotropin-releasing hormone analogs (GnRHa) are a putatively fully reversible[13] medical intervention intended to relieve distress that gender dysphoric adolescents experience when their secondary sex characteristics develop. A protocol designed by Cohen-Kettenis and Delemarre-van de Waal[14] (sometimes referred to as "the Dutch model")[4,7] considers adolescents, after a comprehensive psychological evaluation with many sessions over a longer period of time, eligible for puberty suppression, cross-sex hormones (CSH), and gender reassignment surgery (GRS) at the respective ages of 12, 16, and 18 years when there is a history of GD; no psychosocial problems interfering with assessment or treatment, for example, treatment might be postponed because of continuous moving from 1 institution to another or repeated psychiatric crises; adequate family or other support; and good comprehension of the impact of medical interventions.[12] Puberty suppression is only started after the adolescent actually enters the first stages of puberty (Tanner stages 2–3), because although in most prepubertal children GD will desist, onset of puberty serves as a critical diagnostic stage, because the likelihood that GD will persist into adulthood is much higher in adolescence than in the case of childhood GD.[15,16]

Despite the apparent usefulness of puberty suppression, there is only limited evidence available about the effectiveness of this approach. In the first cohort of adolescents who received GnRHa, we demonstrated an improvement in several domains of psychological functioning after, on average, 2 years of puberty suppression while GD remained unchanged.[16] The current study is a longer-term evaluation of the same cohort, on average, 6 years after their initial presentation at the gender identity clinic. This time, we were not only interested in psychological functioning and GD, but added as important outcome measures objective and subjective well-being (often referred to as "quality of life"), that is, the individuals' social life circumstances and their perceptions of satisfaction with life and happiness.[17–19] After all, treatment cannot be considered a success if GD resolves without young adults reporting they are healthy, content with their lives, and in a position to make a good start with their adult professional and personal lives.[20] Because various studies show that transgender youth may present with psychosocial problems,[21,22] a clinical approach that includes both medical (puberty suppression) and mental health support (regular sessions, treatment when necessary, see Cohen-Kettenis et al[12]) aims to improve long-term well-being in all respects.

In the present longitudinal study, 3 primary research questions are addressed. Do gender dysphoric youth improve over time with medical intervention consisting of GnRHa, CSH, and GRS? After gender reassignment, how satisfied are young adults with their treatment and how do they evaluate their objective and subjective well-being? Finally, do young people who report relatively greater gains in psychological functioning also report a higher subjective well-being after gender reassignment?

METHODS

Participants and Procedure

Participants included 55 young adults (22 transwomen [natal males who have a female gender identity] and 33 transmen [natal females who have a male gender identity]) of the first cohort of 70 adolescents who had GD who were prescribed puberty suppression at the Center of Expertise on Gender Dysphoria of the VU University Medical Center and continued with GRS between 2004 and 2011. These adolescents belonged to a group of 196 consecutively referred adolescents between 2000 and 2008, of whom 140 had been considered eligible for medical intervention and 111 were prescribed puberty suppression (see de Vries et al[16]). The young adults were invited between 2008 and 2012, when they were at least 1 year past their GRS (vaginoplasty for transwomen, mastectomy and hysterectomy with ovariectomy for transmen; many transmen chose not to undergo a phalloplasty or were on a long waiting list). Nonparticipation (n = 15, 11 transwomen and 4 transmen) was attributable to not being 1 year postsurgical yet (n = 6), refusal (n = 2), failure to return questionnaires (n = 2), being medically not eligible (eg, uncontrolled diabetes, morbid obesity) for surgery (n = 3), dropping out of care (n = 1), and 1 transfemale died after her vaginoplasty owing to a postsurgical necrotizing fasciitis. Between the 55 participants and the 15 nonparticipating individuals, Student's t tests revealed no significant differences on any of the pretreatment variables. A similar lack of differences was found between the 40 participants who had complete data and the 15 who were missing some data.

Participants were assessed 3 times: pre-treatment (T0, at intake), during treatment (T1, at initiation of CSH), and post-treatment (T2, 1 year after GRS). See Table 1 for age at the different time points. The VU University Medical Center medical ethics committee approved the study, and all participants gave informed consent.

TABLE 1 Age at Different Treatment Milestones and Intelligence by Gender

Variable	All Participants[a] (*N* = 55)		Transwomen (Natal Males) (*N* = 22)	Transmen (Natal Females) (*N* = 33)
Age, y	Mean (SD)	Range	Mean (SD)	Mean (SD)
At assessment PreT	13.6 (1.9)	11.1–17.0	13.6 (1.8)	13.7 (2.0)
At start of GnRHa	14.8 (1.8)	11.5–18.5	14.8 (2.0)	14.9 (1.9)
At start of CSH	16.7 (1.1)	13.9–19.0	16.5 (1.3)	16.8 (1.0)
At GRS	19.2 (0.9)	18.0–21.3	19.6 (0.9)	19.0 (0.8)
At assessment PostT	20.7 (1.0)	19.5–22.8	21.0 (1.1)	20.5 (0.8)
Full-scale intelligence[b]	99.0 (14.3)	70–128	97.8 (14.2)	100.4 (14.3)

PostT, post-treatment; PreT, pre-treatment.

[a] Comparisons between those who had complete data (*n* = 40) and those who had missing data on the CBCL/ABCL (*n* = 15) reveal no significant differences between the groups in age at any point in the study or in natal sex.

[b] WISC-R, the WISC-III, or the WAIS-III at first assessment, depending on age and time.[45–47]

Measures

Time was the predominate independent variable. Other demographic characteristics were incorporated in some models, including, age, natal sex, Full Scale Intelligence, and parent marital status; where significantly different they are reported.

Gender Dysphoria/Body Image

There was 1 indicator measuring GD (Utrecht Gender Dysphoria Scale [UGDS]) and 3 indicators measuring body image (Body Image Scale [BIS] with primary, secondary, and neutral subscales). Higher UGDS (12 items, 1–5 range, total score ranging from 12–60) total scores indicate higher levels of GD, for example, "I feel a continuous desire to be treated as a man/woman."[23] There are separate versions of the UGDS for males and females with mostly different items, permitting no gender difference analyses. BIS (30 items, 1–5 range) higher scores indicate more dissatisfaction with primary sex characteristics (important gender-defining body characteristics, eg, genitals, breasts), secondary sex characteristics (less obvious gender-defining features, eg, hips, body hair), and neutral (hormonally unresponsive) body characteristics (eg, face, height).[24] The male and the female BIS are identical except for the sexual body parts. The UGDS and the BIS of the natal gender were administered at T0 and T1. At T1, we chose the UGDS of the assigned gender, because no physical changes had occurred yet and some were still treated as their assigned gender. This way, however, decreased GD caused by social transitioning was not measured. At T2 young adults filled out the versions of their affirmed gender.

Psychological Functioning

There were 10 indicators assessing psychological functioning. To assess global functioning, the Children's Global Assessment Scale (CGAS) was used.[25] The Beck Depression Inventory (BDI; 21 items, 0–3 range) indicates presence and severity of depressive symptoms.[26] Spielberger's Trait Anger (TPI) and Spielberger's Trait Anxiety (STAI; 10 and 20 items, respectively, 1–4 range) scales of the State-Trait Personality Inventory were administered to assess the tendency to respond with anxiety or anger, respectively, to a threatening or annoying situation.[27,28]

Behavioral and emotional problems were assessed by the total, internalizing, and externalizing T scores as well as clinical range scores for these 3 indices (T score >63) of the Child/Adult Behavior Checklist (CBCL at T0 and T1, ABCL at T2), the Youth/Adult Self-Report (YSR at T0 and T1, ASR at T2).[29–31] Items referring to GD in the CBCL/YSR and ABCL/ASR were scored as 0 (for more explanation, see Cohen-Kettenis et al[32]).

Objective and Subjective Well-Being (T2 Only)

A self-constructed questionnaire was used to ask the young adults about their current life circumstances, such as living conditions, school and employment, and social support (objective well-being), and satisfaction with treatment (subjective well-being). Three instruments further assessed subjective well-being. To measure quality of life, the WHOQOL-BREF (quality of life measure developed by the World Health Organization) was administered (24 items, 4 domains: Physical Health, Psychological Health, Social Relationships, and Environment, 1–5 range with higher scores indicating better quality of life).[17] The Satisfaction With Life Scale (SWLS, 5 items, 5–35 range, 20 being neutral) was used to assess life satisfaction.[18] Higher scores on the Subjective Happiness Scale (SHS, 4 items, 7-point Likert scale, average score 1–7) reflect greater happiness.[19]

Data Analyses

General Linear Models examined the repeated measures with an analysis of variance-based model, incorporating continuous and categorical predictors, and correcting for the unbalanced cell sizes. Linear and quadratic effects of the 14 indicators across 3 time points, with time as the within-subjects factor, and sex as a between-subjects factor in a second set of analyses are reported in Tables 2 and 3 and Fig 1. A linear effect signifies an overall change across T0 to T2. A quadratic effect signifies that the change was not continuous, such as when an indicator does not improve from T0 to T1 but improves from T1 to T2. It is possible to have both a significant linear and quadratic effect on the same

TABLE 2 Gender Dysphoria and Body Image of Adolescents at Intake (T0), While on Puberty Suppression (T1), and After Gender Reassignment (T2)

	N[a]	T0	T1	T2	T0–T2	Time	Time × Sex
					t test	Linear Effect Quadratic Effect	Linear Effect Quadratic Effect
		Mean (SD)	Mean (SD)	Mean (SD)	*P*	*P*	*P*
UGDS	33	53.51 (8.29)	54.39 (7.70)	15.81 (2.78)	<.001		
MtF	11	47.07 (11.05)	48.95 (10.80)	17.27 (2.57)	<.001	<.001 <.001	n/a
FtM	22	56.74 (3.74)	57.11 (3.40)	15.08 (2.64)	<.001	<.001 <.001	n/a
Body Image (BIS)							
Primary sex characteristics	45	4.13 (0.59)	4.05 (0.60)	2.59 (0.82)	<.001	<.001 <.001	.01 .45
MtF	17	4.03 (0.68)	3.82 (0.56)	2.07 (0.74)	<.001		
FtM	28	4.18 (0.53)	4.13 (0.60)	2.89 (0.71)	<.001		
Secondary sex characteristics	45	2.73 (0.72)	2.86 (0.67)	2.27 (0.56)	<.001	<.001 <.001	.10 <.001
MtF	17	2.63 (0.60)	2.34 (0.68)	1.93 (0.63)	<.001		
FtM	28	2.80 (0.72)	3.18 (0.43)	2.48 (0.40)	.05		
Neutral body characteristics	45	2.35 (0.68)	2.49 (0.53)	2.23 (0.49)	.29	.29 .01	.007 .01
MtF	17	2.57 (0.70)	2.29 (0.50)	2.09 (0.56)	.014		
FtM	28	2.21 (0.64)	2.61 (0.52)	2.32 (0.44)	.40		

FtM, female to male transgender; MtF, male to female transgender; n/a, not applicable.

[a] Participants who had complete data at all 3 waves were included. Some assessments were added to the study later, yielding fewer total participants for those scales.

indicator. Other potential between-subjects factors (age, total IQ, parental marital status) were examined but excluded owing to a lack of relationship with the 14 indicators at T0. The 1 exception, age predicting secondary sex characteristics, is described below in the findings. We compared T2 sample means to population norms for subjective well-being using 1-sample *t* tests from previously published validation studies. Finally, we examined T2 subjective well-being correlations with residual change scores from T0 to T2 on the 14 indicators (an indicator of who improved relatively more or less over time).

All measures used were self-reported, except the CGAS (attending clinician) and the CBCL/ASR (parents). Each participant was given all measures at each of 3 assessments. Numbers varied across indicators owing to the later inclusion of the YSR, CGAS, BDI, TPI, and STAI, yielding 8 persons who had missing data at T0 and a clinician error yielding missing data at T1 for 10 participants on the UGDS. Dutch versions were used (see de Vries et al[16]).

RESULTS

Gender Dysphoria and Body Satisfaction

Figure 1 and Table 2 show that GD and body image difficulties persisted through puberty suppression (at T0 and T1) and remitted after the administration of CSH and GRS (at T2) (significant linear effects in 3 of 4 indicators, and significant quadratic effects in all indicators). Time by sex interactions revealed that transwomen reported more satisfaction over time with primary sex characteristics than transmen and a continuous improvement in satisfaction with secondary and neutral sex characteristics. Transmen reported more dissatisfaction with secondary and neutral sex characteristics at T1 than T0, but improvement in both from T1 to T2. Age was a significant covariate with secondary sex characteristics (the only significant demographic covariate with any outcome indicator in the study), indicating that older individuals were more dissatisfied at T0, but the age gap in body satisfaction narrowed over time ($F(1, 42) = 8.18$; $P < .01$).

Psychological Functioning

As presented in Table 3, significant linear effects showed improvement over time in global functioning (CGAS), CBCL/ABCL total, internalizing and externalizing *T* scores, and YSR/ASR total and internalizing *T* scores. Quadratic effects revealed decreases from T0 to T1 followed by increases from T1 to T2 in depression and YSR/ASR internalizing *T* scores. Quadratic trends revealed decreases from T0 to T1, followed by increases from T1 to T2 in depression and YSR/ASR internalizing *T* scores. For all CBCL/ABCL and YSR/ASR indicators except YSR/ASR externalizing, the percentage in the clinical range dropped significantly (McNemar's test, *P* value <0.05) from T0 to T1, from T0 to T2, or from T1 to T2.

Over time, transmen showed reduced anger, anxiety, and CBCL/ABCL externalizing *T* scores, whereas transwomen showed stable or slightly more symptomatology on these measures. Transwomen improved in CBCL/ABCL total *T* scores in a quadratic fashion (all the improvement between T1 and T2),

TABLE 3 Psychological Functioning of Adolescents at Intake (T0), While on Puberty Suppression (T1), and After Gender Reassignment (T2)

	N[a]	T0	T1	T2	T0–T2	Time	Time × Sex
					t test	Linear Effect Quadratic Effect	Linear Effect Quadratic Effect
		Mean (SD)	Mean (SD)	Mean (SD)	*P*	*P*	*P*
Global functioning (CGAS)	32	71.13 (10.46)	74.81 (9.86)	79.94 (11.56)	<.001	<.001	.89
						.61	.68
MtF	15	74.33 (7.53)	78.20 (9.56)	82.40 (8.28)	<.001		
FtM	17	67.65 (11.87)	70.65 (9.89)	76.29 (14.48)	.02		
Depression (BDI)	32	7.89 (7.52)	4.10 (6.17)	5.44 (8.40)	.21	.23	.66
						.04	.49
MtF	12	4.73 (4.20)	2.25 (3.54)	3.38 (4.40)	.12		
FtM	20	10.09 (8.34)	5.05 (7.08)	6.95 (9.83)	.32		
Anger (TPI)	32	17.55 (5.72)	17.22 (5.61)	16.01 (5.28)	.20	.15	.04
						.52	.12
MtF	12	14.17 (3.01)	14.00 (3.36)	5.58 (3.92)	.18		
FtM	20	19.55 (5.96)	19.25 (5.69)	16.56 (6.06)	.05		
Anxiety (STAI)	32	39.57 (10.53)	37.52 (9.87)	37.61 (10.39)	.45	.42	.05
						.47	.52
MtF	12	31.87 (7.42)	31.71 (8.36)	35.83 (10.22)	.14		
FtM	20	44.41 (9.06)	41.59 (9.03)	39.20 (10.53)	.12		
CBCL–ABCL							
Total *T* score	40	60.20 (12.66)	54.70 (11.58)	48.10 (9.30)	<.001	<.001	.25
% Clinical		38_x	20_y	5_y		.68	.03
MtF	15	57.40 (12.76)	49.67 (12.29)	48.13 (12.58)	.002		
FtM	25	61.88 (12.56)	57.72 (10.23)	48.08 (6.95)	<.001		
Int *T* score	40	60.83 (12.36)	54.42 (10.58)	50.45 (10.04)	<.001	<.001	.91
% Clinical		30_x	12.5_y	10_y		.42	.33
MtF	15	59.40 (10.03)	50.93 (11.15)	48.73 (12.61)	<.001		
FtM	25	61.68 (13.70)	56.52 (9.86)	51.48 (8.25)	<.001		
Ext *T* score	40	57.85 (13.73)	53.85 (12.77)	47.85 (8.59)	<.001	<.001	.19
% Clinical		40_x	25_x	2.5_y		.43	.12
MtF	15	52.53 (14.11)	47.87 (12.07)	46.33 (10.95)	.10		
FtM	25	61.04 (12.71)	57.44 (12.01)	48.76 (6.89)	<.001		
YSR-ASR							
Total *T* score	43	54.72 (12.08)	49.16 (11.16)	48.53 (9.46)	.005	.005	.28
% Clinical		30_x	14_{xy}	7_y		.07	.75
MtF	17	50.65 (12.19)	45.94 (12.24)	47.24 (12.28)	.28		
FtM	26	57.38 (11.47)	51.27 (10.08)	49.38 (7.21)	.01		
Int *T* score	43	55.47 (13.08)	48.65 (12.33)	50.07 (11.15)	.03	.03	.87
% Clinical		30_x	9.3_y	11.6_{xy}		.008	.73
MtF	17	54.00 (12.31)	47.59 (14.26)	48.12 (12.54)	.04		
FtM	26	56.42 (13.86)	49.35 (11.13)	51.35 (10.19)	.17		
Ext *T* score	43	52.77 (12.47)	49.44 (9.59)	49.44 (9.37)	.14	.14	.005
% Clinical		21_x	11.6_x	7_x		.09	.14
MtF	17	46.00 (11.58)	44.71 (9.53)	50.24 (11.18)	.17		
FtM	26	57.16 (11.14)	52.54 (8.43)	48.92 (8.18)	.006		

FtM, female to male transgender; MtF, male to female transgender.

$_{xy}$ Percent clinical range, shared subscripts indicate no significant difference in values. In no case was an increase in percent in the clinical range significant from 1 time point to any other time point, indicating an overall decline or stability of clinical symptoms over time.

[a] Participants who had complete data at all 3 waves were included. Some assessments were added to the study later, yielding fewer total participants for those scales.

whereas transmen improved steadily across the 3 time points (linear effect only).

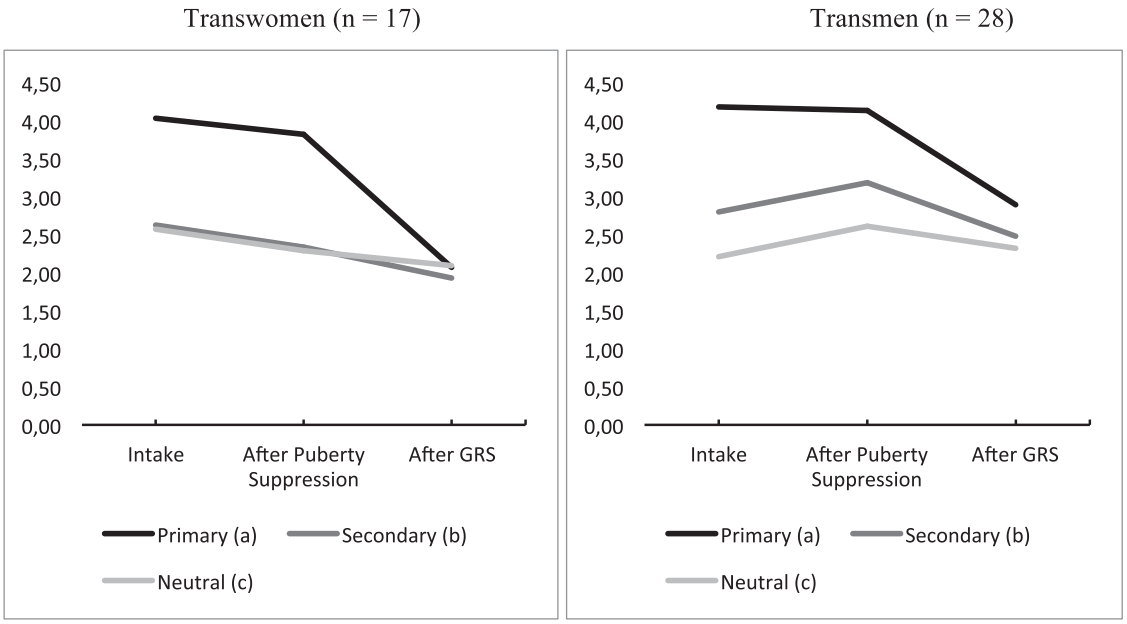
Objective Well-Being

At T2, the participants were vocationally similar to the Dutch population except they were slightly more likely to live with parents (67% vs 63%), and more likely, when studying, to be pursuing higher education (58% vs 31%).[33]

Families were supportive of the transitioning process: 95% of mothers, 80% of fathers, and 87% of siblings. Most (79%) young adults reported having 3 or more friends, were satisfied with their male (82%) and female peers (88%), and almost all (95%) had received support from friends regarding their gender reassignment. After their GRS, many participants (89%) reported having been never or seldom called names or harassed. The majority (71%) had experienced social transitioning as easy.

Subjective Well-Being

None of the participants reported regret during puberty suppression, CSH



Eta Squared for Linear and Quadratic Effects

(a) Primary sex characteristics
Time: .79 ($P < .001$), .66 ($P < .001$),
Time × sex: .14 ($P = .01$), .01 ($P = .45$),

(b) Secondary sex characteristics
Time: .31($P < .001$), .30 ($P < .001$),
Time × sex: .06 ($P = .10$), .22 ($P < .001$)

(c) Neutral body characteristics
Time: .07($P < .001$), .09 ($P = .29$)
Time × sex: .16 ($P = .007$), .15 ($P = .01$)

FIGURE 1
BIS[23] for transwomen and transmen at T0 (pretreatment, at intake), T1 (during treatment, at initiation of cross-gender hormones), and T2 (post-treatment, 1 year after GRS).

treatment, or after GRS. Satisfaction with appearance in the new gender was high, and at T2 no one reported being treated by others as someone of their assigned gender. All young adults reported they were very or fairly satisfied with their surgeries.

Mean scores on WHOQOL-BREF, the SWLS, and the SHS are presented in Table 4, together with scores from large validation and reliability studies of these measures,[17,19,34] revealing similar scores in all areas except WHOQOL-Environment subdomain, which was higher for the participants than the norm. There were some differences across gender; transwomen scored higher than transmen on the SWLS (mean = 27.7; SD = 5.0 vs mean = 23.2; SD = 6.0; t (52) = 2.82; $P < .01$) and on the psychological subdomain of the WHOQOL (mean = 15.77; SD = 2.0 vs mean = 13.92; SD = 2.5; t (53) = 2.95; $P < .01$).

Correlations With Residual Change Scores

The residual change scores of secondary sex characteristics, global functioning, depression, anger, anxiety, and YSR total, internalizing and externalizing from T0 to T2, were significantly correlated with the 6 T2 quality of life indicators. Most correlation coefficients were within the moderate to large magnitude (eg, 0.30–0.60), except depression, which was highly correlated (0.60–0.80) (see Table 5).

DISCUSSION

Results of this first long-term evaluation of puberty suppression among transgender adolescents after CSH treatment and GRS indicate that not only was GD resolved, but well-being was in many respects comparable to peers.

The effectiveness of CSH and GRS for the treatment of GD in adolescents is in line with findings in adult transsexuals.[35,36] Whereas some studies show that poor surgical results are a determinant of postoperative psychopathology and of dissatisfaction and regret,[37,38] all young adults in this study were generally satisfied with their physical appearance and none regretted treatment. Puberty suppression had caused their bodies to

TABLE 4 Subjective Well-Being: Quality of Life, Satisfaction With Life, and Subjective Happiness Mean Scores With Scores From Validation Studies

	N	Mean (SD)	Range	Validation Studies Scores Mean (SD)	Comparison *P*
WHOQOL[a] Physical	55	15.22 (2.49)	8.6–20.0	15.0 (2.9)[b]	.56
WHOQOL Psychological	55	14.66 (2.44)	6.67–20.0	14.3 (2.8)[b]	.24
WHOQOL Social Relations	55	14.91 (2.35)	9.3–20.00	14.5 (3.4)[b]	.18
WHOQOL Environment	55	15.47 (2.06)	10.5–20.00	13.7 (2.6)[b]	<.001
SWLS	54	24.98 (6.0)	9.0–35.0	26.18 (5.7)[c]	.16
SHS	54	4.73 (0.77)	2.75–6.0	4.89 (1.1)[d]	.17

[a] WHOQOL, Bref, Skevington et al.[16]
[b] International field trial, ages 21 to 30 years, Skevington et al.[16]
[c] Dutch young adults, Arindell et al.[33]
[d] US Public College Students, Lyubomirsky.[18]

not (further) develop contrary to their experienced gender.

Psychological functioning improved steadily over time, resulting in rates of clinical problems that are indistinguishable from general population samples (eg, percent in the clinical range dropped from 30% to 7% on the YSR/ASR[30]) and quality of life, satisfaction with life, and subjective happiness comparable to same-age peers.[17,19,34] Apparently the clinical protocol of a multidisciplinary team with mental health professionals, physicians, and surgeons gave these formerly gender dysphoric youth the opportunity to develop into well-functioning young adults. These individuals, of whom an even higher percentage than the general population were pursuing higher education, seem different from the transgender youth in community samples with high rates of mental health disorders, suicidality and self-harming behavior, and poor access to health services.[21,22,39,40]

In this study, young adults who experienced relatively greater improvements in psychological functioning were more likely to also report higher levels of subjective postsurgical well-being. This finding suggests value to the protocol that involves monitoring the adolescents' functioning, physically and psychologically, over many years, and providing more support whenever necessary.

This clinic-referred sample perceived the Environmental subdomain (with items like "access to health and social care" and "physical safety and security") of the WHOQOL-BREF as even better than the Dutch standardization sample.[17] Whereas in some other contexts transgender youth may experience gender-related abuse and victimization,[22,41,42] the positive results may also be attributable to supportive parents, open-minded peers, and the social and financial support (treatment is covered by health insurance) that gender dysphoric individuals can receive in the Netherlands.

Both genders benefitted from the clinical approach, although transwomen showed more improvement in body image satisfaction (secondary sex characteristics) and in psychological functioning (anger and anxiety). None of the transmen in this study had yet had a phalloplasty because of waiting lists or

TABLE 5 Correlations Between Residual Change in Psychological Functioning Over Time and Young Adult Subjective Well-Being

	WHOQOL BREF					
	Physical	Psychological	Social	Environment	SWLS	SHS
Gender dysphoria (UGDS)	0.01 (.97)	0.05 (.75)	−0.09 (.57)	−0.02 (.89)	0.06 (.71)	0.30 (.04)
Body image subscales (BIS)						
Primary sex characteristics	−0.22 (.14)	−0.25 (.09)	−0.35 (.02)	−0.04 (.78)	−0.22 (.14)	−0.21 (.17)
Secondary sex characteristics	−0.39 (.006)	−0.45 (<.001)	−0.47 (<.001)	−0.34 (.02)	−0.35 (.02)	−0.26 (.08)
Neutral body characteristics	−0.21 (.16)	−0.27 (.07)	−0.15 (.32)	−0.28 (.06)	−0.26 (.08)	−0.16 (.28)
Psychological functioning						
Global functioning (CGAS)	0.60 (<.001)	0.52 (.002)	0.52 (.002)	0.27 (.14)	0.58 (<.001)	0.50 (.004)
Depression (BDI)	−0.76 (<.001)	−0.72 (<.001)	−0.51 (.002)	−0.49 (.003)	−0.61 (<.001)	−0.77 (<.001)
Trait anger (TPI)	−0.37 (.03)	−0.18 (.31)	−0.22 (.20)	−0.29 (.09)	−0.33 (.07)	−0.35 (.05)
Trait anxiety (STAI)	−0.58 (<.001)	−0.64 (<.001)	−0.38 (.03)	−0.44 (.01)	−0.49 (.004)	−0.57 (<.001)
CBCL–ABCL						
Total *T* score	−0.20 (.20)	−0.12 (.45)	−0.07 (.65)	−0.14 (.35)	−0.32 (.03)	−0.16 (.29)
Internalizing *T* score	−0.29 (.06)	−0.29 (.06)	−0.23 (.14)	−0.12 (.44)	−0.48 (<.001)	−0.36 (.02)
Externalizing *T* score	−0.13 (.40)	−0.05 (.75)	0.16 (.29)	−0.20 (.19)	−0.15 (.36)	0.00 (.99)
Youth Self Report (YSR–ASR)						
Total *T* score	−0.53 (<.001)	−0.45 (.002)	−0.33 (.03)	−0.42 (.005)	−0.52 (<.001)	−0.55 (<.001)
Internalizing *T* score	−0.62 (<.001)	−0.61 (<.001)	−0.47 (<.001)	−0.40 (.007)	−0.66 (<.001)	−0.60 (<.001)
Externalizing *T* score	−0.23 (.13)	−0.10 (.53)	−0.07 (.67)	−0.37 (.02)	−0.22 (.15)	−0.35 (.02)

P values are in parentheses.

a desire for improved surgery techniques. This finding warrants further study of the specific concerns of young transmen.

Despite promising findings, there were various limitations. First, the study sample was small and came from only 1 clinic. Second, this study did not focus on physical side effects of treatment. Publications on physical parameters of the same cohort of adolescents are submitted or in preparation. A concurring finding exists in the 22-year follow-up of the well-functioning first case now at age 35 years who has no clinical signs of a negative impact of earlier puberty suppression on brain development, metabolic and endocrine parameters, or bone mineral density.[43] Third, despite the absence of pretreatment differences on measured indicators, a selection bias could exist between adolescents of the original cohort that participated in this study compared with nonparticipants.

Age criteria for puberty suppression and CSH are under debate, although they worked well for adolescents in the current study. Especially in natal females, puberty will often start before the age of 12 years. Despite the fact that developing evidence suggests that cognitive and affective cross-gender identification, social role transition, and age at assessment are related to persistence of childhood GD into adolescence, predicting individual persistence at a young age will always remain difficult.[44] The age criterion of 16 years for the start of CSH may be problematic especially for transwomen, as growth in height continues as long as cross-sex steroids are not provided (causing the growth plates to close). Therefore, psychological maturity and the capacity to give full informed consent may surface as the required criteria for puberty suppression and CSH[45] in cases that meet other eligibility criteria.

CONCLUSIONS

Results of this study provide first evidence that, after CSH and GRS, a treatment protocol including puberty suppression leads to improved psychological functioning of transgender adolescents. While enabling them to make important age-appropriate developmental transitions, it contributes to a satisfactory objective and subjective well-being in young adulthood. Clinicians should realize that it is not only early medical intervention that determines this success, but also a comprehensive multidisciplinary approach that attends to the adolescents' GD as well as their further well-being and a supportive environment.

ACKNOWLEDGMENTS

The authors thank the young adults and their parents for their repeated participation in this study over the years.

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(Continued from first page)

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by a personal grant awarded to the first author by the Netherlands Organization for Health Research and Development (ZonMw 100002028).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

Young Adult Psychological Outcome After Puberty Suppression and Gender Reassignment

Annelou L.C. de Vries, Jenifer K. McGuire, Thomas D. Steensma, Eva C.F. Wagenaar, Theo A.H. Doreleijers and Peggy T. Cohen-Kettenis

Pediatrics 2014;134;696; originally published online September 8, 2014;
DOI: 10.1542/peds.2013-2958

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POLICY STATEMENT Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of all Children

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Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents

Jason Rafferty, MD, MPH, EdM, FAAP, COMMITTEE ON PSYCHOSOCIAL ASPECTS OF CHILD AND FAMILY HEALTH, COMMITTEE ON ADOLESCENCE, SECTION ON LESBIAN, GAY, BISEXUAL, AND TRANSGENDER HEALTH AND WELLNESS

abstract

FREE

As a traditionally underserved population that faces numerous health disparities, youth who identify as transgender and gender diverse (TGD) and their families are increasingly presenting to pediatric providers for education, care, and referrals. The need for more formal training, standardized treatment, and research on safety and medical outcomes often leaves providers feeling ill equipped to support and care for patients that identify as TGD and families. In this policy statement, we review relevant concepts and challenges and provide suggestions for pediatric providers that are focused on promoting the health and positive development of youth that identify as TGD while eliminating discrimination and stigma.

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Dr Rafferty conceptualized the statement, drafted the initial manuscript, reviewed and revised the manuscript, approved the final manuscript as submitted, and agrees to be accountable for all aspects of the work.

To cite: Rafferty J, AAP COMMITTEE ON PSYCHOSOCIAL ASPECTS OF CHILD AND FAMILY HEALTH, AAP COMMITTEE ON ADOLESCENCE, AAP SECTION ON LESBIAN, GAY, BISEXUAL, AND TRANSGENDER HEALTH AND WELLNESS. Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents. *Pediatrics*. 2018;142(4): e20182162

INTRODUCTION

In its dedication to the health of all children, the American Academy of Pediatrics (AAP) strives to improve health care access and eliminate disparities for children and teenagers who identify as lesbian, gay, bisexual, transgender, or questioning (LGBTQ) of their sexual or gender identity.[1,2] Despite some advances in public awareness and legal protections, youth who identify as LGBTQ continue to face disparities that stem from multiple sources, including inequitable laws and policies, societal discrimination, and a lack of access to quality health care, including mental health care. Such challenges are often more intense for youth who do not conform to social expectations and norms regarding gender. Pediatric providers are increasingly encountering such youth and their families, who seek medical advice and interventions, yet they may lack the formal training to care for youth that identify as transgender and gender diverse (TGD) and their families.[3]

This policy statement is focused specifically on children and youth that identify as TGD rather than the larger LGBTQ population, providing brief, relevant background on the basis of current available research

TABLE 1 Relevant Terms and Definitions Related to Gender Care

Term	Definition
Sex	An assignment that is made at birth, usually male or female, typically on the basis of external genital anatomy but sometimes on the basis of internal gonads, chromosomes, or hormone levels
Gender identity	A person's deep internal sense of being female, male, a combination of both, somewhere in between, or neither, resulting from a multifaceted interaction of biological traits, environmental factors, self-understanding, and cultural expectations
Gender expression	The external way a person expresses their gender, such as with clothing, hair, mannerisms, activities, or social roles
Gender perception	The way others interpret a person's gender expression
Gender diverse	A term that is used to describe people with gender behaviors, appearances, or identities that are incongruent with those culturally assigned to their birth sex; gender-diverse individuals may refer to themselves with many different terms, such as transgender, nonbinary, genderqueer,[7] gender fluid, gender creative, gender independent, or noncisgender. "Gender diverse" is used to acknowledge and include the vast diversity of gender identities that exists. It replaces the former term, "gender nonconforming," which has a negative and exclusionary connotation.
Transgender	A subset of gender-diverse youth whose gender identity does not match their assigned sex and generally remains persistent, consistent, and insistent over time; the term "transgender" also encompasses many other labels individuals may use to refer to themselves.
Cisgender	A term that is used to describe a person who identifies and expresses a gender that is consistent with the culturally defined norms of the sex they were assigned at birth
Agender	A term that is used to describe a person who does not identify as having a particular gender
Affirmed gender	When a person's true gender identity, or concern about their gender identity, is communicated to and validated from others as authentic
MTF; affirmed female; trans female	Terms that are used to describe individuals who were assigned male sex at birth but who have a gender identity and/or expression that is asserted to be more feminine
FTM; affirmed male; trans male	Terms that are used to describe individuals who were assigned female sex at birth but who have a gender identity and/or expression that is asserted to be more masculine
Gender dysphoria	A clinical symptom that is characterized by a sense of alienation to some or all of the physical characteristics or social roles of one's assigned gender; also, gender dysphoria is the psychiatric diagnosis in the *DSM-5*, which has focus on the distress that stems from the incongruence between one's expressed or experienced (affirmed) gender and the gender assigned at birth.
Gender identity disorder	A psychiatric diagnosis defined previously in the *DSM-IV* (changed to "gender dysphoria" in the *DSM-5*); the primary criteria include a strong, persistent cross-sex identification and significant distress and social impairment. This diagnosis is no longer appropriate for use and may lead to stigma, but the term may be found in older research.
Sexual orientation	A person's sexual identity in relation to the gender(s) to which they are attracted; sexual orientation and gender identity develop separately.

This list is not intended to be all inclusive. The pronouns "they" and "their" are used intentionally to be inclusive rather than the binary pronouns "he" and "she" and "his" and "her." Adapted from Bonifacio HJ, Rosenthal SM. Gender variance and dysphoria in children and adolescents. *Pediatr Clin North Am.* 2015;62(4):1001–1016. Adapted from Vance SR Jr, Ehrensaft D, Rosenthal SM. Psychological and medical care of gender nonconforming youth. *Pediatrics.* 2014;134(6):1184–1192. DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; FTM, female to male; MTF, male to female.

and expert opinion from clinical and research leaders, which will serve as the basis for recommendations. It is not a comprehensive review of clinical approaches and nuances to pediatric care for children and youth that identify as TGD. Professional understanding of youth that identify as TGD is a rapidly evolving clinical field in which research on appropriate clinical management is limited by insufficient funding.[3,4]

DEFINITIONS

To clarify recommendations and discussions in this policy statement, some definitions are provided. However, brief descriptions of human behavior or identities may not capture nuance in this evolving field. "Sex," or "natal gender," is a label, generally "male" or "female," that is typically assigned at birth on the basis of genetic and anatomic characteristics, such as genital anatomy, chromosomes, and sex hormone levels. Meanwhile, "gender identity" is one's internal sense of who one is, which results from a multifaceted interaction of biological traits, developmental influences, and environmental conditions. It may be male, female, somewhere in between, a combination of both, or neither (ie, not conforming to a binary conceptualization of gender). Self-recognition of gender identity develops over time, much the same way as a child's physical body does. For some people, gender identity can be fluid, shifting in different contexts. "Gender expression" refers to the wide array of ways people display their gender through clothing, hair styles, mannerisms, or social roles. Exploring different ways of expressing gender is common for children and may challenge social expectations. The way others interpret this expression is referred to as "gender perception" (Table 1).[5,6]

These labels may or may not be congruent. The term "cisgender" is used if someone identifies and expresses a gender that is consistent with the culturally defined norms of the sex that was assigned at birth. "Gender diverse" is an umbrella term to describe an ever-evolving array of labels that people may apply when their gender identity, expression, or even perception does not conform

to the norms and stereotypes others expect of their assigned sex. "Transgender" is usually reserved for a subset of such youth whose gender identity does not match their assigned sex and generally remains persistent, consistent, and insistent over time. These terms are not diagnoses; rather, they are personal and often dynamic ways of describing one's own gender experience.

Gender identity is not synonymous with "sexual orientation," which refers to a person's identity in relation to the gender(s) to which they are sexually and romantically attracted. Gender identity and sexual orientation are distinct but interrelated constructs.[8] Therefore, being transgender does not imply a sexual orientation, and people who identify as transgender still identify as straight, gay, bisexual, etc, on the basis of their attractions. (For more information, *The Gender Book*, found at www.thegenderbook.com, is a resource with illustrations that are used to highlight these core terms and concepts.)

EPIDEMIOLOGY

In population-based surveys, questions related to gender identity are rarely asked, which makes it difficult to assess the size and characteristics of the population that is TGD. In the 2014 Behavioral Risk Factor Surveillance System of the Centers for Disease Control and Prevention, only 19 states elected to include optional questions on gender identity. Extrapolation from these data suggests that the US prevalence of adults who identify as transgender or "gender nonconforming" is 0.6% (1.4 million), ranging from 0.3% in North Dakota to 0.8% in Hawaii.[9] On the basis of these data, it has been estimated that 0.7% of youth ages 13 to 17 years (~150 000) identify as transgender.[10] This number is much higher than previous estimates, which were extrapolated from individual states or specialty clinics, and is likely an underestimate given the stigma regarding those who openly identify as transgender and the difficulty in defining "transgender" in a way that is inclusive of all gender-diverse identities.[11]

There have been no large-scale prevalence studies among children and adolescents, and there is no evidence that adult statistics reflect young children or adolescents. In the 2014 Behavioral Risk Factor Surveillance System, those 18 to 24 years of age were more likely than older age groups to identify as transgender (0.7%).[9] Children report being aware of gender incongruence at young ages. Children who later identify as TGD report first having recognized their gender as "different" at an average age of 8.5 years; however, they did not disclose such feelings until an average of 10 years later.[12]

MENTAL HEALTH IMPLICATIONS

Adolescents and adults who identify as transgender have high rates of depression, anxiety, eating disorders, self-harm, and suicide.[13–20] Evidence suggests that an identity of TGD has an increased prevalence among individuals with autism spectrum disorder, but this association is not yet well understood.[21,22] In 1 retrospective cohort study, 56% of youth who identified as transgender reported previous suicidal ideation, and 31% reported a previous suicide attempt, compared with 20% and 11% among matched youth who identified as cisgender, respectively.[13] Some youth who identify as TGD also experience gender dysphoria, which is a specific diagnosis given to those who experience impairment in peer and/or family relationships, school performance, or other aspects of their life as a consequence of the incongruence between their assigned sex and their gender identity.[23]

There is no evidence that risk for mental illness is inherently attributable to one's identity of TGD. Rather, it is believed to be multifactorial, stemming from an internal conflict between one's appearance and identity, limited availability of mental health services, low access to health care providers with expertise in caring for youth who identify as TGD, discrimination, stigma, and social rejection.[24] This was affirmed by the American Psychological Association in 2008[25] (with practice guidelines released in 2015[8]) and the American Psychiatric Association, which made the following statement in 2012:

> *Being transgender or gender variant implies no impairment in judgment, stability, reliability, or general social or vocational capabilities; however, these individuals often experience discrimination due to a lack of civil rights protections for their gender identity or expression.… [Such] discrimination and lack of equal civil rights is damaging to the mental health of transgender and gender variant individuals.*[26]

Youth who identify as TGD often confront stigma and discrimination, which contribute to feelings of rejection and isolation that can adversely affect physical and emotional well-being. For example, many youth believe that they must hide their gender identity and expression to avoid bullying, harassment, or victimization. Youth who identify as TGD experience disproportionately high rates of homelessness, physical violence (at home and in the community), substance abuse, and high-risk sexual behaviors.[5,6,12,27–31] Among the 3 million HIV testing events that were reported in 2015, the highest percentages of new infections were among women who identified as transgender[32] and were also at particular risk for not knowing their HIV status.[30]

GENDER-AFFIRMATIVE CARE

In a gender-affirmative care model (GACM), pediatric providers offer developmentally appropriate care that is oriented toward understanding and appreciating the youth's gender experience. A strong, nonjudgmental partnership with youth and their families can facilitate exploration of complicated emotions and gender-diverse expressions while allowing questions and concerns to be raised in a supportive environment.[5] In a GACM, the following messages are conveyed:

- transgender identities and diverse gender expressions do not constitute a mental disorder;
- variations in gender identity and expression are normal aspects of human diversity, and binary definitions of gender do not always reflect emerging gender identities;
- gender identity evolves as an interplay of biology, development, socialization, and culture; and
- if a mental health issue exists, it most often stems from stigma and negative experiences rather than being intrinsic to the child.[27,33]

The GACM is best facilitated through the integration of medical, mental health, and social services, including specific resources and supports for parents and families.[24] Providers work together to destigmatize gender variance, promote the child's self-worth, facilitate access to care, educate families, and advocate for safer community spaces where children are free to develop and explore their gender.[5] A specialized gender-affirmative therapist, when available, may be an asset in helping children and their families build skills for dealing with gender-based stigma, address symptoms of anxiety or depression, and reinforce the child's overall resiliency.[34,35] There is a limited but growing body of evidence that suggests that using an integrated affirmative model results in young people having fewer mental health concerns whether they ultimately identify as transgender.[24,36,37]

In contrast, "conversion" or "reparative" treatment models are used to prevent children and adolescents from identifying as transgender or to dissuade them from exhibiting gender-diverse expressions. The Substance Abuse and Mental Health Services Administration has concluded that any therapeutic intervention with the goal of changing a youth's gender expression or identity is inappropriate.[33] Reparative approaches have been proven to be not only unsuccessful[38] but also deleterious and are considered outside the mainstream of traditional medical practice.[29,39–42] The AAP described reparative approaches as "unfair and deceptive."[43] At the time of this writing,* conversion therapy was banned by executive regulation in New York and by legislative statutes in 9 other states as well as the District of Columbia.[44]

Pediatric providers have an essential role in assessing gender concerns and providing evidence-based information to assist youth and families in medical decision-making. Not doing so can prolong or exacerbate gender dysphoria and contribute to abuse and stigmatization.[35] If a pediatric provider does not feel prepared to address gender concerns when they occur, then referral to a pediatric or mental health provider with more expertise is appropriate. There is little research on communication and efficacy with transfers in care for youth who identify as TGD, particularly from pediatric to adult providers.

DEVELOPMENTAL CONSIDERATIONS

Acknowledging that the capacity for emerging abstract thinking in childhood is important to conceptualize and reflect on identity, gender-affirmation guidelines are being focused on individually tailored interventions on the basis of the physical and cognitive development of youth who identify as TGD.[45] Accordingly, research substantiates that children who are prepubertal and assert an identity of TGD know their gender as clearly and as consistently as their developmentally equivalent peers who identify as cisgender and benefit from the same level of social acceptance.[46] This developmental approach to gender affirmation is in contrast to the outdated approach in which a child's gender-diverse assertions are held as "possibly true" until an arbitrary age (often after pubertal onset) when they can be considered valid, an approach that authors of the literature have termed "watchful waiting." This outdated approach does not serve the child because critical support is withheld. Watchful waiting is based on binary notions of gender in which gender diversity and fluidity is pathologized; in watchful waiting, it is also assumed that notions of gender identity become fixed at a certain age. The approach is also influenced by a group of early studies with validity concerns, methodologic flaws, and limited follow-up on children who identified as TGD and, by adolescence, did not seek further treatment ("desisters").[45,47] More robust and current research suggests that, rather than focusing on who a child will become, valuing them for who they are, even at a young age, fosters secure attachment and resilience, not only for the child but also for the whole family.[5,45,48,49]

* For more information regarding state-specific laws, please contact the AAP Division of State Government Affairs at stgov@ aap.org.

MEDICAL MANAGEMENT

Pediatric primary care providers are in a unique position to routinely inquire about gender development in children and adolescents as part of recommended well-child visits[50] and to be a reliable source of validation, support, and reassurance. They are often the first provider to be aware that a child may not identify as cisgender or that there may be distress related to a gender-diverse identity. The best way to approach gender with patients is to inquire directly and nonjudgmentally about their experience and feelings before applying any labels.[27,51]

Many medical interventions can be offered to youth who identify as TGD and their families. The decision of whether and when to initiate gender-affirmative treatment is personal and involves careful consideration of risks, benefits, and other factors unique to each patient and family. Many protocols suggest that clinical assessment of youth who identify as TGD is ideally conducted on an ongoing basis in the setting of a collaborative, multidisciplinary approach, which, in addition to the patient and family, may include the pediatric provider, a mental health provider (preferably with expertise in caring for youth who identify as TGD), social and legal supports, and a pediatric endocrinologist or adolescent-medicine gender specialist, if available.[6,28] There is no prescribed path, sequence, or end point. Providers can make every effort to be aware of the influence of their own biases. The medical options also vary depending on pubertal and developmental progression.

Clinical Setting

In the past year, 1 in 4 adults who identified as transgender avoided a necessary doctor's visit because of fear of being mistreated.[31] All clinical office staff have a role in affirming a patient's gender identity. Making flyers available or displaying posters related to LGBTQ health issues, including information for children who identify as TGD and families, reveals inclusivity and awareness. Generally, patients who identify as TGD feel most comfortable when they have access to a gender-neutral restroom. Diversity training that encompasses sensitivity when caring for youth who identify as TGD and their families can be helpful in educating clinical and administrative staff. A patient-asserted name and pronouns are used by staff and are ideally reflected in the electronic medical record without creating duplicate charts.[52,53] The US Centers for Medicare and Medicaid Services and the National Coordinator for Health Information Technology require all electronic health record systems certified under the Meaningful Use incentive program to have the capacity to confidentially collect information on gender identity.[54,55] Explaining and maintaining confidentiality procedures promotes openness and trust, particularly with youth who identify as LGBTQ.[1] Maintaining a safe clinical space can provide at least 1 consistent, protective refuge for patients and families, allowing authentic gender expression and exploration that builds resiliency.

Pubertal Suppression

Gonadotrophin-releasing hormones have been used to delay puberty since the 1980s for central precocious puberty.[56] These reversible treatments can also be used in adolescents who experience gender dysphoria to prevent development of secondary sex characteristics and provide time up until 16 years of age for the individual and the family to explore gender identity, access psychosocial supports, develop coping skills, and further define appropriate treatment goals. If pubertal suppression treatment is suspended, then endogenous puberty will resume.[20,57,58]

Often, pubertal suppression creates an opportunity to reduce distress that may occur with the development of secondary sexual characteristics and allow for gender-affirming care, including mental health support for the adolescent and the family. It reduces the need for later surgery because physical changes that are otherwise irreversible (protrusion of the Adam's apple, male pattern baldness, voice change, breast growth, etc) are prevented. The available data reveal that pubertal suppression in children who identify as TGD generally leads to improved psychological functioning in adolescence and young adulthood.[20,57–59]

Pubertal suppression is not without risks. Delaying puberty beyond one's peers can also be stressful and can lead to lower self-esteem and increased risk taking.[60] Some experts believe that genital underdevelopment may limit some potential reconstructive options.[61] Research on long-term risks, particularly in terms of bone metabolism[62] and fertility,[63] is currently limited and provides varied results.[57,64,65] Families often look to pediatric providers for help in considering whether pubertal suppression is indicated in the context of their child's overall well-being as gender diverse.

Gender Affirmation

As youth who identify as TGD reflect on and evaluate their gender identity, various interventions may be considered to better align their gender expression with their underlying identity. This process of reflection, acceptance, and, for some, intervention is known as "gender affirmation." It was formerly referred to as "transitioning," but many view the process as an affirmation and acceptance of who they have always been rather than a transition

TABLE 2 The Process of Gender Affirmation May Include ≥1 of the Following Components

Component	Definition	General Age Range[a]	Reversibility[a]
Social affirmation	Adopting gender-affirming hairstyles, clothing, name, gender pronouns, and restrooms and other facilities	Any	Reversible
Puberty blockers	Gonadotropin-releasing hormone analogues, such as leuprolide and histrelin	During puberty (Tanner stage 2–5)[b]	Reversible[c]
Cross-sex hormone therapy	Testosterone (for those who were assigned female at birth and are masculinizing); estrogen plus androgen inhibitor (for those who were assigned male at birth and are feminizing)	Early adolescence onward	Partially reversible (skin texture, muscle mass, and fat deposition); irreversible once developed (testosterone: Adam's apple protrusion, voice changes, and male pattern baldness; estrogen: breast development); unknown reversibility (effect on fertility)
Gender-affirming surgeries	"Top" surgery (to create a male-typical chest shape or enhance breasts); "bottom" surgery (surgery on genitals or reproductive organs); facial feminization and other procedures	Typically adults (adolescents on case-by-case basis[d])	Not reversible
Legal affirmation	Changing gender and name recorded on birth certificate, school records, and other documents	Any	Reversible

[a] Note that the provided age range and reversibility is based on the little data that are currently available.
[b] There is limited benefit to starting gonadotropin-releasing hormone after Tanner stage 5 for pubertal suppression. However, when cross-sex hormones are initiated with a gradually increasing schedule, the initial levels are often not high enough to suppress endogenous sex hormone secretion. Therefore, gonadotropin-releasing hormone may be continued in accordance with the Endocrine Society Guidelines.[68]
[c] The effect of sustained puberty suppression on fertility is unknown. Pubertal suppression can be, and often is indicated to be, followed by cross-sex hormone treatment. However, when cross-sex hormones are initiated without endogenous hormones, then fertility may be decreased.[68]
[d] Eligibility criteria for gender-affirmative surgical interventions among adolescents are not clearly defined between established protocols and practice. When applicable, eligibility is usually determined on a case-by-case basis with the adolescent and the family along with input from medical, mental health, and surgical providers.[68–71]

from 1 gender identity to another. Accordingly, some people who have gone through the process prefer to call themselves "affirmed females, males, etc" (or just "females, males, etc"), rather than using the prefix "trans-." Gender affirmation is also used to acknowledge that some individuals who identify as TGD may feel affirmed in their gender without pursuing medical or surgical interventions.[7,66]

Supportive involvement of parents and family is associated with better mental and physical health outcomes.[67] Gender affirmation among adolescents with gender dysphoria often reduces the emphasis on gender in their lives, allowing them to attend to other developmental tasks, such as academic success, relationship building, and future-oriented planning.[64] Most protocols for gender-affirming interventions incorporate World Professional Association of Transgender Health[35] and Endocrine Society[68] recommendations and include ≥1 of the following elements (Table 2):

1. Social Affirmation: This is a reversible intervention in which children and adolescents express partially or completely in their asserted gender identity by adapting hairstyle, clothing, pronouns, name, etc. Children who identify as transgender and socially affirm and are supported in their asserted gender show no increase in depression and only minimal (clinically insignificant) increases in anxiety compared with age-matched averages.[48] Social affirmation can be complicated given the wide range of social interactions children have (eg, extended families, peers, school, community, etc). There is little guidance on the best approach (eg, all at once, gradual, creating new social networks, or affirming within existing networks, etc). Pediatric providers can best support families by anticipating and discussing such complexity proactively, either in their own practice or through enlisting a qualified mental health provider.

2. Legal Affirmation: Elements of a social affirmation, such as a name and gender marker, become official on legal documents, such as birth certificates, passports, identification cards, school documents, etc. The processes for making these changes depend on state laws and may require specific documentation from pediatric providers.

3. Medical Affirmation: This is the process of using cross-sex hormones to allow adolescents who have initiated puberty to develop secondary sex characteristics of the opposite biological sex. Some changes are partially reversible if hormones are stopped, but others become

irreversible once they are fully developed (Table 2).

4. Surgical Affirmation: Surgical approaches may be used to feminize or masculinize features, such as hair distribution, chest, or genitalia, and may include removal of internal organs, such as ovaries or the uterus (affecting fertility). These changes are irreversible. Although current protocols typically reserve surgical interventions for adults,[35,68] they are occasionally pursued during adolescence on a case-by-case basis, considering the necessity and benefit to the adolescent's overall health and often including multidisciplinary input from medical, mental health, and surgical providers as well as from the adolescent and family.[69–71]

For some youth who identify as TGD whose natal gender is female, menstruation, breakthrough bleeding, and dysmenorrhea can lead to significant distress before or during gender affirmation. The American College of Obstetrics and Gynecology suggests that, although limited data are available to outline management, menstruation can be managed without exogenous estrogens by using a progesterone-only pill, a medroxyprogesterone acetate shot, or a progesterone-containing intrauterine or implantable device.[72] If estrogen can be tolerated, oral contraceptives that contain both progesterone and estrogen are more effective at suppressing menses.[73] The Endocrine Society guidelines also suggest that gonadotrophin-releasing hormones can be used for menstrual suppression before the anticipated initiation of testosterone or in combination with testosterone for breakthrough bleeding (enables phenotypic masculinization at a lower dose than if testosterone is used alone).[68] Masculinizing hormones in natal female patients may lead to a cessation of menses, but unplanned pregnancies have been reported, which emphasizes the need for ongoing contraceptive counseling with youth who identify as TGD.[72]

HEALTH DISPARITIES

In addition to societal challenges, youth who identify as TGD face several barriers within the health care system, especially regarding access to care. In 2015, a focus group of youth who identified as transgender in Seattle, Washington, revealed 4 problematic areas related to health care:

1. safety issues, including the lack of safe clinical environments and fear of discrimination by providers;
2. poor access to physical health services, including testing for sexually transmitted infections;
3. inadequate resources to address mental health concerns; and
4. lack of continuity with providers.[74]

This study reveals the obstacles many youth who identify as TGD face in accessing essential services, including the limited supply of appropriately trained medical and psychological providers, fertility options, and insurance coverage denials for gender-related treatments.[74]

Insurance denials for services related to the care of patients who identify as TGD are a significant barrier. Although the Office for Civil Rights of the US Department of Health and Human Services explicitly stated in 2012 that the nondiscrimination provision in the Patient Protection and Affordable Care Act includes people who identify as gender diverse,[75,76] insurance claims for gender affirmation, particularly among youth who identify as TGD, are frequently denied.[54,77] In 1 study, it was found that approximately 25% of individuals who identified as transgender were denied insurance coverage because of being transgender.[31] The burden of covering medical expenses that are not covered by insurance can be financially devastating, and even when expenses are covered, families describe high levels of stress in navigating and submitting claims appropriately.[78] In 2012, a large gender center in Boston, Massachusetts, reported that most young patients who identified as transgender and were deemed appropriate candidates for recommended gender care were unable to obtain it because of such denials, which were based on the premise that gender dysphoria was a mental disorder, not a physical one, and that treatment was not medically or surgically necessary.[24] This practice not only contributes to stigma, prolonged gender dysphoria, and poor mental health outcomes,[77] but it may also lead patients to seek nonmedically supervised treatments that are potentially dangerous.[24] Furthermore, insurance denials can reinforce a socioeconomic divide between those who can finance the high costs of uncovered care and those who cannot.[24,77]

The transgender youth group in Seattle likely reflected the larger TGD population when they described how obstacles adversely affect self-esteem and contribute to the perception that they are undervalued by society and the health care system.[74,77] Professional medical associations, including the AAP, are increasingly calling for equity in health care provisions regardless of gender identity or expression.[1,8,23,72] There is a critical need for investments in research on the prevalence, disparities, biological underpinnings, and standards of care relating to gender-diverse populations. Pediatric providers who work with state government and insurance officials can play an essential role in advocating for

stronger nondiscrimination policies and improved coverage.

There is a lack of quality research on the experience of youth of color who identify as transgender. One theory suggests that the intersection of racism, transphobia, and sexism may result in the extreme marginalization that is experienced among many women of color who identify as transgender,[79] including rejection from their family and dropping out of school at younger ages (often in the setting of rigid religious beliefs regarding gender),[80] increased levels of violence and body objectification,[81] 3 times the risk of poverty compared with the general population,[31] and the highest prevalence of HIV compared with other risk groups (estimated as high as 56.3% in 1 meta-analysis).[30] One model suggests that pervasive stigma and oppression can be associated with psychological distress (anxiety, depression, and suicide) and adoption of risk behaviors by such youth to obtain a sense of validation toward their complex identities.[79]

FAMILY ACCEPTANCE

Research increasingly suggests that familial acceptance or rejection ultimately has little influence on the gender identity of youth; however, it may profoundly affect young people's ability to openly discuss or disclose concerns about their identity. Suppressing such concerns can affect mental health.[82] Families often find it hard to understand and accept their child's gender-diverse traits because of personal beliefs, social pressure, and stigma.[49,83] Legitimate fears may exist for their child's welfare, safety, and acceptance that pediatric providers need to appreciate and address. Families can be encouraged to communicate their concerns and questions. Unacknowledged concerns can contribute to shame and hesitation in regard to offering support and understanding,[84] which is essential for the child's self-esteem, social involvement, and overall health as TGD.[48,85–87] Some caution has been expressed that unquestioning acceptance per se may not best serve questioning youth or their families. Instead, psychological evidence suggests that the most benefit comes when family members and youth are supported and encouraged to engage in reflective perspective taking and validate their own and the other's thoughts and feelings despite divergent views.[49,82]

In this regard, suicide attempt rates among 433 adolescents in Ontario who identified as "trans" were 4% among those with strongly supportive parents and as high as 60% among those whose parents were not supportive.[85] Adolescents who identify as transgender and endorse at least 1 supportive person in their life report significantly less distress than those who only experience rejection. In communities with high levels of support, it was found that nonsupportive families tended to increase their support over time, leading to dramatic improvement in mental health outcomes among their children who identified as transgender.[88]

Pediatric providers can create a safe environment for parents and families to better understand and listen to the needs of their children while receiving reassurance and education.[83] It is often appropriate to assist the child in understanding the parents' concerns as well. Despite expectations by some youth with transgender identity for immediate acceptance after "coming out," family members often proceed through a process of becoming more comfortable and understanding of the youth's gender identity, thoughts, and feelings. One model suggests that the process resembles grieving, wherein the family separates from their expectations for their child to embrace a new reality. This process may proceed through stages of shock, denial, anger, feelings of betrayal, fear, self-discovery, and pride.[89] The amount of time spent in any of these stages and the overall pace varies widely. Many family members also struggle as they are pushed to reflect on their own gender experience and assumptions throughout this process. In some situations, youth who identify as TGD may be at risk for internalizing the difficult emotions that family members may be experiencing. In these cases, individual and group therapy for the family members may be helpful.[49,78]

Family dynamics can be complex, involving disagreement among legal guardians or between guardians and their children, which may affect the ability to obtain consent for any medical management or interventions. Even in states where minors may access care without parental consent for mental health services, contraception, and sexually transmitted infections, parental or guardian consent is required for hormonal and surgical care of patients who identify as TGD.[72,90] Some families may take issue with providers who address gender concerns or offer gender-affirming care. In rare cases, a family may deny access to care that raises concerns about the youth's welfare and safety; in those cases, additional legal or ethical support may be useful to consider. In such rare situations, pediatric providers may want to familiarize themselves with relevant local consent laws and maintain their primary responsibility for the welfare of the child.

SAFE SCHOOLS AND COMMUNITIES

Youth who identify as TGD are becoming more visible because gender-diverse expression is increasingly admissible in the media, on social media, and in schools and communities. Regardless of whether a youth with a gender-diverse

identity ultimately identifies as transgender, challenges exist in nearly every social context, from lack of understanding to outright rejection, isolation, discrimination, and victimization. In the US Transgender Survey of nearly 28 000 respondents, it was found that among those who were out as or perceived to be TGD between kindergarten and eighth grade, 54% were verbally harassed, 24% were physically assaulted, and 13% were sexually assaulted; 17% left school because of maltreatment.[31] Education and advocacy from the medical community on the importance of safe schools for youth who identify as TGD can have a significant effect.

At the time of this writing,* only 18 states and the District of Columbia had laws that prohibited discrimination based on gender expression when it comes to employment, housing, public accommodations, and insurance benefits. Over 200 US cities have such legislation. In addition to basic protections, many youth who identify as TGD also have to navigate legal obstacles when it comes to legally changing their name and/or gender marker.[54] In addition to advocating and working with policy makers to promote equal protections for youth who identify as TGD, pediatric providers can play an important role by developing a familiarity with local laws and organizations that provide social work and legal assistance to youth who identify as TGD and their families.

School environments play a significant role in the social and emotional development of children. Every child has a right to feel safe and respected at school, but for youth who identify as TGD, this can be challenging. Nearly every aspect of school life may present safety concerns and require negotiations regarding their gender expression, including name/pronoun use, use of bathrooms and locker rooms, sports teams, dances and activities, overnight activities, and even peer groups. Conflicts in any of these areas can quickly escalate beyond the school's control to larger debates among the community and even on a national stage.

The formerly known Gay, Lesbian, and Straight Education Network (GLSEN), an advocacy organization for youth who identify as LGBTQ, conducts an annual national survey to measure LGBTQ well-being in US schools. In 2015, students who identified as LGBTQ reported high rates of being discouraged from participation in extracurricular activities. One in 5 students who identified as LGBTQ reported being hindered from forming or participating in a club to support lesbian, gay, bisexual, or transgender students (eg, a gay straight alliance, now often referred to as a genders and sexualities alliance) despite such clubs at schools being associated with decreased reports of negative remarks about sexual orientation or gender expression, increased feelings of safety and connectedness at school, and lower levels of victimization. In addition, >20% of students who identified as LGBTQ reported being blocked from writing about LGBTQ issues in school yearbooks or school newspapers or being prevented or discouraged by coaches and school staff from participating in sports because of their sexual orientation or gender expression.[91]

One strategy to prevent conflict is to proactively support policies and protections that promote inclusion and safety of all students. However, such policies are far from consistent across districts. In 2015, GLSEN found that 43% of children who identified as LGBTQ reported feeling unsafe at school because of their gender expression, but only 6% reported that their school had official policies to support youth who identified as TGD, and only 11% reported that their school's antibullying policies had specific protections for gender expression.[91] Consequently, more than half of the students who identified as transgender in the study were prevented from using the bathroom, names, or pronouns that aligned with their asserted gender at school. A lack of explicit policies that protected youth who identified as TGD was associated with increased reported victimization, with more than half of students who identified as LGBTQ reporting verbal harassment because of their gender expression. Educators and school administrators play an essential role in advocating for and enforcing such policies. GLSEN found that when students recognized actions to reduce gender-based harassment, both students who identified as transgender and cisgender reported a greater connection to staff and feelings of safety.[91] In another study, schools were open to education regarding gender diversity and were willing to implement policies when they were supported by external agencies, such as medical professionals.[92]

Academic content plays an important role in building a safe school environment as well. The 2015 GLSEN survey revealed that when positive representations of people who identified as LGBTQ were included in the curriculum, students who identified as LGBTQ reported less hostile school environments, less victimization and greater feelings of safety, fewer school absences because of feeling unsafe, greater feelings of connectedness to their school

* For more information regarding state-specific laws, please contact the AAP Division of State Government Affairs at stgov@ aap.org.

community, and an increased interest in high school graduation and postsecondary education.[91] At the time of this writing,* 8 states had laws that explicitly forbade teachers from even discussing LGBTQ issues.[54]

MEDICAL EDUCATION

One of the most important ways to promote high-quality health care for youth who identify as TGD and their families is increasing the knowledge base and clinical experience of pediatric providers in providing culturally competent care to such populations, as recommended by the recently released guidelines by the Association of American Medical Colleges.[93] This begins with the medical school curriculum in areas such as human development, sexual health, endocrinology, pediatrics, and psychiatry. In a 2009–2010 survey of US medical schools, it was found that the median number of hours dedicated to LGBTQ health was 5, with one-third of US medical schools reporting no LGBTQ curriculum during the clinical years.[94]

During residency training, there is potential for gender diversity to be emphasized in core rotations, especially in pediatrics, psychiatry, family medicine, and obstetrics and gynecology. Awareness could be promoted through the inclusion of topics relevant to caring for children who identify as TGD in the list of core competencies published by the American Board of Pediatrics, certifying examinations, and relevant study materials. Continuing education and maintenance of certification activities can include topics relevant to TGD populations as well.

* For more information regarding state-specific laws, please contact the AAP Division of State Government Affairs at stgov@ aap.org.

RECOMMENDATIONS

The AAP works toward all children and adolescents, regardless of gender identity or expression, receiving care to promote optimal physical, mental, and social well-being. Any discrimination based on gender identity or expression, real or perceived, is damaging to the socioemotional health of children, families, and society. In particular, the AAP recommends the following:

1. that youth who identify as TGD have access to comprehensive, gender-affirming, and developmentally appropriate health care that is provided in a safe and inclusive clinical space;
2. that family-based therapy and support be available to recognize and respond to the emotional and mental health needs of parents, caregivers, and siblings of youth who identify as TGD;
3. that electronic health records, billing systems, patient-centered notification systems, and clinical research be designed to respect the asserted gender identity of each patient while maintaining confidentiality and avoiding duplicate charts;
4. that insurance plans offer coverage for health care that is specific to the needs of youth who identify as TGD, including coverage for medical, psychological, and, when indicated, surgical gender-affirming interventions;
5. that provider education, including medical school, residency, and continuing education, integrate core competencies on the emotional and physical health needs and best practices for the care of youth who identify as TGD and their families;
6. that pediatricians have a role in advocating for, educating, and developing liaison relationships with school districts and other community organizations to promote acceptance and inclusion of all children without fear of harassment, exclusion, or bullying because of gender expression;
7. that pediatricians have a role in advocating for policies and laws that protect youth who identify as TGD from discrimination and violence;
8. that the health care workforce protects diversity by offering equal employment opportunities and workplace protections, regardless of gender identity or expression; and
9. that the medical field and federal government prioritize research that is dedicated to improving the quality of evidence-based care for youth who identify as TGD.

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ACKNOWLEDGMENTS

We thank Isaac Albanese, MPA, and Jayeson Watts, LICSW, for their thoughtful reviews and contributions.

ABBREVIATIONS

AAP: American Academy of Pediatrics
GACM: gender-affirmative care model
GLSEN: Gay, Lesbian, and Straight Education Network
LGBTQ: lesbian, gay, bisexual, transgender, or questioning
TGD: transgender and gender diverse

DOI: https://doi.org/10.1542/peds.2018-2162

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The author has indicated he has no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The author has indicated he has no potential conflicts of interest to disclose.

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Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents

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Pediatrics 2018;142;
DOI: 10.1542/peds.2018-2162 originally published online September 17, 2018;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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Pediatrics 2018;142;
DOI: 10.1542/peds.2018-2162 originally published online September 17, 2018;

Guidelines for Psychological Practice With Transgender and Gender Nonconforming People

American Psychological Association

Transgender and gender nonconforming[1] (TGNC) people are those who have a gender identity that is not fully aligned with their sex assigned at birth. The existence of TGNC people has been documented in a range of historical cultures (Coleman, Colgan, & Gooren, 1992; Feinberg, 1996; Miller & Nichols, 2012; Schmidt, 2003). Current population estimates of TGNC people have ranged from 0.17 to 1,333 per 100,000 (Meier & Labuski, 2013). The Massachusetts Behavioral Risk Factor Surveillance Survey found 0.5% of the adult population aged 18 to 64 years identified as TGNC between 2009 and 2011 (Conron, Scott, Stowell, & Landers, 2012). However, population estimates likely underreport the true number of TGNC people, given difficulties in collecting comprehensive demographic information about this group (Meier & Labuski, 2013). Within the last two decades, there has been a significant increase in research about TGNC people. This increase in knowledge, informed by the TGNC community, has resulted in the development of progressively more trans-affirmative practice across the multiple health disciplines involved in the care of TGNC people (Bockting, Knudson, & Goldberg, 2006; Coleman et al., 2012). Research has documented the extensive experiences of stigma and discrimination reported by TGNC people (Grant et al., 2011) and the mental health consequences of these experiences across the life span (Bockting, Miner, Swinburne Romine, Hamilton, & Coleman, 2013), including increased rates of depression (Fredriksen-Goldsen et al., 2014) and suicidality (Clements-Nolle, Marx, & Katz, 2006). TGNC people's lack of access to trans-affirmative mental and physical health care is a common barrier (Fredriksen-Goldsen et al., 2014; Garofalo, Deleon, Osmer, Doll, & Harper, 2006; Grossman & D'Augelli, 2006), with TGNC people sometimes being denied care because of their gender identity (Xavier et al., 2012).

In 2009, the American Psychological Association (APA) Task Force on Gender Identity and Gender Variance (TFGIGV) survey found that less than 30% of psychologist and graduate student participants reported familiarity with issues that TGNC people experience (APA TFGIGV, 2009). Psychologists and other mental health professionals who have limited training and experience in TGNC-affirmative care may cause harm to TGNC people (Mikalson, Pardo, & Green, 2012; Xavier et al., 2012). The significant level of societal stigma and discrimination that TGNC people face, the associated mental health consequences, and psychologists' lack of familiarity with trans-affirmative care led the APA Task Force to recommend that psychological practice guidelines be developed to help psychologists maximize the effectiveness of services offered and avoid harm when working with TGNC people and their families.

Purpose

The purpose of the *Guidelines for Psychological Practice with Transgender and Gender Nonconforming People* (hereafter *Guidelines*) is to assist psychologists in the provision of culturally competent, developmentally appropriate, and trans-affirmative psychological practice with TGNC people. Trans-affirmative practice is the provision

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The Task Force is grateful to BT, Robin Buhrke, Jenn Burleton, Theo Burnes, Loree Cook-Daniels, Ed Delgado-Romero, Maddie Deutsch, Michelle Emerick, Terry S. Gock, Kristin Hancock, Razia Kosi, Kimberly Lux, Shawn MacDonald, Pat Magee, Tracee McDaniel, Edgardo Menvielle, Parrish Paul, Jamie Roberts, Louise Silverstein, Mary Alice Silverman, Holiday Simmons, Michael C. Smith, Cullen Sprague, David Whitcomb, and Milo Wilson for their assistance in providing important input and feedback on drafts of the guidelines. The Task Force is especially grateful to Clinton Anderson, Director, and Ron Schlittler, Program Coordinator, of APA's Office on LGBT Concerns, who adeptly assisted and provided counsel to the Task Force throughout this project. The Task Force would also like to thank liaisons from the APA Committee on Professional Practice and Standards (COPPS), April Harris-Britt and Scott Hunter, and their staff support, Mary Hardiman. Additionally, members of the Task Force would like to thank the staff at the Phillip Rush Center and Agnes Scott College Counseling Center in Atlanta, Georgia, who served as hosts for face-to-face meetings.

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[1] For the purposes of these guidelines, we use the term *transgender and gender nonconforming* (TGNC). We intend for the term to be as broadly inclusive as possible, and recognize that some TGNC people do not ascribe to these terms. Readers are referred to Appendix A for a listing of terms that include various TGNC identity labels.

Vol. 70, No. 9, 832–864 http://dx.doi.org/10.1037/a0039906

of care that is respectful, aware, and supportive of the identities and life experiences of TGNC people (Korell & Lorah, 2007). The *Guidelines* are an introductory resource for psychologists who will encounter TGNC people in their practice, but can also be useful for psychologists with expertise in this area of practice to improve the care already offered to TGNC people. The *Guidelines* include a set of definitions for readers who may be less familiar with language used when discussing gender identity and TGNC populations (see Appendix A). Distinct from TGNC, the term "cisgender" is used to refer to people whose sex assigned at birth is aligned with their gender identity (E. R. Green, 2006; Serano, 2006).

Given the added complexity of working with TGNC and gender-questioning youth[2] and the limitations of the available research, the *Guidelines* focus primarily, though not exclusively, on TGNC adults. Future revisions of the *Guidelines* will deepen a focus on TGNC and gender-questioning children and adolescents. The *Guidelines* address the strengths of TGNC people, the challenges they face, ethical and legal issues, life span considerations, research, education, training, and health care. Because issues of gender identity are often conflated with issues of gender expression or sexual orientation, psychological practice with the TGNC population warrants the acquisition of specific knowledge about concerns unique to TGNC people that are not addressed by other practice guidelines (APA, 2012). It is important to note that these *Guidelines* are not intended to address some of the conflicts that cisgender people may experience due to societal expectations regarding gender roles (Butler, 1990), nor are they intended to address intersex people (Dreger, 1999; Preves, 2003).

Documentation of Need

In 2005, the APA Council of Representatives authorized the creation of the Task Force on Gender Identity and Gender Variance (TFGIGV), charging the Task Force to review APA policies related to TGNC people and to offer recommendations for APA to best meet the needs of TGNC people (APA TFGIGV, 2009). In 2009, the APA Council of Representatives adopted the Resolution on Transgender, Gender Identity, & Gender Expression Non-Discrimination, which calls upon psychologists in their professional roles to provide appropriate, nondiscriminatory treatment; encourages psychologists to take a leadership role in working against discrimination; supports the provision of adequate and necessary mental and medical health care; recognizes the efficacy, benefit, and medical necessity of gender transition; supports access to appropriate treatment in institutional settings; and supports the creation of educational resources for all psychologists (Anton, 2009). In 2009, in an extensive report on the current state of psychological practice with TGNC people, the TFGIGV determined that there was sufficient knowledge and expertise in the field to warrant the development of practice guidelines for TGNC populations (APA TFGIGV, 2009). The report identified that TGNC people constituted a population with unique needs and that the creation of practice guidelines would be a valuable resource for the field (APA TFGIGV, 2009). Psychologists' relative lack of knowledge about TGNC people and trans-affirmative care, the level of societal stigma and discrimination that TGNC people face, and the significant mental health consequences that TGNC people experience as a result offer a compelling need for psychological practice guidelines for this population.

Users

The intended audience for these *Guidelines* includes psychologists who provide clinical care, conduct research, or provide education or training. Given that gender identity issues can arise at any stage in a TGNC person's life (Lev, 2004), clinicians can encounter a TGNC person in practice or have a client's presenting problem evolve into an issue related to gender identity and gender expression. Researchers, educators, and trainers will benefit from use of these *Guidelines* to inform their work, even when not specifically focused on TGNC populations. Psychologists who focus on TGNC populations in their clinical practice, research, or educational and training activities will also benefit from the use of these *Guidelines*.

Distinction Between Standards and Guidelines

When using these *Guidelines*, psychologists should be aware that APA has made an important distinction between *standards* and *guidelines* (Reed, McLaughlin, & Newman, 2002). Standards are mandates to which all psychologists must adhere (e.g., the *Ethical Principles of Psychologists and Code of Conduct*; APA, 2010), whereas guidelines are aspirational. Psychologists are encouraged to use these *Guidelines* in tandem with the *Ethical Principles of Psychologists and Code of Conduct*, and should be aware that state and federal laws may override these *Guidelines* (APA, 2010).

In addition, these *Guidelines* refer to psychological practice (e.g., clinical work, consultation, education, research, and training) rather than treatment. Practice guidelines are practitioner-focused and provide guidance for professionals regarding "conduct and the issues to be considered in particular areas of clinical practice" (Reed et al., 2002, p. 1044). Treatment guidelines are client-focused and address intervention-specific recommendations for a clinical population or condition (Reed et al., 2002). The current *Guidelines* are intended to complement treatment guidelines for TGNC people seeking mental health services, such as those set forth by the World Professional Association for Transgender Health Standards of Care (Coleman et al., 2012) and the Endocrine Society (Hembree et al., 2009).

[2] For the purposes of these guidelines, "youth" refers to both children and adolescents under the age of 18.

Compatibility

These *Guidelines* are consistent with the APA *Ethical Principles of Psychologists and Code of Conduct* (APA, 2010), the *Standards of Accreditation for Health Service Psychology* (APA, 2015), the APA TFGIGV (2009) report, and the APA Council of Representatives Resolution on Transgender, Gender Identity, & Gender Expression Non-Discrimination (Anton, 2009).

Practice Guidelines Development Process

To address one of the recommendations of the APA TFGIGV (2009), the APA Committee on Sexual Orientation and Gender Diversity (CSOGD; then the Committee on Lesbian, Gay, Bisexual, and Transgender Concerns) and Division 44 (the Society for the Psychological Study of Lesbian, Gay, Bisexual and Transgender Issues) initiated a joint Task Force on Psychological Practice Guidelines with Transgender and Gender Nonconforming People in 2011. Task Force members were selected through an application and review process conducted by the leadership of CSOGD and Division 44. The Task Force included 10 members who had substantial psychological practice expertise with TGNC people. Of the 10 task force members, five individuals identified as TGNC with a range of gender identities and five identified as cisgender. In terms of race/ethnicity, six of the task force members identified as White and four identified as people of color (one Indian American, one Chinese American, one Latina American, and one mixed race).

The Task Force conducted a comprehensive review of the extant scholarship, identified content most pertinent to the practice of psychology with TGNC people, and evaluated the level of evidence to support guidance within each guideline. To ensure the accuracy and comprehensiveness of these *Guidelines*, Task Force members met with TGNC community members and groups and consulted with subject matter experts within and outside of psychology. When the Task Force discovered a lack of professional consensus, every effort was made to include divergent opinions in the field relevant to that issue. When this occurred, the Task Force described the various approaches documented in the literature. Additionally, these *Guidelines* were informed by comments received at multiple presentations held at professional conferences and comments obtained through two cycles of open public comment on earlier *Guideline* drafts.

This document contains 16 guidelines for TGNC psychological practice. Each guideline includes a Rationale section, which reviews relevant scholarship supporting the need for the guideline, and an Application section, which describes how the particular guideline may be applied in psychological practice. The *Guidelines* are organized into five clusters: (a) foundational knowledge and awareness; (b) stigma, discrimination, and barriers to care; (c) life span development; (d) assessment, therapy, and intervention; and (e) research, education, and training.

Funding for this project was provided by Division 44 (Society for the Psychological Study of LGBT Issues); the APA Office on Lesbian, Gay, Bisexual, and Transgender (LGBT) Concerns; a grant from the Committee on Division/APA Relations (CODAPAR); and donations from Randall Ehrbar and Pamela St. Amand. Some members of the Task Force have received compensation through presentations (e.g., honoraria) or royalties (e.g., book contracts) based in part on information contained in these *Guidelines.*

Selection of Evidence

Although the number of publications on the topic of TGNC-affirmative practice has been increasing, this is still an emerging area of scholarly literature and research. When possible, the Task Force relied on peer-reviewed publications, but books, chapters, and reports that do not typically receive a high level of peer review have also been cited when appropriate. These sources are from a diverse range of fields addressing mental health, including psychology, counseling, social work, and psychiatry. Some studies of TGNC people utilize small sample sizes, which limits the generalizability of results. Few studies of TGNC people utilize probability samples or randomized control groups (e.g., Conron et al., 2012; Dhejne et al., 2011). As a result, the Task Force relied primarily on studies using convenience samples, which limits the generalizability of results to the population as a whole, but can be adequate for describing issues and situations that arise within the population.

Foundational Knowledge and Awareness

Guideline 1. Psychologists understand that gender is a nonbinary construct that allows for a range of gender identities and that a person's gender identity may not align with sex assigned at birth.

Rationale. Gender identity is defined as a person's deeply felt, inherent sense of being a girl, woman, or female; a boy, a man, or male; a blend of male or female; or an alternative gender (Bethea & McCollum, 2013; Institute of Medicine [IOM], 2011). In many cultures and religious traditions, gender has been perceived as a binary construct, with mutually exclusive categories of male or female, boy or girl, man or woman (Benjamin, 1966; Mollenkott, 2001; Tanis, 2003). These mutually exclusive categories include an assumption that gender identity is always in alignment with sex assigned at birth (Bethea & McCollum, 2013). For TGNC people, gender identity differs from sex assigned at birth to varying degrees, and may be experienced and expressed outside of the gender binary (Harrison, Grant, & Herman, 2012; Kuper, Nussbaum, & Mustanski, 2012).

Gender as a nonbinary construct has been described and studied for decades (Benjamin, 1966; Herdt, 1994; Kulick, 1998). There is historical evidence of recognition, societal acceptance, and sometimes reverence of diversity in gender identity and gender expression in several different cultures (Coleman et al., 1992; Feinberg, 1996; Miller

& Nichols, 2012; Schmidt, 2003). Many cultures in which gender nonconforming persons and groups were visible were diminished by westernization, colonialism, and systemic inequity (Nanda, 1999). In the 20th century, TGNC expression became medicalized (Hirschfeld, 1910/1991), and medical interventions to treat discordance between a person's sex assigned at birth, secondary sex characteristics, and gender identity became available (Meyerowitz, 2002).

As early as the 1950s, research found variability in how an individual described their[3] gender, with some participants reporting a gender identity different from the culturally defined, mutually exclusive categories of "man" or "woman" (Benjamin, 1966). In several recent large online studies of the TGNC population in the United States, 30% to 40% of participants identified their gender identity as other than man or woman (Harrison et al., 2012; Kuper et al., 2012). Although some studies have cultivated a broader understanding of gender (Conron, Scout, & Austin, 2008), the majority of research has required a forced choice between man and woman, thus failing to represent or depict those with different gender identities (IOM, 2011). Research over the last two decades has demonstrated the existence of a wide spectrum of gender identity and gender expression (Bockting, 2008; Harrison et al., 2012; Kuper et al., 2012), which includes people who identify as either man or woman, neither man nor woman, a blend of man and woman, or a unique gender identity. A person's identification as TGNC can be healthy and self-affirming, and is not inherently pathological (Coleman et al., 2012). However, people may experience distress associated with discordance between their gender identity and their body or sex assigned at birth, as well as societal stigma and discrimination (Coleman et al., 2012).

Between the late 1960s and the early 1990s, health care to alleviate gender dysphoria largely reinforced a binary conceptualization of gender (APA TFGIGV, 2009; Bolin, 1994; Hastings, 1974). At that time, it was considered an ideal outcome for TGNC people to conform to an identity that aligned with either sex assigned at birth or, if not possible, with the "opposite" sex, with a heavy emphasis on blending into the cisgender population or "passing" (APA TFGIGV, 2009; Bolin, 1994; Hastings, 1974). Variance from these options could raise concern for health care providers about a TGNC person's ability to transition successfully. These concerns could act as a barrier to accessing surgery or hormone therapy because medical and mental health care provider endorsement was required before surgery or hormones could be accessed (Berger et al., 1979). Largely because of self-advocacy of TGNC individuals and communities in the 1990s, combined with advances in research and models of trans-affirmative care, there is greater recognition and acknowledgment of a spectrum of gender diversity and corresponding individualized, TGNC-specific health care (Bockting et al., 2006; Coleman et al., 2012).

Application. A nonbinary understanding of gender is fundamental to the provision of affirmative care for TGNC people. Psychologists are encouraged to adapt or modify their understanding of gender, broadening the range of variation viewed as healthy and normative. By understanding the spectrum of gender identities and gender expressions that exist, and that a person's gender identity may not be in full alignment with sex assigned at birth, psychologists can increase their capacity to assist TGNC people, their families, and their communities (Lev, 2004). Respecting and supporting TGNC people in authentically articulating their gender identity and gender expression, as well as their lived experience, can improve TGNC people's health, well-being, and quality of life (Witten, 2003).

Some TGNC people may have limited access to visible, positive TGNC role models. As a result, many TGNC people are isolated and must cope with the stigma of gender nonconformity without guidance or support, worsening the negative effect of stigma on mental health (Fredriksen-Goldsen et al., 2014; Singh, Hays, & Watson, 2011). Psychologists may assist TGNC people in challenging gender norms and stereotypes, and in exploring their unique gender identity and gender expression. TGNC people, partners, families, friends, and communities can benefit from education about the healthy variation of gender identity and gender expression, and the incorrect assumption that gender identity automatically aligns with sex assigned at birth.

Psychologists may model an acceptance of ambiguity as TGNC people develop and explore aspects of their gender, especially in childhood and adolescence. A nonjudgmental stance toward gender nonconformity can help to counteract the pervasive stigma faced by many TGNC people and provide a safe environment to explore gender identity and make informed decisions about gender expression.

Guideline 2. Psychologists understand that gender identity and sexual orientation are distinct but interrelated constructs.

Rationale. The constructs of gender identity and sexual orientation are theoretically and clinically distinct, even though professionals and nonprofessionals frequently conflate them. Although some research suggests a potential link in the development of gender identity and sexual orientation, the mechanisms of such a relationship are unknown (Adelson & American Academy of Child and Adolescent Psychiatry [AACAP] Committee on Quality Issues [CQI], 2012; APA TFGIGV, 2009; A. H. Devor, 2004; Drescher & Byne, 2013). *Sexual orientation* is defined as a person's sexual and/or emotional attraction to another person (Shively & De Cecco, 1977), compared with *gender identity*, which is defined by a person's felt, inherent sense of gender. For most people, gender identity develops earlier than sexual orientation. Gender identity is often established in young toddlerhood (Adelson & AACAP CQI, 2012; Kohlberg, 1966), compared with aware-

[3] The third person plural pronouns "they," "them," and "their" in some instances function in these guidelines as third-person singular pronouns to model a common technique used to avoid the use of gendered pronouns when speaking to or about TGNC people.

ness of same-sex attraction, which often emerges in early adolescence (Adelson & AACAP CQI, 2012; D'Augelli & Hershberger, 1993; Herdt & Boxer, 1993; Ryan, 2009; Savin-Williams & Diamond, 2000). Although gender identity is usually established in childhood, individuals may become aware that their gender identity is not in full alignment with sex assigned at birth in childhood, adolescence, or adulthood. The developmental pathway of gender identity typically includes a progression through multiple stages of awareness, exploration, expression, and identity integration (Bockting & Coleman, 2007; A. H. Devor, 2004; Vanderburgh, 2007). Similarly, a person's sexual orientation may progress through multiple stages of awareness, exploration, and identity through adolescence and into adulthood (Bilodeau & Renn, 2005). Just as some people experience their sexual orientation as being fluid or variable (L. M. Diamond, 2013), some people also experience their gender identity as fluid (Lev, 2004).

The experience of questioning one's gender can create significant confusion for some TGNC people, especially for those who are unfamiliar with the range of gender identities that exist. To explain any discordance they may experience between their sex assigned at birth, related societal expectations, patterns of sexual and romantic attraction, and/or gender role nonconformity and gender identity, some TGNC people may assume that they must be gay, lesbian, bisexual, or queer (Bockting, Benner, & Coleman, 2009). Focusing solely on sexual orientation as the cause for discordance may obscure awareness of a TGNC identity. It can be very important to include sexual orientation and gender identity in the process of identity exploration as well as in the associated decisions about which options will work best for any particular person. In addition, many TGNC adults have disguised or rejected their experience of gender incongruence in childhood or adolescence to conform to societal expectations and minimize their fear of difference (Bockting & Coleman, 2007; Byne et al., 2012).

Because gender and patterns of attraction are used to identify a person's sexual orientation, the articulation of sexual orientation is made more complex when sex assigned at birth is not aligned with gender identity. A person's sexual orientation identity cannot be determined by simply examining external appearance or behavior, but must incorporate a person's identity and self-identification (Broido, 2000).

Application. Psychologists may assist people in differentiating gender identity and sexual orientation. As clients become aware of previously hidden or constrained aspects of their gender identity or sexuality, psychologists may provide acceptance, support, and understanding without making assumptions or imposing a specific sexual orientation or gender identity outcome (APA TFGIGV, 2009). Because of their roles in assessment, treatment, and prevention, psychologists are in a unique position to help TGNC people better understand and integrate the various aspects of their identities. Psychologists may assist TGNC people by introducing and normalizing differences in gender identity and expression. As a TGNC person finds a comfortable way to actualize and express their gender identity, psychologists may notice that previously incongruent aspects of their sexual orientation may become more salient, better integrated, or increasingly egosyntonic (Bockting et al., 2009; H. Devor, 1993; Schleifer, 2006). This process may allow TGNC people the comfort and opportunity to explore attractions or aspects of their sexual orientation that previously had been repressed, hidden, or in conflict with their identity. TGNC people may experience a renewed exploration of their sexual orientation, a widened spectrum of attraction, or a shift in how they identify their sexual orientation in the context of a developing TGNC identity (Coleman, Bockting, & Gooren, 1993; Meier, Pardo, Labuski, & Babcock, 2013; Samons, 2008).

Psychologists may need to provide TGNC people with information about TGNC identities, offering language to describe the discordance and confusion TGNC people may be experiencing. To facilitate TGNC people's learning, psychologists may introduce some of the narratives written by TGNC people that reflect a range of outcomes and developmental processes in exploring and affirming gender identity (e.g., Bornstein & Bergman, 2010; Boylan, 2013; J. Green, 2004; Krieger, 2011; Lawrence, 2014). These resources may potentially aid TGNC people in distinguishing between issues of sexual orientation and gender identity and in locating themselves on the gender spectrum. Psychologists may also educate families and broader community systems (e.g., schools, medical systems) to better understand how gender identity and sexual orientation are different but related; this may be particularly useful when working with youth (Singh & Burnes, 2009; Whitman, 2013). Because gender identity and sexual orientation are often conflated, even by professionals, psychologists are encouraged to carefully examine resources that claim to provide affirmative services for lesbian, gay, bisexual, transgender, and queer (LGBTQ) people, and to confirm which are knowledgeable about and inclusive of the needs of TGNC people before offering referrals or recommendations to TGNC people and their families.

Guideline 3. Psychologists seek to understand how gender identity intersects with the other cultural identities of TGNC people.

Rationale. Gender identity and gender expression may have profound intersections with other aspects of identity (Collins, 2000; Warner, 2008). These aspects may include, but are not limited to, race/ethnicity, age, education, socioeconomic status, immigration status, occupation, disability status, HIV status, sexual orientation, relational status, and religion and/or spiritual affiliation. Whereas some of these aspects of identity may afford privilege, others may create stigma and hinder empowerment (Burnes & Chen, 2012; K. M. de Vries, 2015). In addition, TGNC people who transition may not be prepared for changes in privilege or societal treatment based on gender identity and gender expression. To illustrate, an African American trans man may gain male privilege, but may face racism and

societal stigma particular to African American men. An Asian American/Pacific Islander trans woman may experience the benefit of being perceived as a cisgender woman, but may also experience sexism, misogyny, and objectification particular to Asian American/Pacific Islander cisgender women.

The intersection of multiple identities within TGNC people's lives is complex and may obstruct or facilitate access to necessary support (A. Daley, Solomon, Newman, & Mishna, 2008). TGNC people with less privilege and/or multiple oppressed identities may experience greater stress and restricted access to resources. They may also develop resilience and strength in coping with disadvantages, or may locate community-based resources available to specific groups (e.g., for people living with HIV; Singh et al., 2011). Gender identity affirmation may conflict with religious beliefs or traditions (Bockting & Cesaretti, 2001). Finding an affirmative expression of their religious and spiritual beliefs and traditions, including positive relationships with religious leaders, can be an important resource for TGNC people (Glaser, 2008; Porter, Ronneberg, & Witten, 2013; Xavier, 2000).

Application. In practice, psychologists strive to recognize the salient multiple and intersecting identities of TGNC people that influence coping, discrimination, and resilience (Burnes & Chen, 2012). Improved rapport and therapeutic alliance are likely to develop when psychologists avoid overemphasizing gender identity and gender expression when not directly relevant to TGNC people's needs and concerns. Even when gender identity is the main focus of care, psychologists are encouraged to understand that a TGNC person's experience of gender may also be shaped by other important aspects of identity (e.g., age, race/ethnicity, sexual orientation), and that the salience of different aspects of identity may evolve as the person continues psychosocial development across the life span, regardless of whether they complete a social or medical transition.

At times, a TGNC person's intersection of identities may result in conflict, such as a person's struggle to integrate gender identity with religious and/or spiritual upbringing and beliefs (Kidd & Witten, 2008; Levy & Lo, 2013; Rodriguez & Follins, 2012). Psychologists may aid TGNC people in understanding and integrating identities that may be differently privileged within systems of power and systemic inequity (Burnes & Chen, 2012). Psychologists may also highlight and strengthen the development of TGNC people's competencies and resilience as they learn to manage the intersection of stigmatized identities (Singh, 2012).

Guideline 4. Psychologists are aware of how their attitudes about and knowledge of gender identity and gender expression may affect the quality of care they provide to TGNC people and their families.

Rationale. Psychologists, like other members of society, come to their personal understanding and acceptance of different aspects of human diversity through a process of socialization. Psychologists' cultural biases, as well as the cultural differences between psychologists and their clients, have a clinical impact (Israel, Gorcheva, Burnes, & Walther, 2008; Vasquez, 2007). The assumptions, biases, and attitudes psychologists hold regarding TGNC people and gender identity and/or gender expression can affect the quality of services psychologists provide and their ability to develop an effective therapeutic alliance (Bess & Stabb, 2009; Rachlin, 2002). In addition, a lack of knowledge or training in providing affirmative care to TGNC people can limit a psychologist's effectiveness and perpetuate barriers to care (Bess & Stabb, 2009; Rachlin, 2002). Psychologists experienced with lesbian, gay, or bisexual (LGB) people may not be familiar with the unique needs of TGNC people (Israel, 2005; Israel et al., 2008). In community surveys, TGNC people have reported that many mental health care providers lack basic knowledge and skills relevant to care of TGNC people (Bradford, Xavier, Hendricks, Rives, & Honnold, 2007; Xavier, Bobbin, Singer, & Budd, 2005) and receive little training to prepare them to work with TGNC people (APA TFGIGV, 2009; Lurie, 2005). The National Transgender Discrimination Survey (Grant et al., 2011) reported that 50% of TGNC respondents shared that they had to educate their health care providers about TGNC care, 28% postponed seeking medical care due to antitrans bias, and 19% were refused care due to discrimination.

The APA ethics code (APA, 2010) specifies that psychologists practice in areas only within the boundaries of their competence (Standard 2.01), participate in proactive and consistent ways to enhance their competence (Standard 2.03), and base their work upon established scientific and professional knowledge (Standard 2.04). Competence in working with TGNC people can be developed through a range of activities, such as education, training, supervised experience, consultation, study, or professional experience.

Application. Psychologists may engage in practice with TGNC people in various ways; therefore, the depth and level of knowledge and competence required by a psychologist depends on the type and complexity of service offered to TGNC people. Services that psychologists provide to TGNC people require a basic understanding of the population and its needs, as well as the ability to respectfully interact in a trans-affirmative manner (L. Carroll, 2010).

APA emphasizes the use of evidence-based practice (APA Presidential Task Force on Evidence-Based Practice, 2006). Given how easily assumptions or stereotypes could influence treatment, evidence-based practice may be especially relevant to psychological practice with TGNC people. Until evidence-based practices are developed specifically for TGNC people, psychologists are encouraged to utilize existing evidence-based practices in the care they provide. APA also promotes collaboration with clients concerning clinical decisions, including issues related to costs, potential benefits, and the existing options and resources related to treatment (APA Presidential Task Force on Evidence-Based Practice, 2006). TGNC people could benefit from such collaboration and active engagement in decision

making, given the historical disenfranchisement and disempowerment of TGNC people in health care.

In an effort to develop competence in working with TGNC people, psychologists are encouraged to examine their personal beliefs regarding gender and sexuality, gender stereotypes, and TGNC identities, in addition to identifying gaps in their own knowledge, understanding, and acceptance (American Counseling Association [ACA], 2010). This examination may include exploring one's own gender identity and gendered experiences related to privilege, power, or marginalization, as well as seeking consultation and training with psychologists who have expertise in working with TGNC people and communities.

Psychologists are further encouraged to develop competence in working with TGNC people and their families by seeking up-to-date basic knowledge and understanding of gender identity and expression, and learning how to interact with TGNC people and their families respectfully and without judgment. Competence in working with TGNC people may be achieved and maintained in formal and informal ways, ranging from exposure in the curriculum of training programs for future psychologists and continuing education at professional conferences, to affirmative involvement as allies in the TGNC community. Beyond acquiring general competence, psychologists who choose to specialize in working with TGNC people presenting with gender-identity-related concerns are strongly encouraged to obtain advanced training, consultation, and professional experience (ACA, 2010; Coleman et al., 2012).

Psychologists may gain knowledge about the TGNC community and become more familiar with the complex social issues that affect the lives of TGNC people through first-hand experiences (e.g., attending community meetings and conferences, reading narratives written by TGNC people). If psychologists have not yet developed competence in working with TGNC people, it is recommended that they refer TGNC people to other psychologists or providers who are knowledgeable and able to provide trans-affirmative care.

Stigma, Discrimination, and Barriers to Care

Guideline 5. Psychologists recognize how stigma, prejudice, discrimination, and violence affect the health and well-being of TGNC people.

Rationale. Many TGNC people experience discrimination, ranging from subtle to severe, when accessing housing, health care, employment, education, public assistance, and other social services (Bazargan & Galvan, 2012; Bradford, Reisner, Honnold, & Xavier, 2013; Dispenza, Watson, Chung, & Brack, 2012; Grant et al., 2011). Discrimination can include assuming a person's assigned sex at birth is fully aligned with that person's gender identity, not using a person's preferred name or pronoun, asking TGNC people inappropriate questions about their bodies, or making the assumption that psychopathology exists given a specific gender identity or gender expression (Nadal, Rivera, & Corpus, 2010; Nadal, Skolnik, & Wong, 2012). Discrimination may also include refusing access to housing or employment or extreme acts of violence (e.g., sexual assault, murder). TGNC people who hold multiple marginalized identities are more vulnerable to discrimination and violence. TGNC women and people of color disproportionately experience severe forms of violence and discrimination, including police violence, and are less likely to receive help from law enforcement (Edelman, 2011; National Coalition of Anti-Violence Programs, 2011; Saffin, 2011).

TGNC people are at risk of experiencing antitrans prejudice and discrimination in educational settings. In a national representative sample of 7,898 LGBT youth in K-12 settings, 55.2% of participants reported verbal harassment, 22.7% reported physical harassment, and 11.4% reported physical assault based on their gender expression (Kosciw, Greytak, Palmer, & Boesen, 2014). In a national community survey of TGNC adults, 15% reported prematurely leaving educational settings ranging from kindergarten through college as a result of harassment (Grant et al., 2011). Many schools do not include gender identity and gender expression in their school nondiscrimination policies; this leaves TGNC youth without needed protections from bullying and aggression in schools (Singh & Jackson, 2012). TGNC youth in rural settings may be even more vulnerable to bullying and hostility in their school environments due to antitrans prejudice (Kosciw et al., 2014).

Inequities in educational settings and other forms of TGNC-related discrimination may contribute to the significant economic disparities TGNC people have reported. Grant and colleagues (2011) found that TGNC people were four times more likely to have a household income of less than $10,000 compared with cisgender people, and almost half of a sample of TGNC older adults reported a household income at or below 200% of poverty (Fredriksen-Goldsen et al., 2014). TGNC people often face workplace discrimination both when seeking and maintaining employment (Brewster, Velez, Mennicke, & Tebbe, 2014; Dispenza et al., 2012; Mizock & Mueser, 2014). In a nonrepresentative national study of TGNC people, 90% reported having "directly experienced harassment or mistreatment at work and felt forced to take protective actions that negatively impacted their careers or their well-being, such as hiding who they were to avoid workplace repercussions" (Grant et al., 2011, p. 56). In addition, 78% of respondents reported experiencing some kind of direct mistreatment or discrimination at work (Grant et al., 2011). Employment discrimination may be related to stigma based on a TGNC person's appearance, discrepancies in identity documentation, or being unable to provide job references linked to that person's pretransition name or gender presentation (Bender-Baird, 2011).

Issues of employment discrimination and workplace harassment are particularly salient for TGNC military personnel and veterans. Currently, TGNC people cannot serve openly in the U.S. military. Military regulations cite "transsexualism" as a medical exclusion from service (Department of Defense, 2011; Elders & Steinman, 2014). When

enlisted, TGNC military personnel are faced with very difficult decisions related to coming out, transition, and seeking appropriate medical and mental health care, which may significantly impact or end their military careers. Not surprisingly, research documents very high rates of suicidal ideation and behavior among TGNC military and veteran populations (Blosnich et al., 2013; Matarazzo et al., 2014). Being open about their TGNC identity with health care providers can carry risk for TGNC military personnel (OutServe-Servicemembers Legal Defense Network, n.d.). Barriers to accessing health care noted by TGNC veterans include viewing the VA health care system as an extension of the military, perceiving the VA as an unwelcoming environment, and fearing providers' negative reactions to their identity (Sherman, Kauth, Shipherd, & Street, 2014; Shipherd, Mizock, Maguen, & Green, 2012). A recent study shows 28% of LGBT veterans perceived their VA as welcoming and one third as unwelcoming (Sherman et al., 2014). Multiple initiatives are underway throughout the VA system to improve the quality and sensitivity of services to LGBT veterans.

Given widespread workplace discrimination and possible dismissal following transition, TGNC people may engage in sex work or survival sex (e.g., trading sex for food), or sell drugs to generate income (Grant et al., 2011; Hwahng & Nuttbrock, 2007; Operario, Soma, & Underhill, 2008; Stanley, 2011). This increases the potential for negative interactions with the legal system, such as harassment by the police, bribery, extortion, and arrest (Edelman, 2011; Testa et al., 2012), as well as increased likelihood of mental health symptoms and greater health risks, such as higher incidence of sexually transmitted infections, including HIV (Nemoto, Operario, Keatley, & Villegas, 2004).

Incarcerated TGNC people report harassment, isolation, forced sex, and physical assault, both by prison personnel and other inmates (American Civil Liberties Union National Prison Project, 2005; Brotheim, 2013; C. Daley, 2005). In sex-segregated facilities, TGNC people may be subjected to involuntary solitary confinement (also called "administrative segregation"), which can lead to severe negative mental and physical health consequences and may block access to services (Gallagher, 2014; National Center for Transgender Equality, 2012). Another area of concern is for TGNC immigrants and refugees. TGNC people in detention centers may not be granted access to necessary care and experience significant rates of assault and violence in these facilities (Gruberg, 2013). TGNC people may seek asylum in the United States to escape danger as a direct result of lack of protections in their country of origin (APA Presidential Task Force on Immigration, 2012; Cerezo, Morales, Quintero, & Rothman, 2014; Morales, 2013).

TGNC people have difficulty accessing necessary health care (Fredriksen-Goldsen et al., 2014; Lambda Legal, 2012) and often feel unsafe sharing their gender identity or their experiences of antitrans prejudice and discrimination due to historical and current discrimination from health care providers (Grant et al., 2011; Lurie, 2005; Singh & McKleroy, 2011). Even when TGNC people have health insurance, plans may explicitly exclude coverage related to gender transition (e.g., hormone therapy, surgery). TGNC people may also have difficulty accessing trans-affirmative primary health care if coverage for procedures is denied based on gender. For example, trans men may be excluded from necessary gynecological care based on the assumption that men do not need these services. These barriers often lead to a lack of preventive health care for TGNC people (Fredriksen-Goldsen et al., 2014; Lambda Legal, 2012). Although the landscape is beginning to change with the recent revision of Medicare policy (National Center for Transgender Equality, 2014) and changes to state laws (Transgender Law Center, n.d.), many TGNC people are still likely to have little to no access to TGNC-related health care as a result of the exclusions in their insurance.

Application. Awareness of and sensitivity to the effects of antitrans prejudice and discrimination can assist psychologists in assessing, treating, and advocating for their TGNC clients. When a TGNC person faces discrimination based on gender identity or gender expression, psychologists may facilitate emotional processing of these experiences and work with the person to identify supportive resources and possible courses of action. Specific needs of TGNC people might vary from developing self-advocacy strategies, to navigating public spaces, to seeking legal recourse for harassment and discrimination in social services and other systems. Additionally, TGNC people who have been traumatized by physical or emotional violence may need therapeutic support.

Psychologists may be able to assist TGNC people in accessing relevant social service systems. For example, psychologists may be able to assist in identifying health care providers and housing resources that are affirming and affordable, or locating affirming religious and spiritual communities (Glaser, 2008; Porter et al., 2013). Psychologists may also assist in furnishing documentation or official correspondence that affirms gender identity for the purpose of accessing appropriate public accommodations, such as bathroom use or housing (Lev, 2009; W. J. Meyer, 2009).

Additionally, psychologists may identify appropriate resources, information, and services to help TGNC people in addressing workplace discrimination, including strategies during a social and/or medical transition for identity disclosure at work. For those who are seeking employment, psychologists may help strategize about how and whether to share information about gender history. Psychologists may also work with employers to develop supportive policies for workplace gender transition or to develop training to help employees adjust to the transition of a coworker.

For TGNC military and veteran populations, psychologists may help to address the emotional impact of navigating TGNC identity development in the military system. Psychologists are encouraged to be aware that issues of confidentiality may be particularly sensitive with active duty or reserve status service members, as the consequences of being identified as TGNC may prevent the client's disclosure of gender identity in treatment.

In educational settings, psychologists may advocate for TGNC youth on a number of levels (APA & National

Association of School Psychologists, 2014; Boulder Valley School District, 2012). Psychologists may consult with administrators, teachers, and school counselors to provide resources and trainings on antitrans prejudice and developing safer school environments for TGNC students (Singh & Burnes, 2009). Peer support from other TGNC people has been shown to buffer the negative effect of stigma on mental health (Bockting et al., 2013). As such, psychologists may consider and develop peer-based interventions to facilitate greater understanding and respectful treatment of TGNC youth by cisgender peers (Case & Meier, 2014). Psychologists may work with TGNC youth and their families to identify relevant resources, such as school policies that protect gender identity and gender expression (APA & National Association of School Psychologists, 2014; Gonzalez & McNulty, 2010), referrals to TGNC-affirmative organizations, and online resources, which may be especially helpful for TGNC youth in rural settings.

Guideline 6. Psychologists strive to recognize the influence of institutional barriers on the lives of TGNC people and to assist in developing TGNC-affirmative environments.

Rationale. Antitrans prejudice and the adherence of mainstream society to the gender binary adversely affect TGNC people within their families, schools, health care, legal systems, workplaces, religious traditions, and communities (American Civil Liberties Union National Prison Project, 2005; Bradford et al., 2013; Brewster et al., 2014; Levy & Lo, 2013; McGuire, Anderson, & Toomey, 2010). TGNC people face challenges accessing gender-inclusive restrooms, which may result in discomfort when being forced to use a men's or women's restroom (Transgender Law Center, 2005). In addition to the emotional distress the forced binary choice that public restrooms may create for some, TGNC people are frequently concerned with others' reactions to their presence in public restrooms, including potential discrimination, harassment, and violence (Herman, 2013).

Many TGNC people may be distrustful of care providers due to previous experiences of being pathologized (Benson, 2013). Experiences of discrimination and prejudice with health care providers may be complicated by power differentials within the therapeutic relationship that may greatly affect or complicate the care that TGNC people experience. TGNC people have routinely been asked to obtain an endorsement letter from a psychologist attesting to the stability of their gender identity as a prerequisite to access an endocrinologist, surgeon, or legal institution (e.g., driver's license bureau; Lev, 2009). The need for such required documentation from a psychologist may influence rapport, resulting in TGNC people fearing prejudicial treatment in which this documentation is withheld or delayed by the treating provider (Bouman et al., 2014). Whether a TGNC person has personally experienced interactions with providers as disempowering or has learned from community members to expect such a dynamic, psychologists are encouraged to be prepared for TGNC people to be very cautious when entering into a therapeutic relationship. When TGNC people feel validated and empowered within the environment in which a psychologist practices, the therapeutic relationship will benefit and the person may be more willing to explore their authentic selves and share uncertainties and ambiguities that are a common part of TGNC identity development.

Application. Because many TGNC people experience antitrans prejudice or discrimination, psychologists are encouraged to ensure that their work settings are welcoming and respectful of TGNC people, and to be mindful of what TGNC people may perceive as unwelcoming. To do so, psychologists may educate themselves about the many ways that cisgender privilege and antitrans prejudice may be expressed. Psychologists may also have specific conversations with TGNC people about their experiences of the mental health system and implement feedback to foster TGNC-affirmative environments. As a result, when TGNC people access various treatment settings and public spaces, they may experience less harm, disempowerment, or pathologization, and thus will be more likely to avail themselves of resources and support.

Psychologists are encouraged to be proactive in considering how overt or subtle cues in their workplaces and other environments may affect the comfort and safety of TGNC people. To increase the comfort of TGNC people, psychologists are encouraged to display TGNC-affirmative resources in waiting areas and to avoid the display of items that reflect antitrans attitudes (Lev, 2009). Psychologists are encouraged to examine how their language (e.g., use of incorrect pronouns and names) may reinforce the gender binary in overt or subtle and unintentional ways (Smith, Shin, & Officer, 2012). It may be helpful for psychologists to provide training for support staff on how to respectfully interact with TGNC people. A psychologist may consider making changes to paperwork, forms, or outreach materials to ensure that these materials are more inclusive of TGNC people (Spade, 2011b). For example, demographic questionnaires can communicate respect through the use of inclusive language and the inclusion of a range of gender identities. In addition, psychologists may also work within their institutions to advocate for restrooms that are inclusive and accessible for people of all gender identities and/or gender expressions.

When working with TGNC people in a variety of care and institutional settings (e.g., inpatient medical and psychiatric hospitals, substance abuse treatment settings, nursing homes, foster care, religious communities, military and VA health care settings, and prisons), psychologists may become liaisons and advocates for TGNC people's mental health needs and for respectful treatment that addresses their gender identity in an affirming manner. In playing this role, psychologists may find guidance and best practices that have been published for particular institutional contexts to be helpful (e.g., Department of Veterans Affairs, Veterans' Health Administration, 2013; Glezer, McNiel, & Binder, 2013; Merksamer, 2011).

Guideline 7: Psychologists understand the need to promote social change that reduces the negative effects of stigma on the health and well-being of TGNC people.

Rationale. The lack of public policy that addresses the needs of TGNC people creates significant hardships for them (Taylor, 2007). Although there have been major advances in legal protections for TGNC people in recent years (Buzuvis, 2013; Harvard Law Review Association, 2013), many TGNC people are still not afforded protections from discrimination on the basis of gender identity or expression (National LGBTQ Task Force, 2013; Taylor, 2007). For instance, in many states, TGNC people do not have employment or housing protections and may be fired or lose their housing based on their gender identity. Many policies that protect the rights of cisgender people, including LGB people, do not protect the rights of TGNC people (Currah, & Minter, 2000; Spade, 2011a).

TGNC people can experience challenges obtaining gender-affirming identity documentation (e.g., birth certificate, passport, social security card, driver's license). For TGNC people experiencing poverty or economic hardship, requirements for obtaining this documentation may be impossible to meet, in part due to the difficulty of securing employment without identity documentation that aligns with their gender identity and gender expression (Sheridan, 2009). Additionally, systemic barriers related to binary gender identification systems prevent some TGNC people from changing their documents, including those who are incarcerated, undocumented immigrants, and people who live in jurisdictions that explicitly forbid such changes (Spade, 2006). Documentation requirements can also assume a universal TGNC experience that marginalizes some TGNC people, especially those who do not undergo a medical transition. This may affect a TGNC person's social and psychological well-being and interfere with accessing employment, education, housing and shelter, health care, public benefits, and basic life management resources (e.g., opening a bank account).

Application. Psychologists are encouraged to inform public policy to reduce negative systemic impact on TGNC people and to promote positive social change. Psychologists are encouraged to identify and improve systems that permit violence; educational, employment, and housing discrimination; lack of access to health care; unequal access to other vital resources; and other instances of systemic inequity that TGNC people experience (ACA, 2010). Many TGNC people experience stressors from constant barriers, inequitable treatment, and forced release of sensitive and private information about their bodies and their lives (Hendricks & Testa, 2012). To obtain proper identity documentation, TGNC people may be required to provide court orders, proof of having had surgery, and documentation of psychotherapy or a psychiatric diagnosis. Psychologists may assist TGNC people by normalizing their reactions of fatigue and traumatization while interacting with legal systems and requirements; TGNC people may also benefit from guidance about alternate avenues of recourse, self-advocacy, or appeal. When TGNC people feel that it is unsafe to advocate for themselves, psychologists may work with their clients to access appropriate resources in the community.

Psychologists are encouraged to be sensitive to the challenges of attaining gender-affirming identity documentation and how the receipt or denial of such documentation may affect social and psychological well-being, the person's ability to obtain education and employment, find safe housing, access public benefits, obtain student loans, and access health insurance. It may be of significant assistance for psychologists to understand and offer information about the process of a legal name change, gender marker change on identification, or the process for accessing other gender-affirming documents. Psychologists may consult the National Center for Transgender Equality, the Sylvia Rivera Law Project, or the Transgender Law Center for additional information on identity documentation for TGNC people.

Psychologists may choose to become involved with an organization that seeks to revise law and public policy to better protect the rights and dignities of TGNC people. Psychologists may participate at the local, state, or national level to support TGNC-affirmative health care accessibility, human rights in sex-segregated facilities, or policy change regarding gender-affirming identity documentation. Psychologists working in institutional settings may also expand their roles to work as collaborative advocates for TGNC people (Gonzalez & McNulty, 2010). Psychologists are encouraged to provide written affirmations supporting TGNC people and their gender identity so that they may access necessary services (e.g., hormone therapy).

Life Span Development

Guideline 8. Psychologists working with gender-questioning [4] and TGNC youth understand the different developmental needs of children and adolescents, and that not all youth will persist in a TGNC identity into adulthood.

Rationale. Many children develop stability (constancy across time) in their gender identity between Ages 3 to 4 (Kohlberg, 1966), although gender consistency (recognition that gender remains the same across situations) often does not occur until Ages 4 to 7 (Siegal & Robinson, 1987). Children who demonstrate gender nonconformity in preschool and early elementary years may not follow this trajectory (Zucker & Bradley, 1995). Existing research suggests that between 12% and 50% of children diagnosed with gender dysphoria may persist in their identification with a gender different than sex assigned at birth into late adolescence and young adulthood (Drummond, Bradley,

[4] Gender-questioning youth are differentiated from TGNC youth in this section of the guidelines. Gender-questioning youth may be questioning or exploring their gender identity but have not yet developed a TGNC identity. As such, they may not be eligible for some services that would be offered to TGNC youth. Gender-questioning youth are included here because gender questioning may lead to a TGNC identity.

Peterson-Badaali, & Zucker, 2008; Steensma, McGuire, Kreukels, Beekman, & Cohen-Kettenis, 2013; Wallien & Cohen-Kettenis, 2008). However, several research studies categorized 30% to 62% of youth who did not return to the clinic for medical intervention after initial assessment, and whose gender identity may be unknown, as "desisters" who no longer identified with a gender different than sex assigned at birth (Steensma et al., 2013; Wallien & Cohen-Kettenis, 2008; Zucker, 2008a). As a result, this research runs a strong risk of inflating estimates of the number of youth who do not persist with a TGNC identity. Research has suggested that children who identify more intensely with a gender different than sex assigned at birth are more likely to persist in this gender identification into adolescence (Steensma et al., 2013), and that when gender dysphoria persists through childhood and intensifies into adolescence, the likelihood of long-term TGNC identification increases (A. L. de Vries, Steensma, Doreleijers, & Cohen-Kettenis, 2011; Steensma et al., 2013; Wallien & Cohen-Kettenis, 2008; Zucker, 2008b). Gender-questioning children who do not persist may be more likely to later identify as gay or lesbian than non-gender-questioning children (Bailey & Zucker, 1995; Drescher, 2014; Wallien & Cohen-Kettenis, 2008).

A clear distinction between care of TGNC and gender-questioning children and adolescents exists in the literature. Due to the evidence that not all children persist in a TGNC identity into adolescence or adulthood, and because no approach to working with TGNC children has been adequately, empirically validated, consensus does not exist regarding best practice with prepubertal children. Lack of consensus about the preferred approach to treatment may be due in part to divergent ideas regarding what constitutes optimal treatment outcomes for TGNC and gender-questioning youth (Hembree et al., 2009). Two distinct approaches exist to address gender identity concerns in children (Hill, Menvielle, Sica, & Johnson, 2010; Wallace & Russell, 2013), with some authors subdividing one of the approaches to suggest three (Byne et al., 2012; Drescher, 2014; Stein, 2012).

One approach encourages an affirmation and acceptance of children's expressed gender identity. This may include assisting children to socially transition and to begin medical transition when their bodies have physically developed, or allowing a child's gender identity to unfold without expectation of a specific outcome (A. L. de Vries & Cohen-Kettenis, 2012; Edwards-Leeper & Spack, 2012; Ehrensaft, 2012; Hidalgo et al., 2013; Tishelman et al., 2015). Clinicians using this approach believe that an open exploration and affirmation will assist children to develop coping strategies and emotional tools to integrate a positive TGNC identity should gender questioning persist (Edwards-Leeper & Spack, 2012).

In the second approach, children are encouraged to embrace their given bodies and to align with their assigned gender roles. This includes endorsing and supporting behaviors and attitudes that align with the child's sex assigned at birth prior to the onset of puberty (Zucker, 2008a; Zucker, Wood, Singh, & Bradley, 2012). Clinicians using this approach believe that undergoing multiple medical interventions and living as a TGNC person in a world that stigmatizes gender nonconformity is a less desirable outcome than one in which children may be assisted to happily align with their sex assigned at birth (Zucker et al., 2012). Consensus does not exist regarding whether this approach may provide benefit (Zucker, 2008a; Zucker et al., 2012) or may cause harm or lead to psychosocial adversities (Hill et al., 2010; Pyne, 2014; Travers et al., 2012; Wallace & Russell, 2013). When addressing psychological interventions for children and adolescents, the World Professional Association for Transgender Health Standards of Care identify interventions "aimed at trying to change gender identity and expression to become more congruent with sex assigned at birth" as unethical (Coleman et al., 2012, p. 175). It is hoped that future research will offer improved guidance in this area of practice (Adelson & AACAP CQI, 2012; Malpas, 2011).

Much greater consensus exists regarding practice with adolescents. Adolescents presenting with gender identity concerns bring their own set of unique challenges. This may include having a late-onset (i.e., postpubertal) presentation of gender nonconforming identification, with no history of gender role nonconformity or gender questioning in childhood (Edwards-Leeper & Spack, 2012). Complicating their clinical presentation, many gender-questioning adolescents also present with co-occurring psychological concerns, such as suicidal ideation, self-injurious behaviors (Liu & Mustanski, 2012; Mustanski, Garofalo, & Emerson, 2010), drug and alcohol use (Garofalo et al., 2006), and autism spectrum disorders (A. L. de Vries, Noens, Cohen-Kettenis, van Berckelaer-Onnes, & Doreleijers, 2010; Jones et al., 2012). Additionally, adolescents can become intensely focused on their immediate desires, resulting in outward displays of frustration and resentment when faced with any delay in receiving the medical treatment from which they feel they would benefit and to which they feel entitled (Angello, 2013; Edwards-Leeper & Spack, 2012). This intense focus on immediate needs may create challenges in assuring that adolescents are cognitively and emotionally able to make life-altering decisions to change their name or gender marker, begin hormone therapy (which may affect fertility), or pursue surgery.

Nonetheless, there is greater consensus that treatment approaches for adolescents affirm an adolescents' gender identity (Coleman et al., 2012). Treatment options for adolescents extend beyond social approaches to include medical approaches. One particular medical intervention involves the use of puberty-suppressing medication or "blockers" (GnRH analogue), which is a reversible medical intervention used to delay puberty for appropriately screened adolescents with gender dysphoria (Coleman et al., 2012; A. L. C. de Vries et al., 2014; Edwards-Leeper, & Spack, 2012). Because of their age, other medical interventions may also become available to adolescents, and psychologists are frequently consulted to provide an assessment of whether such procedures would be advisable (Coleman et al., 2012).

Application. Psychologists working with TGNC and gender-questioning youth are encouraged to regularly review the most current literature in this area, recognizing the limited available research regarding the potential benefits and risks of different treatment approaches for children and for adolescents. Psychologists are encouraged to offer parents and guardians clear information about available treatment approaches, regardless of the specific approach chosen by the psychologist. Psychologists are encouraged to provide psychological service to TGNC and gender-questioning children and adolescents that draws from empirically validated literature when available, recognizing the influence psychologists' values and beliefs may have on the treatment approaches they select (Ehrbar & Gorton, 2010). Psychologists are also encouraged to remain aware that what one youth and/or parent may be seeking in a therapeutic relationship may not coincide with a clinician's approach (Brill & Pepper, 2008). In cases in which a youth and/or parent identify different preferred treatment outcomes than a clinician, it may not be clinically appropriate for the clinician to continue working with the youth and family, and alternative options, including referral, might be considered. Psychologists may also find themselves navigating family systems in which youth and their caregivers are seeking different treatment outcomes (Edwards-Leeper & Spack, 2012). Psychologists are encouraged to carefully reflect on their personal values and beliefs about gender identity development in conjunction with the available research, and to keep the best interest of the child or adolescent at the forefront of their clinical decisions at all times.

Because gender nonconformity may be transient for younger children in particular, the psychologist's role may be to help support children and their families through the process of exploration and self-identification (Ehrensaft, 2012). Additionally, psychologists may provide parents with information about possible long-term trajectories children may take in regard to their gender identity, along with the available medical interventions for adolescents whose TGNC identification persists (Edwards-Leeper & Spack, 2012).

When working with adolescents, psychologists are encouraged to recognize that some TGNC adolescents will not have a strong history of childhood gender role nonconformity or gender dysphoria either by self-report or family observation (Edwards-Leeper & Spack, 2012). Some of these adolescents may have withheld their feelings of gender nonconformity out of a fear of rejection, confusion, conflating gender identity and sexual orientation, or a lack of awareness of the option to identify as TGNC. Parents of these adolescents may need additional assistance in understanding and supporting their youth, given that late-onset gender dysphoria and TGNC identification may come as a significant surprise. Moving more slowly and cautiously in these cases is often advisable (Edwards-Leeper & Spack, 2012). Given the possibility of adolescents' intense focus on immediate desires and strong reactions to perceived delays or barriers, psychologists are encouraged to validate these concerns and the desire to move through the process quickly while also remaining thoughtful and deliberate in treatment. Adolescents and their families may need support in tolerating ambiguity and uncertainty with regard to gender identity and its development (Brill & Pepper, 2008). It is encouraged that care should be taken not to foreclose this process.

For adolescents who exhibit a long history of gender nonconformity, psychologists may inform parents that the adolescent's self-affirmed gender identity is most likely stable (A. L. de Vries et al., 2011). The clinical needs of these adolescents may be different than those who are in the initial phases of exploring or questioning their gender identity. Psychologists are encouraged to complete a comprehensive evaluation and ensure the adolescent's and family's readiness to progress while also avoiding unnecessary delay for those who are ready to move forward.

Psychologists working with TGNC and gender-questioning youth are encouraged to become familiar with medical treatment options for adolescents (e.g., puberty-suppressing medication, hormone therapy) and work collaboratively with medical providers to provide appropriate care to clients. Because the ongoing involvement of a knowledgeable mental health provider is encouraged due to the psychosocial implications, and is often also a required part of the medical treatment regimen that may be offered to TGNC adolescents (Coleman et al., 2012; Hembree et al., 2009), psychologists often play an essential role in assisting in this process.

Psychologists may encourage parents and caregivers to involve youth in developmentally appropriate decision making about their education, health care, and peer networks, as these relate to children's and adolescents' gender identity and gender expression (Ryan, Russell, Huebner, Diaz, & Sanchez, 2010). Psychologists are also encouraged to educate themselves about the advantages and disadvantages of social transition during childhood and adolescence, and to discuss these factors with both their young clients and clients' parents. Emphasizing to parents the importance of allowing their child the freedom to return to a gender identity that aligns with sex assigned at birth or another gender identity at any point cannot be overstated, particularly given the research that suggests that not all young gender nonconforming children will ultimately express a gender identity different from that assigned at birth (Wallien, & Cohen-Kettenis, 2008; Zucker & Bradley, 1995). Psychologists are encouraged to acknowledge and explore the fear and burden of responsibility that parents and caregivers may feel as they make decisions about the health of their child or adolescent (Grossman, D'Augelli, Howell, & Hubbard, 2006). Parents and caregivers may benefit from a supportive environment to discuss feelings of isolation, explore loss and grief they may experience, vent anger and frustration at systems that disrespect or discriminate against them and their youth, and learn how to communicate with others about their child's or adolescent's gender identity or gender expression (Brill & Pepper, 2008).

Guideline 9. Psychologists strive to understand both the particular challenges that TGNC elders experience and the resilience they can develop.

Rationale. Little research has been conducted about TGNC elders, leaving much to be discovered about this life stage for TGNC people (Auldridge, Tamar-Mattis, Kennedy, Ames, & Tobin, 2012). Socialization into gender role behaviors and expectations based on sex assigned at birth, as well as the extent to which TGNC people adhere to these societal standards, is influenced by the chronological age at which a person self-identifies as TGNC, the age at which a person comes out or socially and/or medically transitions (Birren & Schaie, 2006; Bockting & Coleman, 2007; Cavanaugh & Blanchard-Fields, 2010; Nuttbrock et al., 2010; Wahl, Iwarsson, & Oswald, 2012), and a person's generational cohort (e.g., 1950 vs. 2010; Fredriksen-Goldsen et al., 2011).

Even decades after a medical or social transition, TGNC elders may still subscribe to the predominant gender role expectations that existed at the time of their transition (Knochel, Croghan, Moore, & Quam, 2011). Prior to the 1980s, TGNC people who transitioned were strongly encouraged by providers to pass in society as cisgender and heterosexual and to avoid associating with other TGNC people (Benjamin, 1966; R. Green & Money, 1969; Hastings, 1974; Hastings & Markland, 1978). Even TGNC elders who were comfortable telling others about their TGNC identity when they were younger may choose not to reveal their identity at a later stage of life (Ekins & King, 2005; Ippolito & Witten, 2014). Elders' unwillingness to disclose their TGNC identity can result from feelings of physical vulnerability or increased reliance on others who may discriminate against them or treat them poorly as a result of their gender identity (Bockting & Coleman, 2007), especially if the elder resides in an institutionalized setting (i.e., nursing home, assisted living facility) and relies on others for many daily needs (Auldridge et al., 2012). TGNC elders are also at a heightened risk for depression, suicidal ideation, and loneliness compared with LGB elders (Auldridge et al., 2012; Fredriksen-Goldsen et al., 2011).

A Transgender Law Center survey found that TGNC and LGB elders had less financial well-being than their younger cohorts, despite having a higher than average educational level for their age group compared with the general population (Hartzell, Frazer, Wertz, & Davis, 2009). Survey research has also revealed that TGNC elders experience underemployment and gaps in employment, often due to discrimination (Auldridge et al., 2012; Beemyn & Rankin, 2011; Factor & Rothblum, 2007). In the past, some TGNC people with established careers may have been encouraged by service providers to find new careers or jobs to avoid undergoing a gender transition at work or being identified as TGNC, potentially leading to a significant loss of income and occupational identity (Cook-Daniels, 2006). Obstacles to employment can increase economic disparities that result in increased needs for supportive housing and other social services (National Center for Transgender Equality, 2012; Services and Advocacy for GLBT Elders & National Center for Transgender Equality, 2012).

TGNC elders may face obstacles to seeking or accessing resources that support their physical, financial, or emotional well-being. For instance, they may be concerned about applying for social security benefits, fearing that their TGNC identity may become known (Hartzell et al., 2009). A TGNC elder may avoid medical care, increasing the likelihood of later needing a higher level of medical care (e.g., home-based care, assisted living, or nursing home) than their same-age cisgender peers (Hartzell et al., 2009; Ippolito & Witten, 2014; Mikalson et al., 2012). Nursing homes and assisted living facilities are rarely sensitive to the unique medical needs of TGNC elders (National Senior Citizens Law Center, 2011). Some TGNC individuals who enter congregate housing, assisted living, or long-term care settings may feel the need to reverse their transition to align with sex assigned at birth to avoid discrimination and persecution by other residents and staff (Ippolito & Witten, 2014).

Older age may both facilitate and complicate medical treatment related to gender transition. TGNC people who begin hormone therapy later in life may have a smoother transition due to waning hormone levels that are a natural part of aging (Witten & Eyler, 2012). Age may also influence the decisions TGNC elders make regarding sex-affirmation surgeries, especially if physical conditions exist that could significantly increase risks associated with surgery or recovery.

Much has been written about the resilience of elders who have endured trauma (Fuhrmann & Shevlowitz, 2006; Hardy, Concato, & Gill, 2004; Mlinac, Sheeran, Blissmer, Lees, & Martins, 2011; Rodin & Stewart, 2012). Although some TGNC elders have experienced significant psychological trauma related to their gender identity, some also have developed resilience and effective ways of coping with adversity (Fruhauf & Orel, 2015). Despite the limited availability of LGBTQ-affirmative religious organizations in many local communities, TGNC elders make greater use of these resources than their cisgender peers (Porter et al., 2013).

Application. Psychologists are encouraged to seek information about the biopsychosocial needs of TGNC elders to inform case conceptualization and treatment planning to address psychological, social, and medical concerns. Many TGNC elders are socially isolated. Isolation can occur as a result of a loss of social networks through death or through disclosure of a TGNC identity. Psychologists may assist TGNC elders in establishing new social networks that support and value their TGNC identity, while also working to strengthen existing family and friend networks after a TGNC identity has been disclosed. TGNC elders may find special value in relationships with others in their generational cohort or those who may have similar coming-out experiences. Psychologists may encourage TGNC elders to identify ways they can mentor and improve the resilience of younger TGNC generations, creating a sense of generativity (Erikson, 1968) and contribu-

tion while building new supportive relationships. Psychologists working with TGNC elders may help them recognize the sources of their resilience and encourage them to connect with and be active in their communities (Fuhrmann & Craffey, 2014).

For TGNC elders who have chosen not to disclose their gender identity, psychologists may provide support to address shame, guilt, or internalized antitrans prejudice, and validate each person's freedom to choose their pattern of disclosure. Clinicians may also provide validation and empathy when TGNC elders have chosen a model of transition that avoids any disclosure of gender identity and is heavily focused on passing as cisgender.

TGNC elders who choose to undergo a medical or social transition in older adulthood may experience antitrans prejudice from people who question the value of transition at an older age or who believe that these elders are not truly invested in their transition or in a TGNC identity given the length of time they have waited (Auldridge et al., 2012). Some TGNC elders may also grieve lost time and missed opportunities. Psychologists may validate elders' choices to come out, transition, or evolve their gender identity or gender expression at any age, recognizing that such choices may have been much less accessible or viable at earlier stages of TGNC elders' lives.

Psychologists may assist congregate housing, assisted living, or long-term care settings to best meet TGNC elders' needs through respectful communication and affirmation of each person's gender identity and gender expression. Psychologists may work with TGNC people in hospice care systems to develop an end-of-life plan that respects the person's wishes about disclosure of gender identity during and after death.

Assessment, Therapy, and Intervention

Guideline 10. Psychologists strive to understand how mental health concerns may or may not be related to a TGNC person's gender identity and the psychological effects of minority stress.

Rationale. TGNC people may seek assistance from psychologists in addressing gender-related concerns, other mental health issues, or both. Mental health problems experienced by a TGNC person may or may not be related to that person's gender identity and/or may complicate assessment and intervention of gender-related concerns. In some cases, there may not be a relationship between a person's gender identity and a co-occurring condition (e.g., depression, PTSD, substance abuse). In other cases, having a TGNC identity may lead or contribute to a co-occurring mental health condition, either directly by way of gender dysphoria, or indirectly by way of minority stress and oppression (Hendricks & Testa, 2012; I. H. Meyer, 1995, 2003). In extremely rare cases, a co-occurring condition can mimic gender dysphoria (i.e., a psychotic process that distorts the perception of one's gender; Baltieri & De Andrade, 2009; Hepp, Kraemer, Schnyder, Miller, & Delsignore, 2004).

Regardless of the presence or absence of an etiological link, gender identity may affect how a TGNC person experiences a co-occurring mental health condition, and/or a co-occurring mental health condition may complicate the person's gender expression or gender identity. For example, an eating disorder may be influenced by a TGNC person's gender expression (e.g., rigid eating patterns used to manage body shape or menstruation may be related to gender identity or gender dysphoria; Ålgars, Alanko, Santtila, & Sandnabba, 2012; Murray, Boon, & Touyz, 2013). In addition, the presence of autism spectrum disorder may complicate a TGNC person's articulation and exploration of gender identity (Jones et al., 2012). In cases in which gender dysphoria is contributing to other mental health concerns, treatment of gender dysphoria may be helpful in alleviating those concerns as well (Keo-Meier et al., 2015).

A relationship also exists between mental health conditions and the psychological sequelae of minority stress that TGNC people can experience. Given that TGNC people experience physical and sexual violence (Clements-Nolle et al., 2006; Kenagy & Bostwick, 2005; Lombardi, Wilchins, Priesing, & Malouf, 2001; Xavier et al., 2005), general harassment and discrimination (Beemyn & Rankin, 2011; Factor & Rothblum, 2007), and employment and housing discrimination (Bradford et al., 2007), they are likely to experience significant levels of minority stress. Studies have demonstrated the disproportionately high levels of negative psychological sequelae related to minority stress, including suicidal ideation and suicide attempts (Center for Substance Abuse Treatment, 2012; Clements-Nolle et al., 2006; Cochran & Cauce, 2006; Nuttbrock et al., 2010; Xavier et al., 2005) and completed suicides (Dhejne et al., 2011; van Kesteren, Asscheman, Megens, & Gooren, 1997). Recent studies have begun to demonstrate an association between sources of external stress and psychological distress (Bockting et al., 2013; Nuttbrock et al., 2010), including suicidal ideation and attempts and self-injurious behavior (dickey, Reisner, & Juntunen, 2015; Goldblum et al., 2012; Testa et al., 2012).

The minority stress model accounts for both the negative mental health effects of stigma-related stress and the processes by which members of the minority group may develop resilience and resistance to the negative effects of stress (I. H. Meyer, 1995, 2003). Although the minority stress model was developed as a theory of the relationship between sexual orientation and mental disorders, the model has been adapted to TGNC populations (Hendricks & Testa, 2012).

Application. Because of the increased risk of stress-related mental health conditions, psychologists are encouraged to conduct a careful diagnostic assessment, including a differential diagnosis, when working with TGNC people (Coleman et al., 2012). Taking into account the intricate interplay between the effects of mental health symptoms and gender identity and gender expression, psychologists are encouraged to neither ignore mental health problems a TGNC person is experiencing, nor erroneously

assume that those mental health problems are a result of the person's gender identity or gender expression. Psychologists are strongly encouraged to be cautious before determining that gender nonconformity or dysphoria is due to an underlying psychotic process, as this type of causal relationship is rare.

When TGNC people seek to access transition-related health care, a psychosocial assessment is often part of this process (Coleman et al., 2012). A comprehensive and balanced assessment typically includes not only information about a person's past experiences of antitrans prejudice or discrimination, internalized messages related to these experiences, and anticipation of future victimization or rejection (Coolhart, Provancher, Hager, & Wang, 2008), but also coping strategies and sources of resilience (Hendricks & Testa, 2012; Singh et al., 2011). Gathering information about negative life events directly related to a TGNC person's gender identity and gender expression may assist psychologists in understanding the sequelae of stress and discrimination, distinguishing them from concurrent and potentially unrelated mental health problems. Similarly, when a TGNC person has a primary presenting concern that is not gender focused, a comprehensive assessment takes into account that person's experience relative to gender identity and gender expression, including any discrimination, just as it would include assessing other potential trauma history, medical concerns, previous experience with helping professionals, important future goals, and important aspects of identity. Strategies a TGNC person uses to navigate antitrans discrimination could be sources of strength to deal with life challenges or sources of distress that increase challenges and barriers.

Psychologists are encouraged to help TGNC people understand the pervasive influence of minority stress and discrimination that may exist in their lives, potentially including internalized negative attitudes about themselves and their TGNC identity (Hendricks & Testa, 2012). With this support, clients can better understand the origins of their mental health symptoms and normalize their reactions when faced with TGNC-related inequities and discrimination. Minority stress models also identify potentially important sources of resilience. TGNC people can develop resilience when they connect with other TGNC people who provide information on how to navigate antitrans prejudice and increase access to necessary care and resources (Singh et al., 2011). TGNC people may need help developing social support systems to nurture their resilience and bolster their ability to cope with the adverse effects of antitrans prejudice and/or discrimination (Singh & McKleroy, 2011).

Feminizing or masculinizing hormone therapy can positively or negatively affect existing mood disorders (Coleman et al., 2012). Psychologists may also help TGNC people who are in the initial stages of hormone therapy adjust to normal changes in how they experience emotions. For example, trans women who begin estrogens and antiandrogens may experience a broader range of emotions than they are accustomed to, or trans men beginning testosterone might be faced with adjusting to a higher libido and feeling more emotionally reactive in stressful situations. These changes can be normalized as similar to the emotional adjustments that cisgender women and men experience during puberty. Some TGNC people will be able to adapt existing coping strategies, whereas others may need help developing additional skills (e.g., emotional regulation or assertiveness). Readers are encouraged to refer to the World Professional Association for Transgender Health Standards of Care for discussion of the possible effects of hormone therapy on a TGNC person's mood, affect, and behavior (Coleman et al., 2012).

Guideline 11. Psychologists recognize that TGNC people are more likely to experience positive life outcomes when they receive social support or trans-affirmative care.

Rationale. Research has primarily shown positive treatment outcomes when TGNC adults and adolescents receive TGNC-affirmative medical and psychological services (i.e., psychotherapy, hormones, surgery; Byne et al., 2012; R. Carroll, 1999; Cohen-Kettenis, Delemarre-van de Waal, & Gooren, 2008; Davis & Meier, 2014; De Cuypere et al., 2006; Gooren, Giltay, & Bunck, 2008; Kuhn et al., 2009), although sample sizes are frequently small with no population-based studies. In a meta-analysis of the hormone therapy treatment literature with TGNC adults and adolescents, researchers reported that 80% of participants receiving trans-affirmative care experienced an improved quality of life, decreased gender dysphoria, and a reduction in negative psychological symptoms (Murad et al., 2010).

In addition, TGNC people who receive social support about their gender identity and gender expression have improved outcomes and quality of life (Brill & Pepper, 2008; Pinto, Melendez, & Spector, 2008). Several studies indicate that family acceptance of TGNC adolescents and adults is associated with decreased rates of negative outcomes, such as depression, suicide, and HIV risk behaviors and infection (Bockting et al., 2013; Dhejne et al., 2011; Grant et al., 2011; Liu & Mustanski, 2012; Ryan, 2009). Family support is also a strong protective factor for TGNC adults and adolescents (Bockting et al., 2013; Moody & Smith, 2013; Ryan et al., 2010). TGNC people, however, frequently experience blatant or subtle antitrans prejudice, discrimination, and even violence within their families (Bradford et al., 2007). Such family rejection is associated with higher rates of HIV infection, suicide, incarceration, and homelessness for TGNC adults and adolescents (Grant et al., 2011; Liu & Mustanski, 2012). Family rejection and lower levels of social support are significantly correlated with depression (Clements-Nolle et al., 2006; Ryan, 2009). Many TGNC people seek support through peer relationships, chosen families, and communities in which they may be more likely to experience acceptance (Gonzalez & McNulty, 2010; Nuttbrock et al., 2009). Peer support from other TGNC people has been found to be a moderator between antitrans discrimination and mental health, with higher levels of peer support associated with better mental health (Bockting et al., 2013). For some TGNC people, support from religious and spiritual communities provides

an important source of resilience (Glaser, 2008; Kidd & Witten, 2008; Porter et al., 2013).

Application. Given the strong evidence for the positive influence of affirmative care, psychologists are encouraged to facilitate access to and provide trans-affirmative care to TGNC people. Whether through the provision of assessment and psychotherapy, or through assisting clients to access hormone therapy or surgery, psychologists may play a critical role in empowering and validating TGNC adults' and adolescents' experiences and increasing TGNC people's positive life outcomes (Bess & Stabb, 2009; Rachlin, 2002).

Psychologists are also encouraged to be aware of the importance of affirmative social support and assist TGNC adults and adolescents in building social support networks in which their gender identity is accepted and affirmed. Psychologists may assist TGNC people in negotiating family dynamics that may arise in the course of exploring and establishing gender identity. Depending on the context of psychological practice, these issues might be addressed in individual work with TGNC clients, conjoint sessions including members of their support system, family therapy, or group therapy. Psychologists may help TGNC people decide how and when to reveal their gender identity at work or school, in religious communities, and to friends and contacts in other settings. TGNC people who decide not to come out in all aspects of their lives can still benefit from TGNC-affirmative in-person or online peer support groups.

Clients may ask psychologists to assist family members in exploring feelings about their loved one's gender identity and gender expression. Published models of family adjustment (Emerson & Rosenfeld, 1996) may be useful to help normalize family members' reactions upon learning that they have a TGNC family member, and to reduce feelings of isolation. When working with family members or significant others, it may be helpful to normalize feelings of loss or fear of what may happen to current relationships as TGNC people disclose their gender identity and expression to others. Psychologists may help significant others adjust to changing relationships and consider how to talk to extended family, friends, and other community members about TGNC loved ones. Providing significant others with referrals to TGNC-affirmative providers, educational resources, and support groups can have a profound impact on their understanding of gender identity and their communication with TGNC loved ones. Psychologists working with couples and families may also help TGNC people identify ways to include significant others in their social or medical transition.

Psychologists working with TGNC people in rural settings may provide clients with resources to connect with other TGNC people online or provide information about in-person support groups in which they can explore the unique challenges of being TGNC in these geographic areas (Walinsky & Whitcomb, 2010). Psychologists serving TGNC military and veteran populations are encouraged to be sensitive to the barriers these individuals face, especially for people who are on active duty in the U.S. military (OutServe-Servicemembers Legal Defense Network, n.d.). Psychologists may help TGNC military members and veterans establish specific systems of support that create a safe and affirming space to reduce isolation and to create a network of peers with a shared military experience. Psychologists who work with veterans are encouraged to educate themselves on recent changes to VA policy that support equal access to VA medical and mental health services (Department of Veterans Affairs, Veterans' Health Administration, 2013).

Guideline 12. Psychologists strive to understand the effects that changes in gender identity and gender expression have on the romantic and sexual relationships of TGNC people.

Rationale. Relationships involving TGNC people can be healthy and successful (Kins, Hoebeke, Heylens, Rubens, & De Cuyprere, 2008; Meier, Sharp, Michonski, Babcock, & Fitzgerald, 2013) as well as challenging (Brown, 2007; Iantaffi & Bockting, 2011). A study of successful relationships between TGNC men and cisgender women found that these couples attributed the success of their relationship to respect, honesty, trust, love, understanding, and open communication (Kins et al., 2008). Just as relationships between cisgender people can involve abuse, so can relationships between TGNC people and their partners (Brown, 2007), with some violent partners threatening to disclose a TGNC person's identity to exact control in the relationship (FORGE, n.d.).

In the early decades of medical and social transition for TGNC people, only those whose sexual orientations would be heterosexual posttransition (e.g., trans woman with a cisgender man) were deemed eligible for medical and social transition (Meyerowitz, 2002). This restriction prescribed only certain relationship partners (American Psychiatric Association, 1980; Benjamin, 1966; Chivers & Bailey, 2000), denied access to surgery for trans men identifying as gay or bisexual (Coleman & Bockting, 1988), or trans women identifying as lesbian or bisexual, and even required that TGNC people's existing legal marriages be dissolved before they could gain access to transition care (Lev, 2004).

Disclosure of a TGNC identity can have an important impact on the relationship between TGNC people and their partners. Disclosure of TGNC status earlier in the relationship tends to be associated with better relationship outcomes, whereas disclosure of TGNC status many years into an existing relationship may be perceived as a betrayal (Erhardt, 2007). When a TGNC person comes out in the context of an existing relationship, it can also be helpful if both partners are involved in decision making about the use of shared resources (i.e., how to balance the financial costs of transition with other family needs) and how to share this news with shared supports (i.e., friends and family). Sometimes relationship roles are renegotiated in the context of a TGNC person coming out to their partner (Samons, 2008). Assumptions about what it means to be a "husband" or a "wife" can shift if the gender identity of one's spouse shifts

(Erhardt, 2007). Depending on when gender issues are disclosed and how much of a change this creates in the relationship, partners may grieve the loss of aspects of their partner and the way the relationship used to be (Lev, 2004).

Although increasing alignment between gender identity and gender expression, whether it be through dress, behavior, or through medical interventions (i.e., hormones, surgery), does not necessarily affect to whom a TGNC person is attracted (Coleman et al., 1993), TGNC people may become more open to exploring their sexual orientation, may redefine sexual orientation as they move through transition, or both (Daskalos, 1998; H. Devor, 1993; Schleifer, 2006). Through increased comfort with their body and gender identity, TGNC people may explore aspects of their sexual orientation that were previously hidden or that felt discordant with their sex assigned at birth. Following a medical and/or social transition, a TGNC person's sexual orientation may remain constant or shift, either temporarily or permanently (e.g., renewed exploration of sexual orientation in the context of TGNC identity, shift in attraction or choice of sexual partners, widened spectrum of attraction, shift in sexual orientation identity; Meier, Sharp et al., 2013; Samons, 2008). For example, a trans man previously identified as a lesbian may later be attracted to men (Coleman et al., 1993; dickey, Burnes, & Singh, 2012), and a trans woman attracted to women pretransition may remain attracted to women posttransition (Lev, 2004).

Some TGNC people and their partners may fear the loss of mutual sexual attraction and other potential effects of shifting gender identities in the relationship. Lesbian-identified partners of trans men may struggle with the idea that being in a relationship with a man may cause others to perceive them as a heterosexual couple (Califia, 1997). Similarly, women in heterosexual relationships who later learn that their partners are trans women may be unfamiliar with navigating stigma associated with sexual minority status when viewed as a lesbian couple (Erhardt, 2007). Additionally, partners may find they are not attracted to a partner after transition. As an example, a lesbian whose partner transitions to a male identity may find that she is no longer attracted to this person because she is not sexually attracted to men. Partners of TGNC people may also experience grief and loss as their partners engage in social and/or medical transitions.

Application. Psychologists may help foster resilience in relationships by addressing issues specific to partners of TGNC people. Psychologists may provide support to partners of TGNC people who are having difficulty with their partner's evolving gender identity or transition, or are experiencing others having difficulty with the partner's transition. Partner peer support groups may be especially helpful in navigating internalized antitrans prejudice, shame, resentment, and relationship concerns related to a partner's gender transition. Meeting or knowing other TGNC people, other partners of TGNC people, and couples who have successfully navigated transition may also help TGNC people and their partners and serve as a protective factor (Brown, 2007). When TGNC status is disclosed during an existing relationship, psychologists may help couples explore which relationship dynamics they want to preserve and which they might like to change.

In working with psychologists, TGNC people may explore a range of issues in their relationships and sexuality (dickey et al., 2012), including when and how to come out to current or potential romantic and sexual partners, communicating their sexual desires, renegotiating intimacy that may be lost during the TGNC partner's transition, adapting to bodily changes caused by hormone use or surgery, and exploring boundaries regarding touch, affection, and safer sex practices (Iantaffi & Bockting, 2011; Sevelius, 2009). TGNC people may experience increased sexual self-efficacy through transition. Although psychologists may aid partners in understanding a TGNC person's transition decisions, TGNC people may also benefit from help in cultivating awareness of the ways in which these decisions influence the lives of loved ones.

Guideline 13. Psychologists seek to understand how parenting and family formation among TGNC people take a variety of forms.

Rationale. Psychologists work with TGNC people across the life span to address parenting and family issues (Kenagy & Hsieh, 2005). There is evidence that many TGNC people have and want children (Wierckx et al., 2012). Some TGNC people conceive a child through sexual intercourse, whereas others may foster, adopt, pursue surrogacy, or employ assisted reproductive technologies, such as sperm or egg donation, to build or expand a family (De Sutter, Kira, Verschoor, & Hotimsky, 2002). Based on a small body of research to date, there is no indication that children of TGNC parents suffer long-term negative impacts directly related to parental gender change (R. Green, 1978, 1988; White & Ettner, 2004). TGNC people may find it both challenging to find medical providers who are willing to offer them reproductive treatment and to afford the cost (Coleman et al., 2012). Similarly, adoption can be quite costly, and some TGNC people may find it challenging to find foster care or adoption agencies that will work with them in a nondiscriminatory manner. Current or past use of hormone therapy may limit fertility and restrict a TGNC person's reproductive options (Darnery, 2008; Wierckx et al., 2012). Other TGNC people may have children or families before coming out as TGNC or beginning a gender transition.

TGNC people may present with a range of parenting and family-building concerns. Some will seek support to address issues within preexisting family systems, some will explore the creation or expansion of a family, and some will need to make decisions regarding potential fertility issues related to hormone therapy, pubertal suppression, or surgical transition. The medical and/or social transition of a TGNC parent may shift family dynamics, creating challenges and opportunities for partners, children, and other family members. One study of therapists' reflections on their experiences with TGNC clients suggested that family constellation and the parental relationship was more significant for children than the parent's social and/or medical

transition itself (White & Ettner, 2004). Although research has not documented that the transitions of TGNC people have an effect on their parenting abilities, preexisting partnerships or marriages may not survive the disclosure of a TGNC identity or a subsequent transition (dickey et al., 2012). This may result in divorce or separation, which may affect the children in the family. A positive relationship between parents, regardless of marital status, has been suggested to be an important protective factor for children (Amato, 2001; White & Ettner, 2007). This seems to be the case especially when children are reminded of the parent's love and assured of the parent's continued presence in their life (White & Ettner, 2007). Based on a small body of literature available, it is generally the case that younger children are best able to incorporate the transition of a parent, followed by adult children, with adolescents generally having the most difficulty (White & Ettner, 2007). If separated or divorced from their partners or spouses, TGNC parents may be at risk for loss of custody or visitation rights because some courts presume that there is a nexus between their gender identity or gender expression and parental fitness (Flynn, 2006). This type of prejudice is especially common for TGNC people of color (Grant et al., 2011).

Application. Psychologists are encouraged to attend to the parenting and family-building concerns of TGNC people. When working with TGNC people who have previous parenting experience, psychologists may help TGNC people identify how being a parent may influence decisions to come out as TGNC or to begin a transition (Freeman, Tasker, & Di Ceglie, 2002; Grant et al., 2011; Wierckx et al., 2012). Some TGNC people may choose to delay disclosure until their children have grown and left home (Bethea & McCollum, 2013). Clinical guidelines jointly developed by a Vancouver, British Columbia, TGNC community organization and a health care provider organization encourage psychologists and other mental health providers working with TGNC people to plan for disclosure to a partner, previous partner, or children, and to pay particular attention to resources that assist TGNC people to discuss their identity with children of various ages in developmentally appropriate ways (Bockting et al., 2006). Lev (2004) uses a developmental stage framework for the process that family members are likely to go through in coming to terms with a TGNC family member's identity that some psychologists may find helpful. Awareness of peer support networks for spouses and children of TGNC people can also be helpful (e.g., PFLAG, TransYouth Family Allies). Psychologists may provide family counseling to assist a family in managing disclosure, improve family functioning, and maintain family involvement of the TGNC person, as well as aiding the TGNC person in attending to the ways that their transition process has affected their family members (Samons, 2008). Helping parents to continue to work together to focus on the needs of their children and to maintain family bonds is likely to lead to the best results for the children (White & Ettner, 2007).

For TGNC people with existing families, psychologists may support TGNC people in seeking legal counsel regarding parental rights in adoption or custody. Depending on the situation, this may be desirable even if the TGNC parent is biologically related to the child (Minter & Wald, 2012). Although being TGNC is not a legal impediment to adoption in the United States, there is the potential for overt and covert discrimination and barriers, given the widespread prejudice against TGNC people. The question of whether to disclose TGNC status on an adoption application is a personal one, and a prospective TGNC parent would benefit from consulting a lawyer for legal advice, including what the laws in their jurisdiction say about disclosure. Given the extensive background investigation frequently conducted, it may be difficult to avoid disclosure. Many lawyers favor disclosure to avoid any potential legal challenges during the adoption process (Minter & Wald, 2012).

In discussing family-building options with TGNC people, psychologists are encouraged to remain aware that some of these options require medical intervention and are not available everywhere, in addition to being quite costly (Coleman et al., 2012). Psychologists may work with clients to manage feelings of loss, grief, anger, and resentment that may arise if TGNC people are unable to access or afford the services they need for building a family (Bockting et al., 2006; De Sutter et al., 2002).

When TGNC people consider beginning hormone therapy, psychologists may engage them in a conversation about the possibly permanent effects on fertility to better prepare TGNC people to make a fully informed decision. This may be of special importance with TGNC adolescents and young adults who often feel that family planning or loss of fertility is not a significant concern in their current daily lives, and therefore disregard the long-term reproductive implications of hormone therapy or surgery (Coleman et al., 2012). Psychologists are encouraged to discuss contraception and safer sex practices with TGNC people, given that they may still have the ability to conceive even when undergoing hormone therapy (Bockting, Robinson, & Rosser, 1998). Psychologists may play a critical role in educating TGNC adolescents and young adults and their parents about the long-term effects of medical interventions on fertility and assist them in offering informed consent prior to pursuing such interventions. Although hormone therapy may limit fertility (Coleman et al., 2012), psychologists may encourage TGNC people to refrain from relying on hormone therapy as the sole means of birth control, even when a person has amenorrhea (Gorton & Grubb, 2014). Education on safer sex practices may also be important, as some segments of the TGNC community (e.g., trans women and people of color) are especially vulnerable to sexually transmitted infections and have been shown to have high prevalence and incidence rates of HIV infection (Kellogg, Clements-Nolle, Dilley, Katz, & McFarland, 2001; Nemoto, Operario, Keatley, Han, & Soma, 2004).

Depending on the timing and type of options selected, psychologists may explore the physical, social, and emotional implications should TGNC people choose to delay or

stop hormone therapy, undergo fertility treatment, or become pregnant. Psychological effects of stopping hormone therapy may include depression, mood swings, and reactions to the loss of physical masculinization or feminization facilitated by hormone therapy (Coleman et al., 2012). TGNC people who choose to halt hormone therapy during attempts to conceive or during a pregnancy may need additional psychological support. For example, TGNC people and their families may need help in managing the additional antitrans prejudice and scrutiny that may result when a TGNC person with stereotypically masculine features becomes visibly pregnant. Psychologists may also assist TGNC people in addressing their loss when they cannot engage in reproductive activities that are consistent with their gender identity, or when they encounter barriers to conceiving, adopting, or fostering children not typically faced by other people (Vanderburgh, 2007). Psychologists are encouraged to assess the degree to which reproductive health services are TGNC-affirmative prior to referring TGNC people to them. Psychologists are also encouraged to provide TGNC-affirmative information to reproductive health service personnel when there is a lack of trans-affirmative knowledge.

Guideline 14. Psychologists recognize the potential benefits of an interdisciplinary approach when providing care to TGNC people and strive to work collaboratively with other providers.

Rationale. Collaboration across disciplines can be crucial when working with TGNC people because of the potential interplay of biological, psychological, and social factors in diagnosis and treatment (Hendricks & Testa, 2012). The challenges of living with a stigmatized identity and the need of many TGNC people to transition, socially and/or medically, may call for the involvement of health professionals from various disciplines, including psychologists, psychiatrists, social workers, primary health care providers, endocrinologists, nurses, pharmacists, surgeons, gynecologists, urologists, electrologists, speech therapists, physical therapists, pastoral counselors and chaplains, and career or educational counselors. Communication, cooperation, and collaboration will ensure optimal coordination and quality of care. Just as psychologists often refer TGNC people to medical providers for assessment and treatment of medical issues, medical providers may rely on psychologists to assess readiness and assist TGNC clients to prepare for the psychological and social aspects of transition before, during, and after medical interventions (Coleman et al., 2012; Hembree et al., 2009; Lev, 2009). Outcome research to date supports the value and effectiveness of an interdisciplinary, collaborative approach to TGNC-specific care (see Coleman et al., 2012 for a review).

Application. Psychologists' collaboration with colleagues in medical and associated health disciplines involved in TGNC clients' care (e.g., hormonal and surgical treatment, primary health care; Coleman et al., 2012; Lev, 2009) may take many forms and should occur in a timely manner that does not complicate access to needed services (e.g., considerations of wait time). For example, a psychologist working with a trans man who has a diagnosis of bipolar disorder may need to coordinate with his primary care provider and psychiatrist to adjust his hormone levels and psychiatric medications, given that testosterone can have an activating effect, in addition to treating gender dysphoria. At a basic level, collaboration may entail the creation of required documentation that TGNC people present to surgeons or medical providers to access gender-affirming medical interventions (e.g., surgery, hormone therapy; Coleman et al., 2012). Psychologists may offer support, information, and education to interdisciplinary colleagues who are unfamiliar with issues of gender identity and gender expression to assist TGNC people in obtaining TGNC-affirmative care (Holman & Goldberg, 2006; Lev, 2009). For example, a psychologist who is assisting a trans woman with obtaining gender-affirming surgery may, with her consent, contact her new gynecologist in preparation for her first medical visit. This contact could include sharing general information about her gender history and discussing how both providers could most affirmatively support appropriate health checks to ensure her best physical health (Holman & Goldberg, 2006).

Psychologists in interdisciplinary settings could also collaborate with medical professionals prescribing hormone therapy by educating TGNC people and ensuring TGNC people are able to make fully informed decisions prior to starting hormone treatment (Coleman et al., 2012; Deutsch, 2012; Lev, 2009). Psychologists working with children and adolescents play a particularly important role on the interdisciplinary team due to considerations of cognitive and social development, family dynamics, and degree of parental support. This role is especially crucial when providing psychological evaluation to determine the appropriateness and timeliness of a medical intervention. When psychologists are not part of an interdisciplinary setting, especially in isolated or rural communities, they can identify interdisciplinary colleagues with whom they may collaborate and/or refer (Walinsky & Whitcomb, 2010). For example, a rural psychologist could identify a trans-affirmative pediatrician in a surrounding area and collaborate with the pediatrician to work with parents raising concerns about their TGNC and questioning children and adolescents.

In addition to working collaboratively with other providers, psychologists who obtain additional training to specialize in work with TGNC people may also serve as consultants in the field (e.g., providing additional support to providers working with TGNC people or assisting school and workplaces with diversity training). Psychologists who have expertise in working with TGNC people may play a consultative role with providers in inpatient settings seeking to provide affirmative care to TGNC clients. Psychologists may also collaborate with social service colleagues to provide TGNC people with affirmative referrals related to housing, financial support, vocational/educational counseling and training, TGNC-affirming religious or spiritual communities, peer support, and other community resources (Gehi & Arkles, 2007). This collaboration might also in-

clude assuring that TGNC people who are minors in the care of the state have access to culturally appropriate care.

Research, Education, and Training

Guideline 15. Psychologists respect the welfare and rights of TGNC participants in research and strive to represent results accurately and avoid misuse or misrepresentation of findings.

Rationale. Historically, in a set of demographic questions, psychological research has included one item on either sex or gender, with two response options—male and female. This approach wastes an opportunity to increase knowledge about TGNC people for whom neither option may fit their identity, and runs the risk of alienating TGNC research participants (IOM, 2011). For example, there is little knowledge about HIV prevalence, risks, and prevention needs of TGNC people because most of the research on HIV has not included demographic questions to identify TGNC participants within their samples. Instead, TGNC people have been historically subsumed within larger demographic categories (e.g., men who have sex with men, women of color), rendering the impact of the HIV epidemic on the TGNC population invisible (Herbst et al., 2008). Scholars have noted that this invisibility fails to draw attention to the needs of TGNC populations that experience the greatest health disparities, including TGNC people who are of color, immigrants, low income, homeless, veterans, incarcerated, live in rural areas, or have disabilities (Bauer et al., 2009; Hanssmann, Morrison, Russian, Shiu-Thornton, & Bowen, 2010; Shipherd et al., 2012; Walinsky & Whitcomb, 2010).

There is a great need for more research to inform practice, including affirmative treatment approaches with TGNC people. Although sufficient evidence exists to support current standards of care (Byne et al., 2012; Coleman et al., 2012), much is yet to be learned to optimize quality of care and outcome for TGNC clients, especially as it relates to the treatment of children (IOM, 2011; Mikalson et al., 2012). In addition, some research with TGNC populations has been misused and misinterpreted, negatively affecting TGNC people's access to health services to address issues of gender identity and gender expression (Namaste, 2000). This has resulted in justifiable skepticism and suspicion in the TGNC community when invited to participate in research initiatives. In accordance with the APA ethics code (APA, 2010), psychologists conduct research and distribute research findings with integrity and respect for their research participants. As TGNC research increases, some TGNC communities may experience being oversampled in particular geographic areas and/or TGNC people of color may not be well-represented in TGNC studies (Hwahng & Lin, 2009; Namaste, 2000).

Application. All psychologists conducting research, even when not specific to TGNC populations, are encouraged to provide a range of options for capturing demographic information about TGNC people so that TGNC people may be included and accurately represented (Conron et al., 2008; Deutsch et al., 2013). One group of experts has recommended that population research, and especially government-sponsored surveillance research, use a two-step method, first asking for sex assigned at birth, and then following with a question about gender identity (GenIUSS, 2013). For research focused on TGNC people, including questions that assess both sex assigned at birth and current gender identity allows the disaggregation of subgroups within the TGNC population and has the potential to increase knowledge of differences within the population. In addition, findings about one subgroup of TGNC people may not apply to other subgroups. For example, results from a study of trans women of color with a history of sex work who live in urban areas (Nemoto, Operario, Keatley, & Villegas, 2004) may not generalize to all TGNC women of color or to the larger TGNC population (Bauer, Travers, Scanlon, & Coleman, 2012; Operario et al., 2008).

In conducting research with TGNC people, psychologists will confront the challenges associated with studying a relatively small, geographically dispersed, diverse, stigmatized, hidden, and hard-to-reach population (IOM, 2011). Because TGNC individuals are often hard to reach (IOM, 2011) and TGNC research is rapidly evolving, it is important to consider the strengths and limitations of the methods that have been or may be used to study the TGNC population, and to interpret and represent findings accordingly. Some researchers have strongly recommended collaborative research models (e.g., participatory action research) in which TGNC community members are integrally involved in these research activities (Clements-Nolle & Bachrach, 2003; Singh, Richmond, & Burnes, 2013). Psychologists who seek to educate the public by communicating research findings in the popular media will also confront challenges, because most journalists have limited knowledge about the scientific method and there is potential for the media to misinterpret, exploit, or sensationalize findings (Garber, 1992; Namaste, 2000).

Guideline 16. Psychologists Seek to Prepare Trainees in Psychology to Work Competently With TGNC People.

Rationale. The *Ethical Principles of Psychologists and Code of Conduct* (APA, 2010) include gender identity as one factor for which psychologists may need to obtain training, experience, consultation, or supervision in order to ensure their competence (APA, 2010). In addition, when APA-accredited programs are required to demonstrate a commitment to cultural and individual diversity, gender identity is specifically included (APA, 2015). Yet surveys of TGNC people suggest that many mental health care providers lack even basic knowledge and skills required to offer trans-affirmative care (Bradford et al., 2007; O'Hara, Dispenza, Brack, & Blood, 2013; Xavier et al., 2005). The APA Task Force on Gender Identity and Gender Variance (2009) projected that many, if not most, psychologists and graduate psychology students will at some point encounter TGNC people among their clients, colleagues, and trainees. Yet professional education and training in psychology includes little or no preparation for

working with TGNC people (Anton, 2009; APA TFGIGV, 2009), and continuing professional education available to practicing mental health clinicians is also scant (Lurie, 2005). Only 52% percent of psychologists and graduate students who responded to a survey conducted by an APA Task Force reported having had the opportunity to learn about TGNC issues in school; of those respondents, only 27% reported feeling adequately familiar with gender concerns (n = 294; APA TFGIGV, 2009).

Training on gender identity in professional psychology has frequently been subsumed under discussions of sexual orientation or in classes on human sexuality. Some scholars have suggested that psychologists and students may mistakenly believe that they have obtained adequate knowledge and awareness about TGNC people through training focused on LGB populations (Harper & Schneider, 2003). However, Israel and colleagues have found important differences between the therapeutic needs of TGNC people and those of LGB people in the perceptions of both clients and providers (Israel et al., 2008; Israel, Walther, Gorcheva, & Perry, 2011). Nadal and colleagues have suggested that the absence of distinct, accurate information about TGNC populations in psychology training not only perpetuates misunderstanding and marginalization of TGNC people by psychologists but also contributes to continued marginalization of TGNC people in society as a whole (Nadal et al., 2010, 2012).

Application. Psychologists strive to continue their education on issues of gender identity and gender expression with TGNC people as a foundational component of affirmative psychological practice. In addition to these guidelines, which educators may use as a resource in developing curricula and training experiences, ACA (2010) has also adopted a set of competencies that may be a helpful resource for educators. In addition to including TGNC people and their issues in foundational education in health service psychology (e.g., personality development, multiculturalism, research methods), some psychology programs may also provide coursework and training for students interested in developing more advanced expertise on issues of gender identity and gender expression.

Because of the high level of societal ignorance and stigma associated with TGNC people, ensuring that psychological education, training, and supervision is affirmative, and does not sensationalize (Namaste, 2000), exploit, or pathologize TGNC people (Lev, 2004), will require care on the part of educators. Students will benefit from support from their educators in developing a professional, nonjudgmental attitude toward people who may have a different experience of gender identity and gender expression from their own. A number of training resources have been published that may be helpful to psychologists in integrating information about TGNC people into the training they offer (e.g., Catalano, McCarthy, & Shlasko, 2007; Stryker, 2008; Wentling, Schilt, Windsor, & Lucal, 2008). Because most psychologists have had little or no training on TGNC populations and do not perceive themselves as having sufficient understanding of issues related to gender identity and gender expression (APA TFGIGV, 2009), psychologists with relevant expertise are encouraged to develop and distribute continuing education and training to help to address these gaps. Psychologists providing education can incorporate activities that increase awareness of cisgender privilege, antitrans prejudice and discrimination, host a panel of TGNC people to offer personal perspectives, or include narratives of TGNC people in course readings (ACA, 2010). When engaging these approaches, it is important to include a wide variety of TGNC experiences to reflect the inherent diversity within the TGNC community.

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Appendix A
Definitions

Terminology within the health care field and transgender and gender nonconforming (TGNC) communities is constantly evolving (Coleman et al., 2012). The evolution of terminology has been especially rapid in the last decade, as the profession's awareness of gender diversity has increased, as more literature and research in this area has been published, and as voices of the TGNC community have strengthened. Some terms or definitions are not universally accepted, and there is some disagreement among professionals and communities as to the "correct" words or definitions, depending on theoretical orientation, geographic region, generation, or culture, with some terms seen as affirming and others as outdated or demeaning. American Psychological Association (APA) Task Force for *Guidelines for Psychological Practice with Transgender and Gender Nonconforming People* developed the definitions below by reviewing existing definitions put forward by professional organizations (e.g., APA Task Force on Gender Identity and Gender Variance, 2009; the Institute of Medicine, 2011; and the World Professional Association for Transgender Health [Coleman et al., 2012]), health care agencies serving TGNC clients (e.g., Fenway Health Center), TGNC community resources (Gender Equity Resource Center, National Center for Transgender Equality), and professional literature. Psychologists are encouraged to refresh their knowledge and familiarity with evolving terminology on a regular basis as changes emerge in the community and/or the professional literature. The definitions below include terms frequently used within the *Guidelines*, by the TGNC community, and within professional literature.

Ally: a cisgender person who supports and advocates for TGNC people and/or communities.

(*Appendices continue*)

Antitrans prejudice (transprejudice, transnegativity, transphobia): prejudicial attitudes that may result in the devaluing, dislike, and hatred of people whose gender identity and/or gender expression do not conform to their sex assigned at birth. Antitrans prejudice may lead to discriminatory behaviors in such areas as employment and public accommodations, and may lead to harassment and violence. When TGNC people hold these negative attitudes about themselves and their gender identity, it is called *internalized transphobia* (a construct analogous to internalized homophobia). Transmisogyny describes a simultaneous experience of sexism and antitrans prejudice with particularly adverse effects on trans women.

Cisgender: an adjective used to describe a person whose gender identity and gender expression align with sex assigned at birth; a person who is not TGNC.

Cisgenderism: a systemic bias based on the ideology that gender expression and gender identities are determined by sex assigned at birth rather than self-identified gender identity. Cisgenderism may lead to prejudicial attitudes and discriminatory behaviors toward TGNC people or to forms of behavior or gender expression that lie outside of the traditional gender binary.

Coming out: a process by which individuals affirm and actualize a stigmatized identity. Coming out as TGNC can include disclosing a gender identity or gender history that does not align with sex assigned at birth or current gender expression. Coming out is an individual process and is partially influenced by one's age and other generational influences.

Cross dressing: wearing clothing, accessories, and/or make-up, and/or adopting a gender expression not associated with a person's assigned sex at birth according to cultural and environmental standards (Bullough & Bullough, 1993). Cross-dressing is not always reflective of gender identity or sexual orientation. People who cross-dress may or may not identify with the larger TGNC community.

Disorders of sex development (DSD, Intersex): term used to describe a variety of medical conditions associated with atypical development of an individual's physical sex characteristics (Hughes, Houk, Ahmed, & Lee, 2006). These conditions may involve differences of a person's internal and/or external reproductive organs, sex chromosomes, and/or sex-related hormones that may complicate sex assignment at birth. DSD conditions may be considered variations in biological diversity rather than disorders (M. Diamond, 2009); therefore some prefer the terms *intersex*, *intersexuality*, or *differences in sex development* rather than "disorders of sex development" (Coleman et al., 2012).

Drag: the act of adopting a gender expression, often as part of a performance. Drag may be enacted as a political comment on gender, as parody, or as entertainment, and is not necessarily reflective of gender identity.

Female-to-male (FTM): individuals assigned a female sex at birth who have changed, are changing, or wish to change their body and/or gender identity to a more masculine body or gender identity. FTM persons are also often referred to as *transgender men*, *transmen*, or *trans men*.

Gatekeeping: the role of psychologists and other mental health professionals of evaluating a TGNC person's eligibility and readiness for hormone therapy or surgery according to the Standards of Care set forth by the World Professional Association for Transgender Health (Coleman et al., 2012). In the past, this role has been perceived as limiting a TGNC adult's autonomy and contributing to mistrust between psychologists and TGNC clients. Current approaches are sensitive to this history and are more affirming of a TGNC adult's autonomy in making decisions with regard to medical transition (American Counseling Association, 2010; Coleman et al., 2012; Singh & Burnes, 2010).

Gender-affirming surgery (sex reassignment surgery or gender reassignment surgery): surgery to change primary and/or secondary sex characteristics to better align a person's physical appearance with their gender identity. Gender-affirming surgery can be an important part of medically necessary treatment to alleviate gender dysphoria and may include mastectomy, hysterectomy, metoidioplasty, phalloplasty, breast augmentation, orchiectomy, vaginoplasty, facial feminization surgery, and/or other surgical procedures.

Gender binary: the classification of gender into two discrete categories of boy/man and girl/woman.

Gender dysphoria: discomfort or distress related to incongruence between a person's gender identity, sex assigned at birth, gender identity, and/or primary and secondary sex characteristics (Knudson, De Cuypere, & Bockting, 2010). In 2013, the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM–5*; American Psychiatric Association, 2013) adopted the term *gender dysphoria* as a diagnosis characterized by "a marked incongruence between" a person's gender assigned at birth and gender identity (American Psychiatric Association, 2013, p. 453). Gender dysphoria replaced the diagnosis of gender identity disorder (GID) in the previous version of the *DSM* (American Psychiatric Association, 2000).

Gender expression: the presentation of an individual, including physical appearance, clothing choice and accessories, and behaviors that express aspects of gender identity or role. Gender expression may or may not conform to a person's gender identity.

(*Appendices continue*)

Gender identity: a person's deeply felt, inherent sense of being a boy, a man, or male; a girl, a woman, or female; or an alternative gender (e.g., genderqueer, gender nonconforming, gender neutral) that may or may not correspond to a person's sex assigned at birth or to a person's primary or secondary sex characteristics. Because gender identity is internal, a person's gender identity is not necessarily visible to others. "Affirmed gender identity" refers to a person's gender identity after coming out as TGNC or undergoing a social and/or medical transition process.

Gender marker: an indicator (M, F) of a person's sex or gender found on identification (e.g., driver's license, passport) and other legal documents (e.g., birth certificate, academic transcripts).

Gender nonconforming (GNC): an adjective used as an umbrella term to describe people whose gender expression or gender identity differs from gender norms associated with their assigned birth sex. Subpopulations of the TGNC community can develop specialized language to represent their experience and culture, such as the term "masculine of center" (MOC; Cole & Han, 2011) that is used in communities of color to describe one's GNC identity.

Gender questioning: an adjective to describe people who may be questioning or exploring their gender identity and whose gender identity may not align with their sex assigned at birth.

Genderqueer: a term to describe a person whose gender identity does not align with a binary understanding of gender (i.e., a person who does not identify fully as either a man or a woman). People who identify as genderqueer may redefine gender or decline to define themselves as gendered altogether. For example, people who identify as genderqueer may think of themselves as both man and woman (bigender, pangender, androgyne); neither man nor woman (genderless, gender neutral, neutrois, agender); moving between genders (genderfluid); or embodying a third gender.

Gender role: refers to a pattern of appearance, personality, and behavior that, in a given culture, is associated with being a boy/man/male or being a girl/woman/female. The appearance, personality, and behavior characteristics may or may not conform to what is expected based on a person's sex assigned at birth according to cultural and environmental standards. Gender role may also refer to the *social* role in which one is living (e.g., as a woman, a man, or another gender), with some role characteristics conforming and others not conforming to what is associated with girls/women or boys/men in a given culture and time.

Hormone therapy (gender-affirming hormone therapy, hormone replacement therapy): the use of hormones to masculinize or feminize a person's body to better align that person's physical characteristics with their gender identity. People wishing to feminize their body receive antiandrogens and/or estrogens; people wishing to masculinize their body receive testosterone. Hormone therapy may be an important part of medically necessary treatment to alleviate gender dysphoria.

Male-to-female (MTF): individuals whose assigned sex at birth was male and who have changed, are changing, or wish to change their body and/or gender role to a more feminized body or gender role. MTF persons are also often referred to as *transgender women*, *transwomen*, or *trans women*.

Passing: the ability to blend in with cisgender people without being recognized as transgender based on appearance or gender role and expression; being perceived as cisgender. Passing may or may not be a goal for all TGNC people.

Puberty suppression (puberty blocking, puberty delaying therapy): a treatment that can be used to temporarily suppress the development of secondary sex characteristics that occur during puberty in youth, typically using gonadotropin-releasing hormone (GnRH) analogues. Puberty suppression may be an important part of medically necessary treatment to alleviate gender dysphoria. Puberty suppression can provide adolescents time to determine whether they desire less reversible medical intervention and can serve as a diagnostic tool to determine if further medical intervention is warranted.

Sex (sex assigned at birth): sex is typically assigned at birth (or before during ultrasound) based on the appearance of external genitalia. When the external genitalia are ambiguous, other indicators (e.g., internal genitalia, chromosomal and hormonal sex) are considered to assign a sex, with the aim of assigning a sex that is most likely to be congruent with the child's gender identity (MacLaughlin & Donahoe, 2004). For most people, gender identity is congruent with sex assigned at birth (see *cisgender*); for TGNC individuals, gender identity differs in varying degrees from sex assigned at birth.

Sexual orientation: a component of identity that includes a person's sexual and emotional attraction to another person and the behavior and/or social affiliation that may result from this attraction. A person may be attracted to men, women, both, neither, or to people who are genderqueer, androgynous, or have other gender identities. Individuals may identify as lesbian, gay, heterosexual, bisexual, queer, pansexual, or asexual, among others.

Stealth (going stealth): a phrase used by some TGNC people across the life span (e.g., children, adolescents) who choose to make a transition in a new environment (e.g., school) in their affirmed gender without openly sharing their identity as a TGNC person.

(*Appendices continue*)

TGNC: an abbreviation used to refer to people who are transgender or gender nonconforming.

Trans: common short-hand for the terms transgender, transsexual, and/or gender nonconforming. Although the term "trans" is commonly accepted, not all transsexual or gender nonconforming people identify as trans.

Trans-affirmative: being respectful, aware and supportive of the needs of TGNC people.

Transgender: an adjective that is an umbrella term used to describe the full range of people whose gender identity and/or gender role do not conform to what is typically associated with their sex assigned at birth. Although the term "transgender" is commonly accepted, not all TGNC people self-identify as transgender.

Transgender man, trans man, or transman: a person whose sex assigned at birth was female, but who identifies as a man (see FTM).

Transgender woman, trans woman, or transwoman: a person whose sex assigned at birth was male, but who identifies as a woman (see MTF).

Transition: a process some TGNC people progress through when they shift toward a gender role that differs from the one associated with their sex assigned at birth. The length, scope, and process of transition are unique to each person's life situation. For many people, this involves developing a gender role and expression that is more aligned with their gender identity. A transition typically occurs over a period of time; TGNC people may proceed through a social transition (e.g., changes in gender expression, gender role, name, pronoun, and gender marker) and/or a medical transition (e.g., hormone therapy, surgery, and/or other interventions).

Transsexual: term to describe TGNC people who have changed or are changing their bodies through medical interventions (e.g., hormones, surgery) to better align their bodies with a gender identity that is different than their sex assigned at birth. Not all people who identify as transsexual consider themselves to be TGNC. For example, some transsexual individuals identify as female or male, without identifying as TGNC. Transsexualism is used as a medical diagnosis in the World Health Organization's (2015) International Classification of Diseases version 10.

Two-spirit: term used by some Native American cultures to describe people who identify with both male and female gender roles; this can include both gender identity and sexual orientation. Two-spirit people are often respected and carry unique spiritual roles for their community.

Appendix B
Guidelines for Psychological Practice With Transgender and Gender Nonconforming People

Foundational Knowledge and Awareness

Guideline 1. Psychologists understand that gender is a nonbinary construct that allows for a range of gender identities and that a person's gender identity may not align with sex assigned at birth.

Guideline 2. Psychologists understand that gender identity and sexual orientation are distinct but interrelated constructs.

Guideline 3. Psychologists seek to understand how gender identity intersects with the other cultural identities of TGNC people.

Guideline 4. Psychologists are aware of how their attitudes about and knowledge of gender identity and gender expression may affect the quality of care they provide to TGNC people and their families.

Stigma, Discrimination, and Barriers to Care

Guideline 5. Psychologists recognize how stigma, prejudice, discrimination, and violence affect the health and well-being of TGNC people.

Guideline 6. Psychologists strive to recognize the influence of institutional barriers on the lives of TGNC people and to assist in developing TGNC-affirmative environments.

Guideline 7. Psychologists understand the need to promote social change that reduces the negative effects of stigma on the health and well-being of TGNC people.

(*Appendices continue*)

Life Span Development

Guideline 8. Psychologists working with gender-questioning and TGNC youth understand the different developmental needs of children and adolescents and that not all youth will persist in a TGNC identity into adulthood.

Guideline 9. Psychologists strive to understand both the particular challenges that TGNC elders experience and the resilience they can develop.

Assessment, Therapy, and Intervention

Guideline 10. Psychologists strive to understand how mental health concerns may or may not be related to a TGNC person's gender identity and the psychological effects of minority stress.

Guideline 11. Psychologists recognize that TGNC people are more likely to experience positive life outcomes when they receive social support or trans-affirmative care.

Guideline 12. Psychologists strive to understand the effects that changes in gender identity and gender expression have on the romantic and sexual relationships of TGNC people.

Guideline 13. Psychologists seek to understand how parenting and family formation among TGNC people take a variety of forms.

Guideline 14. Psychologists recognize the potential benefits of an interdisciplinary approach when providing care to TGNC people and strive to work collaboratively with other providers.

Research, Education, and Training

Guideline 15. Psychologists respect the welfare and rights of TGNC participants in research and strive to represent results accurately and avoid misuse or misrepresentation of findings.

Guideline 16. Psychologists Seek to Prepare Trainees in Psychology to Work Competently With TGNC People.

Suggested citation:
American Psychological Association. (2015). Guidelines for Psychological Practice with Transgender and Gender Nonconforming People. *American Psychologist*, 70 (9), 832-864. doi: 10.1037/a0039906

DEFENDANT'S EXHIBIT 26

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER, *et al.*,	)	
Plaintiffs,	)	
v.	)	No. 2:22-cv-00184-LCB-SRW
KAY IVEY, in her official capacity as Governor of the State of Alabama, *et al.*,	)	
Defendants.	)	

DECLARATION OF CORINNA COHN

My name is Corinna Cohn. I am over the age of 19, I am qualified to give this declaration, and, I have personal knowledge of the matters set forth herein.

In or about 2nd grade, I saw a psychologist for problems related to being bullied and emotional regulation. After less than a year, my parents chose to discontinue therapy. I continued to be bullied and had problems forming friendships. Other boys excluded me from social activities. Later in elementary school I began to pray to be made into a girl, which I thought would allow me to fit in better. This became a fixation for me.

In high school, I confessed to my parents that I wanted to become a woman. They brought me to see the same psychologist I'd had as a child, and she diagnosed me with having gender identity disorder. Upon receiving this diagnosis, my parents again chose to discontinue my therapy. I continued to have problems socializing at school and experienced depression and anxiety on a daily basis.

At the age of 17, I gained access to the Internet. This was prior to the popularization of the World Wide Web, but I was able to use message boards and chat in order to find other members of what today would be called the "trans community". Adult transgender women befriended me, supplied me with validation and support, and provided information on how I could transition to also become a transgender woman.

At the age of 18, I resumed my sessions with my psychologist with the goal of receiving a prescription for cross-sex hormones and eventual sex reassignment surgery. Due to my prior relationship with my psychologist, I was able to gain a letter of recommendation to an endocrinologist and was prescribed estrogen. The endocrinologist was referred to me by transgender friends on the Internet. I began living as a woman and had my legal identification updated to reflect my chosen name.

I had sex reassignment surgery in Neenah, Wisconsin in 1994. I was only 19 years old. Securing the appointment required letters from two therapists along with a letter from my endocrinologist. My surgeon told me I was the second-youngest patient he had operated on. The surgery involved removal of my testicles, penectomy, and vaginoplasty. It was successful and without complication.

After healing from my sex change surgery I thought that my transition journey was over. I discontinued therapy, and I began focusing on my career. I found it was easier to socialize and make new friends with my new confidence and feelings of being my authentic self. As I reached my late twenties, my friends began pairing off and starting families. I discovered that it was very difficult to find a partner who wanted to do the same with me.

Although I was in denial for several years, I eventually realized that my depression and anxiety related to my gender identity had not resolved. It was not unusual for me to spend entire weekends in my room crying and entertaining thoughts of suicide.

In my mid-thirties I became interested in radical feminism. I am not a feminist, nor have I ever been, but I wanted to reconcile how feminist concepts applied to people like myself: males who try to turn ourselves into women. One of the concepts I found pivotal was the feminist criticism of biological essentialism, which challenges the idea that men and women are destined to fulfill rigid sex roles. Once I understood this criticism I realized that my more stereotypically feminine attitudes and behaviors did not therefore make me a woman, but rather a feminine man. In retrospect, my self-perception of being a woman also required that I overlook or discount traits that are more stereotypically masculine. Although it took time for this realization to fully sink in, a side effect was that I stopped having bouts of depression and anxiety related to my gender identity. I have not had any depressive episodes related to gender identity in ten years. As a teenager I was unprepared to understand the consequences of my decision to medicalize my transition despite the rigorous controls that were then in place to ensure that patients would not be harmed from gender affirming care.

In 2019, I co-founded a non-profit dedicated to advocating for patients of gender care services. Through the Gender Care Consumer Advocacy Network (GCCAN), I have spoken with other patients and gender clinicians to identify opportunities that can benefit patients and improve the quality of care delivered. The gender clinicians I have spoken with have admitted that they do not follow the World Professional Association of Transgender Health standards of care because they are viewed to be needlessly restrictive. It is GCCAN's position to oppose

criminalization of gender affirmative care, but it is evident that gender clinicians treating adolescents are not abiding by the existing standards of care and that they are not self-regulating. Individuals are in a difficult position to be made whole when injured as it is common for transgender patients to rationalize or forgive poor treatment lest they lose access to their providers altogether. The reticence of gender clinicians to avoid harming their patients has created a vacuum for legislators to address.

I wish I could persuade other boys who wish to become women that the changes they seek are only superficial. Hormones and surgery are unable to reveal an authentic self, and anyone who promises otherwise is, in my opinion, deliberately misleading young people to follow a one-way track to a lifetime of medicalization. Although some people may choose to transition, and may even enjoy a higher quality of life, there is no reason why this irreversible decision needs to be made in adolescence. Adults who advocate for adolescent transition do so without understanding what tradeoffs early transition entails, which includes the loss of fertility, the likelihood of sexual dysfunction, and the likelihood of surgical complication inflicted at an early age from elective procedures. Unfortunately, I do understand some of these tradeoffs. While I would not want to see well-meaning family doctors prosecuted for trying to help a dysphoric child, until such a time as there is clear evidence that adolescent transition is likely to help, adolescent gender affirming care should be heavily scrutinized.

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct. Executed on April 26, 2022.

Corinna Cohn

DEFENDANT'S EXHIBIT 27

UNITED STATES DISTRICTCOURT
FOR THE MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER; BRIANNA BOE, individually and on behalf of her minor son, MICHAEL BOE; JAMES ZOE, individually and on behalf of his minor son, ZACHARY ZOE; MEGAN POE, individually and on behalf of her minor daughter, ALLISON POE; KATHY NOE, individually and on behalf of her minor son, CHRISTOPHER NOE; JANE MOE, Ph.D; and RACHEL KOE, M.D.

Plaintiffs,

v.

KAY IVEY, in her official capacity As Governor of the State of Alabama; STEVE MARSHALL, in his official capacity as Attorney General of the State of Alabama; DARYL D. BAILEY, in his official capacity as District Attorney for Montgomery County; C. WILSON BAYLOCK, in his official capacity as District Attorney for Cullman County; JESSICA VENTIERE, in her official capacity as District Attorney for Lee County; TOM ANDERSON in his official capacity as District Attorney for the 12th Judicial Circuit; and DANNY CARR, in his official Capacity as District Attorney for Jefferson County.

Defendants

CIVIL ACTION # 2:22-cv-00184-LCB-SRW

Declaration of Sydney Wright In Support of Defendants' Opposition to Plaintiffs' Motion for Preliminary Injunction

I, Sydney Wright, declare as follows:

1. I am over the age of 18 years and am not a party to this action. I have actual knowledge of the following facts and if called upon to testify to them could and would do so competently. I am submitting this Declaration in support of Defendants' opposition to Plaintiffs' Motion for a Temporary Restraining Order and Preliminary Injunction.

2. Alabama's Vulnerable Child Compassion and Protection Act ("VCCAP") is a necessary, potentially life-saving law that will protect vulnerable children and their parents from the heartbreaking regret, irreversible physical changes, and emotional pain that I have experienced after undertaking medical interventions aimed at "transitioning" me from a female to a male.

3. I'm a 23-year-old woman who spent a year as a "transman" after being rushed into taking mega doses of testosterone at age 18.

4. I began to identify as transgender in 2017 during counseling after reading about transgenderism on the internet. I had not experienced feelings of gender dysphoria prior to this time.

5. A neighborhood boy engaged in sexually touching with me from age 5 to 12. This awakened sexual feelings at too young an age and caused me to feel unsafe.

6. I was very tomboyish growing up and was sometimes bullied. I began having same-sex attractions as a teen. I was raised in a strict religious home, where homosexuality was frowned upon. When my father learned that I had same-sex attractions he kicked me out of his house (my parents divorced when I was 12) and I went to live with my mother.

7. I was first introduced to transgenderism on social media at around age 18. I began to question if I was really a man because I was attracted to girls.

8. I cut my long blond hair, which caused me to look more masculine. This made me want to move quickly through transition.

9. I started seeing a counselor on June 13, 2017. I disclosed to the counselor that I had been sexually molested for years as a child, about my parents' contentious divorce, and about my dysfunctional relationship with both parents. I also disclosed that I was in a dysfunctional marriage to a physically abusive woman who brought and sold drugs.

10. The counselor did not explore how any of this history might be contributing to my dysphoria, but simply asked some questions and diagnosed me with gender dysphoria and gave me a recommendation to a physician for testosterone treatment within five weeks of our first meeting.

11. My frame of mind at the time, at age 18, was that I believed I might have been "born in the wrong body" and needed to correct it. But I was also unsure,

confused, and in need of guidance. Had a professional told me the truth and helped me explore why I was distressed by being a girl (and a lesbian) in a nonjudgmental way, I would not have proceeded with testosterone.

12. However, that was not the case, and I met with the doctor to whom the counselor referred me. The visit lasted less than 10 minutes, during which time the doctor was curt and rude. He asked me for my "hormone letter," but did not open it or read it. He did not ask any questions to confirm that I had gender dysphoria or any questions concerning my medical history or past or present physical condition or symptoms.

13. I told the doctor that I was nervous, and he curtly asked, "Do you want to do this?" and told me I could pick up the testosterone that day. I asked the doctor if he would administer the injections in the office. He said no and told me to go home and look on You Tube to find out how to give myself the shots, indicating "There's no wrong way to do it. I later learned that the shots were supposed to be administered intramuscularly after administering them subcutaneously in my stomach which caused pain and bubbles to form under the skin.

14. My voice began to deepen, which I have found out is going to be a permanent, irreversible change.

15. I gained over 50 pounds and became pre-diabetic. When I mentioned this to the physician during a follow up appointment he just told me to start working out.

16. After about a year on testosterone, test results revealed that my blood was starting to thicken, my red blood cell count was too high, and I was developing a blood disorder that could lead to a heart attack or stroke if not controlled. I did some research and believe this was polycythemia. I began experiencing chest pains and was told I had developed tachycardia.

17. I begam suffering excruciating and constant abdominal pain and could not eat. Testing did not reveal any disorders. I was later diagnosed with irritable bowel syndrome, which I continue to suffer with.

18. The pain was becoming so excruciating that I became suicidal. My mental health was deteriorating as I was suffering from depression, irritability, insecurity, and exhaustion.

19. The changes brought on by the testosterone caused my family tremendous emotional distress. Finally, my grandfather sat me down with tears in his eyes and asked me to stop what I was doing to myself. That was a saving grace. I would have let the treatment kill me before admitting that I had made a mistake. My grandfather's intervention saved my life.

20. I stopped taking testosterone and resumed living as a female. My physical and mental health have improved, but I continue to suffer adverse effects from the treatments, including a deepened voice and digestive issues that I've been told will be permanent.

21. I also suffer extreme regret for the choices I made as a teenager. I trusted the doctors' advice. They were the experts, who was I as a confused and scared 18 year old not to listen to them?

22. But telling an 18-year-old girl that mega-doses of testosterone would fix her mental health problems? They didn't even to talk to me about other treatment options! No doctor or therapist suggested I give myself time to grow up, or suggested counseling for what was causing my feelings – no doctor or therapist told me most young people outgrow their feelings of wanting to be the opposite sex. The only advice I got was to take mega-doses of testosterone.

23. Unfortunately, there are more and more young people like me being deceived every day, being told that the solution to their insecurity and identity problems is to get a "sex change." The problem is, a person's sex can't really be changed. You can take hormones and have cosmetic surgeries, but that doesn't really change your sex, or solve your problems. I wish I knew that when I was younger.

24. The VCCAP Act is a critical and necessary law that will help spare my fellow Alabama citizens from being similar misled and suffering the distress I am

continuing to suffer because of the availability of medical interventions to minors under age 19. This law will save lives.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: April 04/29/2022 2022

Sydney Wright

Sydney Wright

Signature: Sydney E Wright
Sydney E Wright (Apr 29, 2022 18:57 EDT)

Email: [redacted]

DEFENDANT'S EXHIBIT 28

UNITED STATES DISTRICTCOURT
FOR THE MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER; BRIANNA BOE, individually and on behalf of her minor son, MICHAEL BOE; JAMES ZOE, individually and on behalf of his minor son, ZACHARY ZOE; MEGAN POE, individually and on behalf of her minor daughter, ALLISON POE; KATHY NOE, individually and on behalf of her minor son, CHRISTOPHER NOE; JANE MOE, Ph.D; and RACHEL KOE, M.D.

Plaintiffs,

v.

KAY IVEY, in her official capacity As Governor of the State of Alabama; STEVE MARSHALL, in his official capacity as Attorney General of the State of Alabama; DARYL D. BAILEY, in his official capacity as District Attorney for Montgomery County; C. WILSON BAYLOCK, in his official capacity as District Attorney for Cullman County; JESSICA VENTIERE, in her official capacity as District Attorney for Lee County; TOM ANDERSON in his official capacity as District Attorney for the 12th Judicial Circuit; and DANNY CARR, in his official Capacity as District Attorney for Jefferson County.

Defendants

CIVIL ACTION # 2:22-cv-00184-LCB-SRW

Declaration of Carol Frietas In Support of Defendants' Opposition to Plaintiffs' Motion for Preliminary Injunction

I, Carol Frietas, declare as follows:

1. I am over the age of 18 years and am not a party to this action. I have actual knowledge of the following facts and if called upon to testify to them could and would do so competently. I am submitting this Declaration in support of Defendants' opposition to Plaintiffs' Motion for a Temporary Restraining Order and Preliminary Injunction.

2. Alabama's Vulnerable Child Compassion and Protection Act ("VCCAP") is a necessary, potentially life-saving law that will protect vulnerable children and their parents from the heartbreaking regret, irreversible physical changes, and emotional pain that I have experienced after undertaking medical and surgical interventions aimed at "transitioning" me from a female to a "male."

3. As a youth, I was what today is called "gender non-conforming," but I lived in a household where gender expression was strictly aligned with cultural stereotypes. I was not allowed to wear boys' clothes or play boys' sports.

4. At puberty I realized I was same-sex attracted with crushes on girls. I became depressed and anxiety-ridden as I feared what "being gay" might mean to how I lived my life and my family relationships. I dropped out of school.

5. At age 20, I began to meet other LGBT youth and my life stabilized. However, I also learned that many masculine females, like me, felt that they were "born in the wrong body" and were transitioning, so I adopted that persona.

6. I went to a gender therapist who diagnosed me with gender dysphoria and told me that transition was the only treatment that would alleviate my discomfort and anxiety.

7. However, at that time there were gatekeeping standards for gender transition, which required that I first live as man for six months, including using a male name, showing a male appearance, and using male spaces. I had very large breasts and could not pass for a male in male spaces, so I did not pursue testosterone at that time. I viewed myself as a male trapped in the "wrong body," but my mental health otherwise was stable.

8. In 2014, I revisited the idea of transitioning, believing it would make me feel better because I was undergoing trauma in various forms. My grandmother who had practically raised me died. I had suffered severe abuse and neglect in childhood, and in retrospect believe I was experiencing symptoms of PTSD from that. I had just become a new mother a couple of months before my brother-in-law committed suicide.

9. I spiraled downward and wanted out. I couldn't commit suicide because I was a mother, so I returned to the idea of transition, believing it would help me feel better. By that time the requirements for testosterone had lessened. I went to Planned Parenthood for testosterone and was given it right away, with no information. I was not given any information on uterine atrophy, vaginal atrophy,

or other effects of testosterone and the staff did not talk about any of my emotional or mental health issues.

10. Four months after starting testosterone, I went to a plastic surgeon for a mastectomy. I needed a letter from a therapist and received one from the therapist who had affirmed me and originally recommended transition. As was true with testosterone, I was not given any information about the procedure. Instead I had a consultation with the surgeon, who said "this is what we are going to do," drew on my chest, took pictures and asked me what I wanted out of the surgery. He said "we'll create a masculine looking chest, you'll look great."

11. During the first four months on testosterone menstruation stopped, my sex drive went way up, my voice deepened, and facial and body hair came in. As I continued on testosterone, my personality changed drastically and my verbal abilities declined. Testosterone lowered and muted my emotions and empathy, but also gave me a lot of energy and a sense of a high. My depression and anxiety worsened to the point that I was having such severe panic attacks that I could not leave home. I told my doctors that I thought the testosterone was making the anxiety worse, but they said no.

12. I went to a psychiatrist to specifically to deal with the depression and I was provided with an anti-depressant that really worked. I felt mentally stable and able to address the trauma that led me to transition.

13. Within a month of starting the anti-depressant, I realized that I had not needed to transition. It was the biggest mistake I had ever made. I did not detransition for a year because I couldn't believe that it was so easy, *i.e.*, that anti-depressants alleviated my depression and enabled me to think clearly and reason better. This allowed me address my internalized homophobia and childhood abuse through therapeutic means.

14. Meanwhile, my health began going downhill. Before going on testosterone, I had no health problems. After being on it for four years, I was pre-diabetic, had high cholesterol, and had a high red blood cell count to the point that doctors were recommending that I donate blood to reduce the volume.

15. I stopped taking testosterone and four months later my blood work was back down to normal. I thought to myself "How do they [doctors] not know about this?" Going off testosterone allowed me to finally sleep. I felt like I never slept all the time that I was taking testosterone. Going off testosterone also helped with empathy and other emotions. My personal relationships, including my relationship with my wife, were better.

16. I believe that healthcare providers did not ask me about mental health issues because they believed that those issues were caused by gender dysphoria and that transitioning would fix the problem. In fact, the opposite was true.

17. I would have been spared physical, psychological, and emotional losses if I had received a proper diagnosis and treatment for PTSD and depression before undergoing years of medical and surgical interventions. Alabama's VCCAP Act is necessary and essential because it will give children and adolescents the chance to work through and address their underlying issues such as depression or PTSD effectively without being pulled onto the affirmation conveyor belt. Hormones and surgery are irreversible decisions that children and adolescents are incapable of making.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: April 29, 2022.

Carol Freitas

DEFENDANT'S EXHIBIT 29

UNITED STATES DISTRICTCOURT
FOR THE MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER; BRIANNA BOE, individually and on behalf of her minor son, MICHAEL BOE; JAMES ZOE, individually and on behalf of his minor son, ZACHARY ZOE; MEGAN POE, individually and on behalf of her minor daughter, ALLISON POE; KATHY NOE, individually and on behalf of her minor son, CHRISTOPHER NOE; JANE MOE, Ph.D; and RACHEL KOE, M.D.

Plaintiffs,

v.

KAY IVEY, in her official capacity As Governor of the State of Alabama; STEVE MARSHALL, in his official capacity as Attorney General of the State of Alabama; DARYL D. BAILEY, in his official capacity as District Attorney for Montgomery County; C. WILSON BAYLOCK, in his official capacity as District Attorney for Cullman County; JESSICA VENTIERE, in her official capacity as District Attorney for Lee County; TOM ANDERSON in his official capacity as District Attorney for the 12th Judicial Circuit; and DANNY CARR, in his official Capacity as District Attorney for Jefferson County.

Defendants

CIVIL ACTION # 2:22-cv-00184-LCB-SRW

Declaration of Barbara F.*
In Support of Defendants'
Opposition to Plaintiffs'
Motion for Preliminary Injunction

I, Barbara F.[1] declare as follows:

1. I am over the age of 18 years and am not a party to this action. I have actual knowledge of the following facts and if called upon to testify to them could and would do so competently. I am submitting this Declaration in support of Defendants' opposition to Plaintiffs' Motion for a Temporary Restraining Order and Preliminary Injunction.

2. Alabama's Vulnerable Child Compassion and Protection Act ("VCCAP") provides parents necessary protections against manipulation and coercion on the part of health care providers, ex-spouses and confused children to comply with demands for medical and surgical interventions aimed at "affirming" a child's professed discordant gender identity under threats of alienation or loss of a child to suicide.

3. Because there is no such parent and child-protective law in place in my home state, I have been subjected to alienation from my daughter, coercion, manipulation, and blatant disregard for my parental right to make medical and mental health decisions for my child. The VCCAP will prevent parents and children in Alabama from suffering similar harms. It will actually restore the rights of all parents, not just those who agree with demands for "gender-affirming" medical

[1] Declarant is submitting this Declaration using a pseudonym to protect the privacy of her children and other family members.

interventions, to make medical and mental health care decisions for their children that are truly in the best interest of their child's healthy development.

4. When my daughter, B., was 11 years old she said she identified as a boy and wanted to be referred to by an alternate male name. This occurred after she had endured ridicule from her father (my ex-husband) for laughing like me and witnessed her brother getting preferential treatment from her father.

5. B's father championed her new 'male" identity and began harassing me for not affirming it. He accused me of emotional abuse and called child protection services against me. B's father convinced B. to not participate in visitations with me unless I affirmed the discordant identity.

6. Shortly after B announced that she identified as a boy, I acted on the advice of our family physician and took B to a gender clinic. I naively believed that I would have an opportunity to seek a psychological evaluation and psychological counseling for B. and discuss her sudden identification as a boy prior to any interventions aimed at "affirming" her choice.

7. However, when my daughter and I arrived at the clinic the staff psychologist did an evaluation, but said that she did not have time to see B. regularly to give more in depth psychological help. I stated that believed that B. needed to have psychological counseling before any medical interventions were begun.

8. I told the clinic staff that I did not consent to further consultations regarding medical intervention. I had done some research on the puberty blockers and hormone therapy being suggested for my daughter and was concerned about their unproven safety and efficacy.

9. The clinic staff ignored my directions and, without telling me, an endocrinologist met with my 12-year-old daughter privately and with her father to discuss beginning puberty blockers. The endocrinologist then came in to meet with my daughter and me. When I raised concerns about the puberty blockers, the endocrinologist said that there are "no studies that show the drugs aren't safe." She also told me *in front of* my daughter that I needed "to get on board [with providing puberty blockers and hormones] if I don't want my daughter to commit suicide."

10. I have repeatedly notified clinic staff orally and in writing that I do not consent to their treating my daughter. My ex-husband and I have shared decision-making authority for our children's medical care, so no care is supposed to be provided unless both of us consent. Nevertheless, the clinic and B.'s father have continued with regular consultations with my daughter without my consent.

11. I have reviewed documents from the clinic in which staff say that they plan to "convince me" to consent to the medical interventions, completely disregarding my legal rights and role as B's mother.

12. The availability and promotion of "gender affirming" medical interventions for minors such as my daughter has been used to drive a wedge between B. and me, to prevent B. from receiving counseling for underlying mental health issues and to expose her to unknown long-term medical and mental health consequences without my consent. The notion of "informed consent" or parental decision-making is non-existent.

13. The VCCAP Act prevents such coercive manipulation and potential harm against Alabama's vulnerable children and should be upheld for the protection of children and their families.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: April 28, 2022.

/s/ Barbara F.
Barbara F. (pseudonym)
[original signature available on request]

DEFENDANT'S EXHIBIT 30

UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER; BRIANNA BOE, individually and on behalf of her minor son, MICHAEL BOE; JAMES ZOE, individually and on behalf of his minor son, ZACHARY ZOE; MEGAN POE, individually and on behalf of her minor daughter, ALLISON POE; KATHY NOE, individually and on behalf of her minor son, CHRISTOPHER NOE; JANE MOE, Ph.D; and RACHEL KOE, M.D.

Plaintiffs,

v.

KAY IVEY, in her official capacity As Governor of the State of Alabama; STEVE MARSHALL, in his official capacity as Attorney General of the State of Alabama; DARYL D. BAILEY, in his official capacity as District Attorney for Montgomery County; C. WILSON BAYLOCK, in his official capacity as District Attorney for Cullman County; JESSICA VENTIERE, in her official capacity as District Attorney for Lee County; TOM ANDERSON in his official capacity as District Attorney for the 12th Judicial Circuit; and DANNY CARR, in his official Capacity as District Attorney for Jefferson County.

Defendants

CIVIL ACTION # 2:22-cv-00184-LCB-SRW

Declaration of John Doe*
In Support of Defendants' Opposition to Plaintiffs' Motion for Preliminary Injunction

I, John Doe[1], declare as follows:

1. I am over the age of 18 years and am not a party to this action. I have actual knowledge of the following facts and if called upon to testify to them could and would do so competently. I am submitting this Declaration in support of Defendants' opposition to Plaintiffs' Motion for a Temporary Restraining Order and Preliminary Injunction.

2. I am the father of two sons including a 17-year-old, C. (a pseudonym), who is being seen by Dr. Stephen Rosenthal and his team at UCSF, who is an expert witness who has been retained by the Plaintiffs in this case.

3. I have read Dr. Rosenthal's Declaration. I can testify that his statements regarding the standard of care for transgender children, and particularly his claims that parents have the opportunity to exercise informed consent regarding medical interventions for their child are not true with regard to my son.

4. Dr. Rosenthal claims that medical treatment is done in consultation with the patient's family. In my case this is not true. Dr. Rosenthal's institution has actively worked to prevent my participation in my son's care to the point of providing information to the attorney representing my son in family court aimed at

[1] Declarant is submitting this Declaration using a pseudonym for himself and his son to protect the privacy of his child and family.

stripping me of custody because I would not affirm my son in a discordant gender identity.

5. In fact, I knew nothing about my son receiving life-altering medical interventions until I received a statement from my insurance carrier showing that it had paid more than $209,000 to a child and adolescent gender clinic at UCSF. Even then, I did not know what the payment was for until I asked my ex-wife. She emailed me that she was "pleased" to report that our son had been given an implant of Supprelin (used to suppress testosterone) and was receiving estradiol (estrogen) pills.

6. My research on these substances showed that they chemically castrate patients and are even used specifically for that purpose in some cases for sex offenders. Yet here my 17-year-old son was receiving these drugs from Dr. Rosenthal ostensibly to improve his health and well-being.

7. I have learned that Supprelin is Dr. Rosenthal's preferred method for administering puberty blockers for adolescents like my son. Supprelin requires surgical implantation, meaning that it is a surgical intervention administered to children under the age of 18, which is contrary to Dr. Rosenthal's testimony that surgical interventions are not prescribed for minors and not recommended by the "Standards of Care."

8. I contend that Dr. Rosenthal's surgical implantation of Supprelin into my son also violates the family court's custody order, which UCSF has a copy of, which states that my son is not permitted to "undergo any gender identity related surgery" until he is 18 absent a written agreement of **both parents** or order of the court. I did not agree to the surgical implantation, nor is there any court order permitting it, yet C.'s records show a surgical procedure performed on him to insert the Supprelin. This further calls into question Dr. Rosenthal's testimony regarding the "standards of care" employed in "gender-affirming" interventions.

9. Dr. Rosenthal's testimony also contradicts his actions with my son in that after UCSF surgically implanted my 17 year old son with Supprelin LA (without my knowledge or consent but paid for by my health insurance), Dr. Rosenthal discussed follow-up surgical options with him without both parents present. Dr. Rosenthal discussed breast implants, facial feminization and bottom surgery with my son at age 17 years and 5 months.

10. Rosenthal claims to "provide the patient and their family the information they need to make an informed decision about whether to proceed with the treatment." Again, that is not true regarding the treatment prescribed for my son. When I sought information about alternatives, such as "watchful waiting," and whether patients are assessed by Ray Blanchard's typology of transsexuals, instead

of receiving an answer I was subjected to actions in the family court aimed at stripping me of custody because of my questioning of the protocols at UCSF.

11. Similarly, when I provided Dr. Rosenthal with research that I had found which suggests that puberty blockers can cause cognitive harm and asked questions I received no response, contrary to his testimony that parents are involved to ensure everyone involved has the information they need to make an informed decision.

12. Further contradicting his claim of "informed" decision-making is seen in the form presented to and discussed with my then 16 year old son. The form did not indicate that permanent and irreversible sterility is a potential and likely outcome of the recommended treatment, particularly when puberty blockers are combined with estrogen as is the case with C.

13. Dr. Rosenthal's actions with regard to the treatment of my son differ significantly from the "safe and effective" protocols that he claims are part of "gender-affirming" treatments. His refusal to respond to my questions as the concerned father of his patient belie his testimony about the information-rich and collaborative environment he claims is part of the "gender-affirming" care he provides.

14. My experiences with Dr. Rosenthal instead point to an ideologically driven conveyor belt onto which vulnerable children like my son are placed and processed without the safeguards usually inherent in medical procedures.

15. Parental participation is tolerated only so long as it is affirming of the ideology. If, as in my case, the parent asks questions instead of immediately affirming the agenda, then that parent is disregarded even to the point, as in my case, of having their rights stripped away.

16. The availability of "gender-affirming" medical interventions for vulnerable children experiencing distress about changes in their bodies enables the ideological conveyor belt to proceed unhindered, leaving in its wake sterilized, drug-dependent and dysfunctional young adults, shattered relationships, and distrust in the medical profession.

17. Alabama's efforts to ban these treatments for minors in the VCCAP is necessary to prevent the irreversible and incalculable harms caused by the unchecked gender medicine machine. The VCCAP law will save Alabama families from similar devastation.

Dated: April 28, 2022.

John Doe

John Doe (pseudonym)

DEFENDANT'S EXHIBIT 31

UNITED STATES DISTRICTCOURT
FOR THE MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER; BRIANNA BOE, individually and on behalf of her minor son, MICHAEL BOE; JAMES ZOE, individually and on behalf of his minor son, ZACHARY ZOE; MEGAN POE, individually and on behalf of her minor daughter, ALLISON POE; KATHY NOE, individually and on behalf of her minor son, CHRISTOPHER NOE; JANE MOE, Ph.D; and RACHEL KOE, M.D.

Plaintiffs,

v.

KAY IVEY, in her official capacity As Governor of the State of Alabama; STEVE MARSHALL, in his official capacity as Attorney General of the State of Alabama; DARYL D. BAILEY, in his official capacity as District Attorney for Montgomery County; C. WILSON BAYLOCK, in his official capacity as District Attorney for Cullman County; JESSICA VENTIERE, in her official capacity as District Attorney for Lee County; TOM ANDERSON in his official capacity as District Attorney for the 12th Judicial Circuit; and DANNY CARR, in his official Capacity as District Attorney for Jefferson County.

Defendants

CIVIL ACTION # 2:22-cv-00184-LCB-SRW

Declaration of John Roe*
In Support of Defendants'
Opposition to Plaintiffs'
Motion for Preliminary Injunction

I, John Roe[1] declare as follows:

1. I am over the age of 18 years and am not a party to this action. I have actual knowledge of the following facts and if called upon to testify to them could and would do so competently. I am a resident of Alabama and the father of a son who said he was gender dysphoric and who was socially transitioned at school without our knowledge and referred for "gender transition" medical treatments. I am submitting this Declaration in support of Defendants' opposition to Plaintiffs' Motion for a Temporary Restraining Order and Preliminary Injunction.

2. Alabama's Vulnerable Child Compassion and Protection Act ("VCCAP") will protect vulnerable children and provide parents necessary protections against manipulation and coercion on the part of health care providers and confused children to comply with demands for medical and surgical interventions aimed at "affirming" a child's professed discordant gender identity under threats of alienation or loss of a child to suicide.

3. The VCCAP will provide parents with the information necessary to exercise their rights to make mental health and medical care decisions for their children without the secrecy and interference from the government, particularly

[1] Declarant is submitting this Declaration using a pseudonym to protect the privacy of his child and other family members.

public school and coercive influence of mental health professionals, that I experienced.

4. My son, J., has been diagnosed with ADHD and anxiety. He never expressed any distress about his sex until middle school, his eighth grade year. During that time, J. spent a lot of time online and was interested in anime and role-playing games. He also became friends with a girl who identified as trans, which piqued his curiosity.

5. Between eighth and ninth grade, J. left a note for his mother stating that that he was "transgender." He signed the note "your daughter." My wife did not tell me about the note at that time. She spoke with J. who said he "felt more female than male."

6. J. later left me a similar note saying that he had gender dysphoria as long as he can remember.

7. During a therapy session J. said he started feeling that he was transgender in the 8th grade, but then "did his research" through online searches and confirmed his conclusion. I learned that he had watched internet trans influencers, viewed YouTube videos, and answered online questionnaires to self-diagnose gender dysphoria in eighth grade.

8. I learned after the fact that J.'s public school had facilitated J. socially transitioning to a female gender identity without the knowledge or consent or my

wife or me. Without informing us, the school went along with J.'s wishes to be called by a female name and pronouns in ninth grade. We also later learned that J. was wearing a skirt at school without our knowledge. I found out about the new female name being used by the school as if by accident through communication with a teacher and learned that J. was using female pronouns at school through an art project.

9. We took J. to a therapist who did not do a psychological evaluation, but diagnosed him with OCD, anxiety, and depression as well as the previously diagnosed ADHD.

10. During a family therapy session, the therapist ignored J.'s other co-morbidities and focused solely on gender dysphoria. The therapist called J. "courageous." The therapist printed out a handout from an advocacy group. She was trying to bring my wife and I on board with letting our child lead with diagnosis and treatment.

11. The therapist said that kids have a sense of their identity by age 3 or 4, but provided no scientific support.

12. *With J. present*, the therapist told me and my wife that kids are more likely to attempt suicide and run away from home if they are not affirmed in their chosen identity.

13. After the third or fourth visit the therapist recommended that we take J. to Magic City gender clinic to receive puberty blockers or cross-sex hormones.

14. We did not follow up on that recommendation. I researched the clinic and the proposed interventions and was concerned about what the interventions would steer my son toward. I believed that for a child of J.'s age struggling as he was with self-esteem, amplified by his other co-morbidities, these medical interventions were not going to solve his real underlying issues long-term. I believed that the interventions were permanent changes with life-long consequences to a child's body for a problem of the mind that could be solved by a less invasive route.

15. I believed my son needed to understand that his body was not the problem, but that his thoughts were and that they could be assisted to bring him more peace with his body through therapy.

16. A total ban on these treatments for children, such as provided in the VCCAP Act is necessary because the medical gatekeepers are not doing their job. They are not following proper professional protocols, are not safeguarding confused adolescents, and not self-regulating. They are allowing adolescents, who are prone to making rash decisions, to self-harm and harm their future. They are also pressuring parents with talk of suicide in front of the adolescent. These treatments have unknown long-term effects and are experimenting on children.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: April 28, 2022.

John Roe

John Roe (pseudonym)

DEFENDANT'S EXHIBIT 32

UNITED STATES DISTRICTCOURT
FOR THE MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER; BRIANNA BOE, individually and on behalf of her minor son, MICHAEL BOE; JAMES ZOE, individually and on behalf of his minor son, ZACHARY ZOE; MEGAN POE, individually and on behalf of her minor daughter, ALLISON POE; KATHY NOE, individually and on behalf of her minor son, CHRISTOPHER NOE; JANE MOE, Ph.D; and RACHEL KOE, M.D.

Plaintiffs,

v.

KAY IVEY, in her official capacity As Governor of the State of Alabama; STEVE MARSHALL, in his official capacity as Attorney General of the State of Alabama; DARYL D. BAILEY, in his official capacity as District Attorney for Montgomery County; C. WILSON BAYLOCK, in his official capacity as District Attorney for Cullman County; JESSICA VENTIERE, in her official capacity as District Attorney for Lee County; TOM ANDERSON in his official capacity as District Attorney for the 12th Judicial Circuit; and DANNY CARR, in his official Capacity as District Attorney for Jefferson County.

Defendants

CIVIL ACTION # 2:22-cv-00184-LCB-SRW

Declaration of Kristine W.*
In Support of Defendants'
Opposition to Plaintiffs'
Motion for Preliminary Injunction

I, Kristine W. [1] declare as follows:

1. I am over the age of 18 years and am not a party to this action. I have actual knowledge of the following facts and if called upon to testify to them could and would do so competently. I am submitting this Declaration in support of Defendants' opposition to Plaintiffs' Motion for a Temporary Restraining Order and Preliminary Injunction.

2. Alabama's Vulnerable Child Compassion and Protection Act ("VCCAP") provides parents necessary protections against manipulation and coercion on the part of health care providers and children to comply with demands for medical and surgical interventions aimed at "affirming" a child's professed discordant gender identity under threats of alienation or loss of a child to suicide and pitting children against their parents.

3. Because there is no such parent and child-protective law in place in my home state, I have been subjected to coercion, manipulation, alienation from my daughter and blatant disregard for my parental right to make medical and mental health decisions. The VCCAP will prevent parents and children in Alabama from suffering similar harms. It will actually restore the rights of all parents, not just those who agree with demands for "gender-affirming" medical interventions, to make

[1] Declarant is submitting this Declaration using a pseudonym to protect the privacy of her children and other family members.

medical and mental health care decisions for their children that are in the best interests of their children and their healthy development into adulthood.

4. My daughter, S., had been diagnosed with OCD, Tourette's Syndrome and bulimia when she began intensive outpatient psychiatric treatment for suicidal ideation. She had spent copious amounts of time online during the pandemic lockdown and was influenced by transgender ideology presentations on the internet.

5. At age 13, S. suddenly declared, in a manner which sounded scripted, that she believed she was a boy and wanted to use a male name. When I spoke to her caregivers, they focused on S. wanting to go by a male name and pronouns. I asked them to address S.'s self-harm, anxiety and bulimia, but they refused. Instead, they told me that I needed to ask, "How can we help you with your gender identity?"

6. The staff told me that "transgender identity is very trendy in the hospital setting right now." They continued to confirm S's obsessive thoughts. During one visit, with S present, the caregivers stated that "trans" people are more likely to commit suicide if not affirmed. In another instance, staff at the hospital said, "You must affirm or she will kill herself. Do you want live son or dead daughter?" The school counselor made similar statements.

7. Following the psychiatric treatment, S. returned to seeing psychiatrists and counselors that she had previously been seeing. Her medication was adjusted, she stopped self-harming and her tics were better controlled.

8. After doing more research and believing it important to ground our child in reality, S's father and I no longer used her preferred male name and pronouns at home. I told S. that she could change her name if she desired when she was an adult but until then she did not get to choose her name.

9. S.'s pediatrician told her father, *in front of S.*, that he needed to use the "chosen" name and to not do so was damaging to her emotionally. That conversation put a wedge between father and daughter. We have switched her to our adult practice so we would not have to deal with doctors pushing the transgender agenda on our child.

10. S. asked why her own parents would not use her new name but everyone else did. She felt that we cared more about the name than her feelings of suicide because of the comments made by doctors about how fragile trans kids are. I explained to her that no one loved her as much and cared about her mental health more than do her father and I, who want to do what was best for her in the long run, which was to hold reality for her.

11. S. had asked for testosterone, but after doing my own research I became concerned about the potential harms to my female child and resisted. S. has since announced "I'm not a boy – boys are awful" and is dressing on and off as a girl. Her mental health is improving.

12. S. has a few separate friend groups across three different schools. Of 10-15 children, only one identifies as her natal sex. These numbers mimic known social contagions such as anorexia and cutting behavior. It is statistically impossible and improbable that all these children will continue to identify as another gender into adulthood.

13. S uses a "chosen" name at school. When enrolling her, I had no choice but to go along with it because the school's policy was to do whatever the child wanted regardless of parental wishes. So I registered her with the "chosen" name as a nickname. (The counselor has since confided to me that it is a huge problem for those who change the whole name when applying to college because the transcripts have different names). I believe that if the school and teachers used her given name, it would be easier for her to completely drop the trans narrative.

14. To allow the medical establishment to push children into irreversible treatments and to pit objecting parents against their children is a great tragedy. Families are being ruined. "Gender-affirming" medical interventions should not be available for children.

15. The VCCAP Act prevents coercive manipulation and potential harm against Alabama's vulnerable children and should be upheld for the protection of children and their families.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: April 28, 2022.

Kristine W. (pseudonym)

DEFENDANT'S EXHIBIT 33

UNITED STATES DISTRICTCOURT
FOR THE MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER; BRIANNA BOE, individually and on behalf of her minor son, MICHAEL BOE; JAMES ZOE, individually and on behalf of his minor son, ZACHARY ZOE; MEGAN POE, individually and on behalf of her minor daughter, ALLISON POE; KATHY NOE, individually and on behalf of her minor son, CHRISTOPHER NOE; JANE MOE, Ph.D; and RACHEL KOE, M.D.

Plaintiffs,

v.

KAY IVEY, in her official capacity As Governor of the State of Alabama; STEVE MARSHALL, in his official capacity as Attorney General of the State of Alabama; DARYL D. BAILEY, in his official capacity as District Attorney for Montgomery County; C. WILSON BAYLOCK, in his official capacity as District Attorney for Cullman County; JESSICA VENTIERE, in her official capacity as District Attorney for Lee County; TOM ANDERSON in his official capacity as District Attorney for the 12th Judicial Circuit; and DANNY CARR, in his official Capacity as District Attorney for Jefferson County.

Defendants

CIVIL ACTION # 2:22-cv-00184-LCB-SRW

Declaration of Yaacov Sheinfeld In Support of Defendants' Opposition to Plaintiffs' Motion for Preliminary Injunction

I, Yaacov Sheinfeld, declare as follows:

1. I am over the age of 18 years and am not a party to this action. I have actual knowledge of the following facts and if called upon to testify to them could and would do so competently. I am submitting this Declaration in support of Defendants' opposition to Plaintiffs' Motion for a Temporary Restraining Order and Preliminary Injunction.

2. Alabama's Vulnerable Child Compassion and Protection Act ("VCCAP") provides parents necessary protections against manipulation and coercion on the part of health care providers and their own distress and confused children to comply with demands for medical and surgical interventions aimed at "affirming" a child's professed discordant gender identity under threats of alienation or loss of a child to suicide. Most importantly, this law protects vulnerable children and young people from grievous harm.

3. Had a law like VCCAP been in effect in my state, my daughter might still be alive today.

4. My daughter, S. had been in counseling for depression since age 15, but had never said anything about gender dysphoria to her counselor.

5. At age 17, S.'s mother told me that S. was transgender. I thought it was a bad idea to pursue transitioning, nevertheless, I told S. that I would help her in any other way.

6. S. had suffered a lot of rejection in school and was seeking affirmation. Five of her friends announced that they were transgender. When S. said she was transgender too it was seen as fashionable and she finally had the peer acceptance she had not previously experienced in high school.

7. When S. went to college at age 18, unbeknownst to me, she began taking testosterone. When I met with her at school, I noticed she was very depressed.

8. A social worker who was also present at my meeting with S. told me that S. was going to get a double mastectomy.

9. When I objected to her taking such a drastic step at such a young age, the social worker told me I was an "Israeli chauvinist", a typical chauvinist male, who doesn't love his child enough. Her approach was that this is what we're going to do and you need to just get on board.

10. The social worker assured me that everything would be fine if I just loved my daughter.

11. After this meeting S. refused to talk to me and began threatening that she would kill herself if she did not get the surgery she wanted. She had a double mastectomy at age 19.

12. I witnessed distressing physical changes in S. The changes in her because of the testosterone were so distressing that I even considered suicide at one time. S. gained and lost lots of weight, had pain all over her body, suffered from

mood swings, could not concentrate, and was briefly hospitalized in a psychiatric hospital.

13. S. was deeply depressed and taking a significant number of medications along with testosterone. I kept assuring her that I would do whatever I could to help her.

14. S.'s pain became so intense that she began taking Fentanyl. S. was found dead on August 6, 2021 with Fentanyl and alcohol in her system. She was 28.

15. Alabama's VCCAP and similar laws to ban medical interventions for minors are critical important because children, especially children with mental health issues such as S, cannot make clear mature decisions about their future, particularly when neither they nor their parents are provided with full information about the effects of these interventions. We know from research that the brain is not fully formed until a person reaches her mid-20s, so even a healthy 18-year-old does not have the mental maturity to make significant decisions such as taking cross-sex hormones that will sterilize them and surgically mutilating their bodies. This is particularly true when, as was true with my daughter, neither the child nor the parents are informed about the medical side effects and harms that the medical interventions cause.

16. The medical interventions that were promoted to my daughter with a promise that they would relieve her problems, in fact, increased them and led to her death.

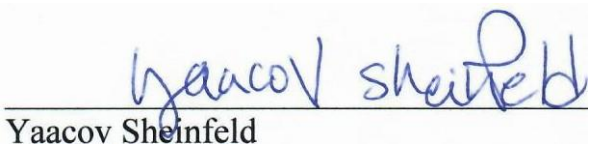
17. Parents should not be put in the position to make decisions for their child that result in sterilization, losing healthy body parts, or other life-long harms, especially when children have mental health issues that are not being addressed.

18. Laws like VCCAP protect parents from being coerced into making these decisions through manipulation and threats like the one leveled at me that my child would commit suicide if she did not get the intervention she demanded.

19. I further declare that certain people in our society think and act in a shameful and destructive way such as this cult, peer group pressure, pitching children against their parents, anarchist ideas. The way my child was treated is like an experiment in bad, unfounded pseudosexual theories that do not hold water. They are dangerous, harmful, destroy the subject of treatment, harm their body, and in many cases- kill them. So much for therapy! Ha! What I went through was hell on earth. I say to you all: Stop this madness now!

I declare under penalty of perjury that the foregoing is true and correct.

Dated: April 29, 2022.



Yaacov Sheinfeld

DEFENDANT'S EXHIBIT 34

UNITED STATES DISTRICTCOURT
FOR THE MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER; BRIANNA BOE, individually and on behalf of her minor son, MICHAEL BOE; JAMES ZOE, individually and on behalf of his minor son, ZACHARY ZOE; MEGAN POE, individually and on behalf of her minor daughter, ALLISON POE; KATHY NOE, individually and on behalf of her minor son, CHRISTOPHER NOE; JANE MOE, Ph.D; and RACHEL KOE, M.D.

Plaintiffs,

v.

KAY IVEY, in her official capacity As Governor of the State of Alabama; STEVE MARSHALL, in his official capacity as Attorney General of the State of Alabama; DARYL D. BAILEY, in his official capacity as District Attorney for Montgomery County; C. WILSON BAYLOCK, in his official capacity as District Attorney for Cullman County; JESSICA VENTIERE, in her official capacity as District Attorney for Lee County; TOM ANDERSON in his official capacity as District Attorney for the 12th Judicial Circuit; and DANNY CARR, in his official Capacity as District Attorney for Jefferson County.

Defendants

CIVIL ACTION # 2:22-cv-00184-LCB-SRW

Declaration of Martha S.*
In Support of Defendants'
Opposition to Plaintiffs'
Motion for Preliminary Injunction

I, Martha S.[1] declare as follows:

1. I am over the age of 18 years and am not a party to this action. I have actual knowledge of the following facts and if called upon to testify to them could and would do so competently. I am submitting this Declaration in support of Defendants' opposition to Plaintiffs' Motion for a Temporary Restraining Order and Preliminary Injunction.

2. Alabama's Vulnerable Child Compassion and Protection Act ("VCCAP") provides parents necessary protections against manipulation and coercion on the part of health care providers and even our own mentally compromised children to comply with demands for medical and surgical interventions aimed at "affirming" a child's professed discordant gender identity under threats of alienation or loss of a child to suicide.

3. The VCCAP will actually restore the rights of all parents, not just those who agree with demands for "gender-affirming" medical interventions, to make medical and mental health care decisions for their children that will protect their healthy physical and mental development and long-term well-being.

4. At age 16, my son, M., began acting out after suffering two traumatic events. When his behavior improved after receiving antibiotics for a sinus infection,

[1] Declarant is submitting this Declaration using a pseudonym to protect the privacy of her children and other family members.

he was diagnosed with Pediatric Auto-immune Neuropsychological Disorder Associated with Strep (PANDAS). PANDAS causes the same kind of psychiatric symptoms that are seen in trans-identified children, *e.g.*, severe anxiety, ADHD, schizophrenia, OCD, and eating disorders.

5. M., who is Caucasian, blonde-haired and blue-eyed, identified as African-American for a semester in high school. Later that year M. told me that he was transgender. When he was home from school during the pandemic M. was depressed and spent a lot of time on the internet asking questions about why he felt so miserable. He was told by sources on Reddit that he was transgender.

6. Our pediatrician referred us to a gender clinic with the expectation that the "experts" at the clinic would help us sort out the issues. Instead the gender clinic staff told me that M. needed to be seen by a gender therapist to get a diagnosis of gender dysphoria.

7. M. had three visits with a gender therapist who did not do any testing and did not address any underlying issues. After the third visit, the therapist prepared a pro forma letter for the clinic that contained an inaccurate history and stated that M. was suffering from gender dysphoria and ready for medical interventions.

8. We saw a psychologist at the gender clinic who after one visit with M. and filling out some questionnaires said that she would recommend that M. see the endocrinologist to be prescribed hormones. She said M. would be put on

spironolactone to block the testosterone instead of puberty blockers, because he was already past most of puberty and on estrogen.

9. I questioned why M. would be recommended for hormone therapy when he did not have a history of gender dysphoria until after he was diagnosed with PANDAS and suffered trauma. The psychologist said, "You have to honor your young person." I replied, "He is not our young person -- he is our child."

10. My husband and I asked to speak to the endocrinologist first to find out about side effects. However, the therapist said we could not see the endocrinologist unless we were ready to get prescriptions for hormones for our son. We said we needed more information.

11. Then a neuropsychologist who was not associated with the gender clinic evaluated our whole family and diagnosed M. with bipolar or possibly dissociative disorder, but not with gender dysphoria. She recommended psychiatric treatment, rather than hormonal treatment without first addressing the other disorders.

12. M. kept demanding hormones because he had been convinced this was what he needed. My husband and I did not follow through on that demand.

However, after M. turned 18 and went away to college, he found a practitioner who prescribed a testosterone suppressor and an estrogen patch. M soon stopped the suppressor because he did not like the effects. He returned home for online

learning in the spring, went on antibiotics and his health improved. He then discontinued the estrogen patch.

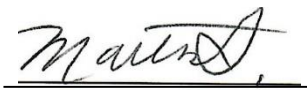
14. The availability of medical and surgical interventions for minors puts parents in a terrible bind. Parents are put in a difficult position when we have a mentally and physically ill child who is convinced that he needs an intervention recommended by a physician that is not based on sound science.

15. This experience has damaged both my and M.'s trust in the medical community. If physicians are legally prevented from recommending these interventions, then parents will not be not put at cross purposes with their child and the medical community.

16. The VCCAP Act prevents coercive manipulation and potential harm against Alabama's vulnerable children and should be upheld for the protection of children and their families.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: April 28, 2022.



Martha S. (pseudonym)

DEFENDANT'S EXHIBIT 35

UNITED STATES DISTRICTCOURT
FOR THE MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER; BRIANNA BOE, individually and on behalf of her minor son, MICHAEL BOE; JAMES ZOE, individually and on behalf of his minor son, ZACHARY ZOE; MEGAN POE, individually and on behalf of her minor daughter, ALLISON POE; KATHY NOE, individually and on behalf of her minor son, CHRISTOPHER NOE; JANE MOE, Ph.D; and RACHEL KOE, M.D.

Plaintiffs,

v.

KAY IVEY, in her official capacity As Governor of the State of Alabama; STEVE MARSHALL, in his official capacity as Attorney General of the State of Alabama; DARYL D. BAILEY, in his official capacity as District Attorney for Montgomery County; C. WILSON BAYLOCK, in his official capacity as District Attorney for Cullman County; JESSICA VENTIERE, in her official capacity as District Attorney for Lee County; TOM ANDERSON in his official capacity as District Attorney for the 12th Judicial Circuit; and DANNY CARR, in his official Capacity as District Attorney for Jefferson County.

Defendants

CIVIL ACTION # 2:22-cv-00184-LCB-SRW

Declaration of KathyGrace Duncan In Support of Defendants' Opposition to Plaintiffs' Motion for Preliminary Injunction

I, KathyGrace Duncan, declare as follows:

1. I am over the age of 18 years and am not a party to this action. I have actual knowledge of the following facts and if called upon to testify to them could and would do so competently. I am submitting this Declaration in support of Defendants' opposition to Plaintiffs' Motion for a Temporary Restraining Order and Preliminary Injunction.

2. Alabama's Vulnerable Child Compassion and Protection Act ("VCCAP") is a necessary, potentially life-saving law that will protect vulnerable children and their parents from the heartbreaking regret, irreversible physical changes, sexual dysfunction and emotional pain that I have experienced after undertaking medical and surgical interventions aimed at "transitioning" me from a female to a "male."

3. From a very young age, I was what is called today "gender non-conforming." I preferred male clothing, I thought I was a "boy" and I wanted to live as one.

4. I grew up in a dysfunctional family in which my mother was often the victim of my father's emotional and verbal abuse. As a result I internalized the message that "my dad would love me if I were a boy."

5. Sexual abuse by a family member between the ages of 10 and 12 further convinced me that being a girl meant being unsafe and unlovable.

6. In sixth grade, I learned about female to male transsexuals. I believed that my distress was caused by not having the "right" body and the only way to live a normal life was to medically transition and become a heterosexual male.

7. At age 19, I began living as a man named Keith and went to a therapist who formally diagnosed me with gender dysphoria. I began testosterone and a year later had a mastectomy. At the time, I believed it was necessary so that what I saw in the mirror matched what I felt on the inside.

8. I never viewed my condition as touching on mental health issues, and neither did the therapist who diagnosed me. The question of whether my self-perception and desire to transition was related to her mental health issues was never explored.

9. After 11 years passing as a man and living what I thought was a relatively "happy" and stable life (which included having a number of girlfriends), I realized that I was living a lie built upon years of repressed pain and abuse. Hormones and surgery had not helped me resolve underlying issues of rejection, abuse, and sexual assault. I came to understand that my desire to live as a man was a symptom of deeper unmet needs.

10. With the help of life coaches and a supportive community, I returned to my female identity and began addressing the underlying issues that had been hidden

in my attempt to live as a man. I experienced depression that I had repressed for years and grieved over the irreversible changes to my body.

11. If someone had walked with me through my feelings instead of affirming my desire to transition, then I would have been able to address my issues more effectively and not spend so many years making and recovering from a grave mistake.

12. Alabama's VCCAP Act is necessary and essential because it will give children and adolescents a chance to walk through their feelings and address their underlying issues effectively without being pulled onto the affirmation conveyor belt. Hormones and surgery are irreversible decisions that children and adolescents are incapable of making.

13. VCCAP is also necessary to protect parents from the coercion and manipulation of their confused children and over-zealous medical practitioners who try to convince parents to consent to the treatments by threatening that their children might be removed from their care or even commit suicide. If the treatments are banned until the children reach majority, then children and health care providers will not be able to use the treatments as a bargaining chip, but will have to explore other alternatives for helping the children.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: April 29, 2022.

KathyGrace Duncan

DEFENDANT'S EXHIBIT 36

UNITED STATES DISTRICTCOURT
FOR THE MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER; BRIANNA BOE, individually and on behalf of her minor son, MICHAEL BOE; JAMES ZOE, individually and on behalf of his minor son, ZACHARY ZOE; MEGAN POE, individually and on behalf of her minor daughter, ALLISON POE; KATHY NOE, individually and on behalf of her minor son, CHRISTOPHER NOE; JANE MOE, Ph.D; and RACHEL KOE, M.D.

Plaintiffs,

v.

KAY IVEY, in her official capacity As Governor of the State of Alabama; STEVE MARSHALL, in his official capacity as Attorney General of the State of Alabama; DARYL D. BAILEY, in his official capacity as District Attorney for Montgomery County; C. WILSON BAYLOCK, in his official capacity as District Attorney for Cullman County; JESSICA VENTIERE, in her official capacity as District Attorney for Lee County; TOM ANDERSON in his official capacity as District Attorney for the 12th Judicial Circuit; and DANNY CARR, in his official Capacity as District Attorney for Jefferson County.

Defendants

CIVIL ACTION # 2:22-cv-00184-LCB-SRW

Declaration of Jeanne Crowley*
In Support of Defendants'
Opposition to Plaintiffs'
Motion for Preliminary Injunction

I, Jeanne Crowley[1] declare as follows:

1. I am over the age of 18 years and am not a party to this action. I have actual knowledge of the following facts and if called upon to testify to them could and would do so competently. I am submitting this Declaration in support of Defendants' opposition to Plaintiffs' Motion for a Temporary Restraining Order and Preliminary Injunction.

2. Alabama's Vulnerable Child Compassion and Protection Act ("VCCAP") provides parents necessary protections against manipulation and coercion on the part of health care providers and children to comply with demands for medical and surgical interventions aimed at "affirming" a child's professed discordant gender identity under threats of alienation or loss of a child to suicide and without providing parents and children the information needed to understanding the long-term implications and potential harms to children's developing bodies.

3. Because there is no such parent and child-protective law in place in my home state, I have been subjected to coercion, manipulation, alienation from my daughter and blatant disregard for my parental right to make medical and mental health decisions for my child. The VCCAP will prevent parents and children in Alabama from suffering similar harms. It will actually restore the rights of all

[1] Declarant is submitting this Declaration using a pseudonym to protect the privacy of her children and other family members.

parents, not just those who agree with demands for "gender-affirming" medical interventions, to make medical and mental health care decisions for their children that will protect their children's developing bodies and long-term mental health.

4. My husband and I were repeatedly told that the puberty blockers our pre-teen daughter, M., was clamoring for were the answer for her anxiety and distress about her changing body. We were advised that children like M. had high rates of suicide and self-harm and puberty blockers would help by stopping the development of secondary sex characteristics that cause children distress and "give the children time to explore their identity."

5. Gender-affirming mental health and medical professionals assured us that acceding to our daughter's demand for puberty blockers was necessary for her mental health. We were repeatedly assured that the puberty blockers were nothing more than a "pause button" and completely reversible. We were not told that these treatments could cause harm to our child's developing bones or that there were no clinical studies establishing them to be safe and effective as a "treatment" for gender dysphoria in children.

6. Based on these assurances we consented to M. receiving a long-lasting puberty-blocking implant. Once the implant was in place, there was no follow up. I had to initiate contact with the clinic to replace the implant and get necessary lab work.

7. M. previously had psychological evaluations that revealed depression, Autism Spectrum Disorder (ASD) with sensory issues, dyslexia, and dysgraphia. M. had also experienced social trauma. However, none of these issues was addressed by health care professionals once they determined M. had gender dysphoria. Nor did they offer any other treatment options.

8. I learned through my own research that puberty blockers were shown to cause loss of bone density and diminished cognitive development. Healthcare professionals did not inform my husband and me about those harms. When we raised the issue, the doctors responded that they have been prescribing the blockers for many years to treat precocious puberty and the reported bone loss was "nothing to worry about."

9. I had a bone density scan done for M. It revealed that M. has an 11 percent loss of bone density in one hip, 14 percent loss in the other, and a 7 percent loss in the lumbar region. She has developed osteopenia at a time in her life when her bone density should be increasing and her body building a reservoir of strong developing bones as an important protection against osteoporosis in adulthood.

10. When my husband and I confronted the physician to have the puberty blocker implant removed, the doctor recommended that M. continue on to cross-sex hormones, *i.e.*, testosterone. We were not informed this would very likely *sterilize*

our child. I declined, pointing out to the doctor that it is estrogen, not testosterone, that improves bone density.

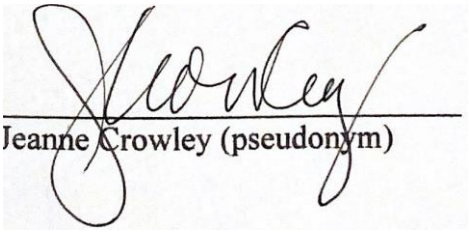
11. Throughout the time that M. was on puberty blockers, we had difficulty finding a therapist to explore M.'s underlying mental health issues. Therapists were unwilling to address anything other than affirming M. as transgender. M. is currently improving working with a psychotherapist we were finally able to find that is willing to explore the underlying issues with M. However, she continues to have loss of bone density that will significantly affect her physical health and growth and having lasting effects possibly for the rest of her life.

12. The availability of these medical interventions for a pre-teen girl distressed by changes in her body meant that neither M nor her healthcare providers would consider other alternatives. VCCAP can overcome that obstacle for parents in Alabama.

13. The VCCAP Act prevents coercive manipulation and potential harm against Alabama's vulnerable children and should be upheld for the protection of children and their families.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: April 28, 2022.



DEFENDANT'S EXHIBIT 37

UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER; BRIANNA BOE, individually and on behalf of her minor son, MICHAEL BOE; JAMES ZOE, individually and on behalf of his minor son, ZACHARY ZOE; MEGAN POE, individually and on behalf of her minor daughter, ALLISON POE; KATHY NOE, individually and on behalf of her minor son, CHRISTOPHER NOE; JANE MOE, Ph.D; and RACHEL KOE, M.D.

Plaintiffs,

v.

KAY IVEY, in her official capacity As Governor of the State of Alabama; STEVE MARSHALL, in his official capacity as Attorney General of the State of Alabama; DARYL D. BAILEY, in his official capacity as District Attorney for Montgomery County; C. WILSON BAYLOCK, in his official capacity as District Attorney for Cullman County; JESSICA VENTIERE, in her official capacity as District Attorney for Lee County; TOM ANDERSON in his official capacity as District Attorney for the 12th Judicial Circuit; and DANNY CARR, in his official Capacity as District Attorney for Jefferson County.

Defendants

CIVIL ACTION # 2:22-cv-00184-LCB-SRW

Declaration of Ted H Halley In Support of Defendants' Opposition to Plaintiffs' Motion for Preliminary Injunction

I, Ted H Halley, declare as follows:

1. I am over the age of 18 years and am not a party to this action. I have actual knowledge of the following facts and if called upon to testify to them could and would do so competently. I am submitting this Declaration in support of Defendants' opposition to Plaintiffs' Motion for a Temporary Restraining Order and Preliminary Injunction.

2. Alabama's Vulnerable Child Compassion and Protection Act ("VCCAP") is a necessary, potentially life-saving law that will protect vulnerable children and their parents from the heartbreaking regret, irreversible physical changes, sexual dysfunction and emotional pain that I have experienced after undertaking medical and surgical interventions aimed at "transitioning" me from a male to a "female."

3. Like many of the children who seek the medical and surgical interventions banned by VCCAP, I experienced distress about my sex beginning in my pre-teens. I wanted God to make me a girl and at age eight I fantasized about cross-dressing in my mother's clothes.

4. I continued to experience feelings of wanting to be a woman and struggling with my gender identity between adolescence and age 50, but as a married father of 5 and active duty member of the Air Force I suppressed those feelings.

5. At age 50 I began attending a heterosexual cross-dressing group, and that confirmed for me that I wanted to go further to fully transition.

6. I had facial feminization surgery in 2009 and a second feminization surgery in 2010.

7. In 2010, I also began taking estrogen and spironolactone, which is a testosterone suppressor.

8. In December 2011, I had genital reassignment surgery in which my male genitalia was removed and a "neo vagina" was created. Dilation of the "neo vagina" was very painful for about six months. This surgery is irreversible. I am no longer able to experience sexual sensation and pleasure and have a life-long sexual dysfunction.

9. In December 2011 I also had my name legally changed to "Teresa" and the gender marker on my birth certificate changed.

10. I transitioned to a female identity at work and had breast augmentation surgery in 2012.

11. I was highly functioning and happy with my transition for a few years.

12. After being on cross-sex hormones and living as a female for twelve years, however, I began to see the irrationality of what I had done. I began to question what I had done and had an internal realization that what I was pretending to be was not real.

13. The internal incongruity grew by the day to the point that I began to become suicidal. I could no longer live what was essentially a lie any longer. I became severely depressed. The only thing that kept me alive was that my granddaughter was living with me.

14. In March 2021 I made the decision to detransition. I re-connected with my male biology, re-established my male identity, and re-established relationships with others as a male.

15. Detransitioning meant that I stopped taking hormones. I removed the breast augmentation and changed my gender marker and name back to male. I did what I could to change my appearance, cut my hair, stopped wearing make-up and women's clothes, but I could not undo the facial surgery or the genital surgery. I could not get back the lost organs, sensations, enjoyment, or functionality.

16. I have no regret detransitioning to my biological sex and wish I had done it sooner. I deeply regret having wasted years of my life, the damage to my body, the permanent loss to my body, the exorbitant cost of these treatments, and the damaged relationships. I think I would dead if I had not detransitioned. The depression was so severe, I think I would have taken my life.

17. VCCAP is necessary and essential because children and adolescents are incapable of making these irreversible decisions. In retrospect, I do not believe I

made a sound decision that I could live with the rest of my life, and I was 50 years old at the time. It is impossible for any adolescent to do so.

18. I am a living example that gender identity is not innate or immutable, like one's sex, race or ethnicity. I had been convinced that I was a "female" born in a male body. I had felt that way since childhood. Based on that consistent and persistent conviction, I fully transitioned in every possible way to live and appear as a woman. Now I realize that it was all a lie, a mental state of mind that was subject to change, and that it didn't solve the internal consternation and deeper emotional problems.

19. VCCAP will help spare my fellow Alabama citizens from similar loss and distress.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: April 28, 2022.

Ted H Halley

DEFENDANT'S EXHIBIT 38

UNITED STATES DISTRICTCOURT
FOR THE MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER; BRIANNA BOE, individually and on behalf of her minor son, MICHAEL BOE; JAMES ZOE, individually and on behalf of his minor son, ZACHARY ZOE; MEGAN POE, individually and on behalf of her minor daughter, ALLISON POE; KATHY NOE, individually and on behalf of her minor son, CHRISTOPHER NOE; JANE MOE, Ph.D; and RACHEL KOE, M.D.

Plaintiffs,

v.

KAY IVEY, in her official capacity As Governor of the State of Alabama; STEVE MARSHALL, in his official capacity as Attorney General of the State of Alabama; DARYL D. BAILEY, in his official capacity as District Attorney for Montgomery County; C. WILSON BAYLOCK, in his official capacity as District Attorney for Cullman County; JESSICA VENTIERE, in her official capacity as District Attorney for Lee County; TOM ANDERSON in his official capacity as District Attorney for the 12th Judicial Circuit; and DANNY CARR, in his official Capacity as District Attorney for Jefferson County.

Defendants

CIVIL ACTION # 2:22-cv-00184-LCB-SRW

Declaration of Kellie C.*
In Support of Defendants'
Opposition to Plaintiffs'
Motion for Preliminary Injunction

I, Kellie C.[1] declare as follows:

1. I am over the age of 18 years and am not a party to this action. I have actual knowledge of the following facts and if called upon to testify to them could and would do so competently. I am submitting this Declaration in support of Defendants' opposition to Plaintiffs' Motion for a Temporary Restraining Order and Preliminary Injunction.

2. Alabama's Vulnerable Child Compassion and Protection Act ("VCCAP") provides parents necessary protections against manipulation and coercion on the part of health care providers, ex-spouses and confused children to comply with demands for medical and surgical interventions aimed at "affirming" a child's professed discordant gender identity under threats of alienation or loss of a child to suicide.

3. Because there is no such parent and child-protective law in place in my home state, I have been subjected to alienation from my daughter, coercion, manipulation, and blatant disregard for my parental right to make sound medical and mental health decisions for my child. The VCCAP will prevent parents and children in Alabama from suffering similar harms. It will actually restore the rights of all parents, not just those who agree with demands for "gender-affirming" medical

[1] Declarant is submitting this Declaration using a pseudonym to protect the privacy of her children and other family members.

interventions, to make medical and mental health care decisions for their children in accordance with their natural, healthy development.

4. My daughter, D., became involved in fan fiction at age 11, when she began puberty. By age 13, D. had diagnosed herself with gender dysphoria and began identifying as a 17-year-old male character from Harry Potter. Every year since then, D. has celebrated the birthday of the fictional identity, and is now, at age 17, identifying as a 23-year-old male.

5. D. underwent a psychiatric evaluation which found that she is delusional and incapable of taking care of herself, on the autism spectrum, has OCD and possibly ADHD, but is not psychotic. The evaluation team admits that D. is identifying as a 23-year-old man and is proclaiming that she has Dissociative Identity ("multiple personality") Disorder, but that they do not believe she has DID. Instead, the psychiatric team believes that D. has researched DID and is using it as a maladaptive coping tool for working through the childhood trauma of being sexually assaulted at age 13 or 14, something I just recently learned about.

6. D. is in a residential treatment center. The treatment team has not engaged in therapy with D. to address her underlying issues. Instead, they have embraced her delusion that she is a 23-year-old fictional male character as a transgender identity. The therapists reiterate that they want D. to feel "safe" so they will not address underlying issues, including the sexual assault, unless D. wants to.

7. D. has asked for puberty blockers and testosterone. Despite her myriad co-morbidities and unaddressed sexual trauma, the treatment team say that D. is ready for "gender-affirming" medical interventions. The therapists and D.'s father have told her the only thing standing in the way of her getting those interventions is my refusal to consent.

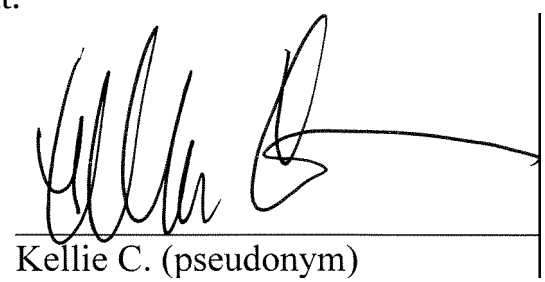
8. The therapists and psychologists have told me that I should do my own research, but if I do not agree with them I "will have a dead daughter instead of a 'live son.'" I am constantly told that I need to "get on board" with what D wants.

9. The VCCAP Act is an important step in preventing harm to vulnerable children. Making these medical interventions unavailable to children will prevent the harms of these interventions on the children and the harms inflicted on parents fighting to protect their mentally disturbed children from irresponsible health care providers.

10. The VCCAP Act prevents coercive manipulation and potential harm against Alabama's vulnerable children and should be upheld for the protection of children and their families.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: April 28, 2022.



Kellie C. (pseudonym)

DEFENDANT'S EXHIBIT 39

UNITED STATES DISTRICTCOURT
FOR THE MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER; BRIANNA BOE, individually and on behalf of her minor son, MICHAEL BOE; JAMES ZOE, individually and on behalf of his minor son, ZACHARY ZOE; MEGAN POE, individually and on behalf of her minor daughter, ALLISON POE; KATHY NOE, individually and on behalf of her minor son, CHRISTOPHER NOE; JANE MOE, Ph.D; and RACHEL KOE, M.D.

Plaintiffs,

v.

KAY IVEY, in her official capacity As Governor of the State of Alabama; STEVE MARSHALL, in his official capacity as Attorney General of the State of Alabama; DARYL D. BAILEY, in his official capacity as District Attorney for Montgomery County; C. WILSON BAYLOCK, in his official capacity as District Attorney for Cullman County; JESSICA VENTIERE, in her official capacity as District Attorney for Lee County; TOM ANDERSON in his official capacity as District Attorney for the 12th Judicial Circuit; and DANNY CARR, in his official Capacity as District Attorney for Jefferson County.

Defendants

CIVIL ACTION # 2:22-cv-00184-LCB-SRW

Declaration of Gary Warner In Support of Defendants' Opposition to Plaintiffs' Motion for Preliminary Injunction

I, Gary Warner, declare as follows:

1. I am over the age of 18 years and am not a party to this action. I have actual knowledge of the following facts and if called upon to testify to them could and would do so competently. I am a resident of Alabama and the father of a daughter who committed suicide after being placed on some of the medical interventions that are the subject of Alabama's Vulnerable Child Compassion and Protection Act ("VCCAP"). I am submitting this Declaration in support of Defendants' opposition to Plaintiffs' Motion for a Temporary Restraining Order and Preliminary Injunction.

2. If VCCAP had been in effect in 2013 then my 18-year-old daughter could not have been offered testosterone as a means of "affirming" what she had been led to believe was her "true" identity as a male after suffering horrific sexual abuse. She would have been provided with other options for dealing with her psychological and emotional pain and perhaps gotten the therapy she needed instead of spiraling into despair and suicide.

3. My daughter, K., struggled with health issues, including kidney stones for much of her life. Beginning at age 11 she was the subject of bullying and cyber-bullying at school, much of it of a sexual nature. This increased her anxiety and made her fear for her safety. One of the incidents during high school included threats of dragging her into the boys' bathroom and forcing her to perform sex acts.

4. K. was under the care of professional counselors and psychiatrists for most of her teen years. She was diagnosed with Borderline Personality Disorder and at one point after the bullying incidents was diagnosed with PTSD.

5. Shortly after turning 18, K. was drugged and raped by the older brother of one of her friends while attending a lake party. Because the rapist was a prominent citizen and K was viewed as a troubled teen, there was no criminal prosecution.

6. After the rape, K. began distancing herself from former romantic partners. Her friends insisted that the reason she no longer wanted to be romantically involved was because she really was a man trapped in a woman's body. K. began wearing male clothing and adopted a male name.

7. One of her friends announced that she was transgender at about the same time.

8. K.'s friends who insisted K. was really a man trapped in a woman's body recommended that she see Keith Abrams, a clinical psychologist in Birmingham and avid promoter of gender transition treatments for trans-identifying youth. Abrams recommended that K begin taking testosterone to "help her transition."

9. We attended a session with Abrams. K. wanted him to explain to us why it was advisable for K to move forward with testosterone. He did not provide us with information that would have allowed us or K. to understand the irreversible

nature of these treatments or their long-term effects. He simply told us we needed to "support" our daughter's decision. We did not give informed consent.

10. There was no attempt to deal with the underlying trauma and co-morbidities K was experiencing, but just a push to begin testosterone.

11. K became fixated on the idea that she was born the wrong gender and rejected any counsel or suggestion that did not align with that belief.

12. She did begin testosterone and it exacerbated her anxiety and also transformed her into an angry, threatening person. She threatened to kill her mother to the point that her mother slept with the door locked from fear. Prior to this K. had never been a violent or angry person.

13. Testosterone was not the solution K had been promised. It did nothing to help her emotional pain, which escalated to the point that she took her own life at age 18.

14. The total ban on medical interventions on children age 19 and under enacted under VCCAP is necessary because, like K., I believe most of the young people dealing with gender dysphoria have underlying trauma and/or mental health problems that are not being addressed so long as the medical transitions interventions are available to young people. The availability of these treatments is causing physicians to ignore these underlying causes and empowering young people to deny biological reality to their harm.

15. VCCAP is also especially necessary because the medical community not giving informed consent – they are cheerleading a lifestyle. Rather than giving young people the professional help they need, doctors are acting as activists pushing parents to consent by claiming this is a medically advisable choice, thereby driving the children toward an irreversible life change.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: April 29, 2022.

Gary Warner (Apr 29, 2022 22:11 MDT)

Gary Warner

DEFENDANT'S EXHIBIT 40

IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER, *et al.*,	)	
Plaintiffs,	)	
v.	)	Civil Action No. 2:22-cv-184-LCB
KAY IVEY, in her official capacity as Governor of Alabama, *et al.*,	)	
Defendants.	)	

DECLARATION OF EDMUND G. LACOUR JR. IN SUPPORT OF DEFENDANTS' RESPONSE IN OPPOSITION TO PLAINTIFFS' MOTION FOR PRELIMINARY INJUNCTION (DOC. 7)

I, Edmund G. LaCour Jr., hereby declare as follows:

1. I am over 18 years of age and am competent to make this declaration.

2. I am the Solicitor General of the State of Alabama and one of the attorneys for Defendants in the above-captioned matter.

3. Attached to this declaration is a copy of an email exchange from April 15, 2022, between myself and Melody H. Eagan, lead counsel for Plaintiffs in the above-captioned matter.

4. The exhibit is a true and correct copy of what it purports to be.

5. I declare under the penalty of perjury that the foregoing is true and correct.

Executed on May 2, 2022

/s/ Edmund G. LaCour Jr.
Counsel for Defendants

LaCour, Edmund

From: LaCour, Edmund
Sent: Friday, April 15, 2022 4:34 PM
To: Melody H. Eagan
Cc: Jeffrey P. Doss; Amie A. Vague; Bowdre, Barrett; Davis, Jim
Subject: RE: Ladinsky v. Ivey, et al. - addendum to our conversation

Melody,

Thank you for your call earlier and the follow-up email. We will note that both sets of plaintiffs consent to consolidation. Have a great weekend.

Best,
Eddie

Edmund LaCour
Solicitor General
Office of Alabama Attorney General Steve Marshall
Direct: 334-353-2196
Fax: 334-353-8400

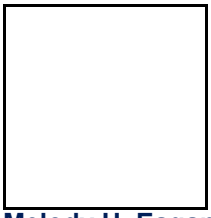
From: Melody H. Eagan <meagan@lightfootlaw.com>
Sent: Friday, April 15, 2022 4:20 PM
To: LaCour, Edmund <Edmund.LaCour@AlabamaAG.gov>
Cc: Jeffrey P. Doss <jdoss@lightfootlaw.com>; Amie A. Vague <avague@lightfootlaw.com>
Subject: Ladinsky v. Ivey, et al. - addendum to our conversation

Eddie,

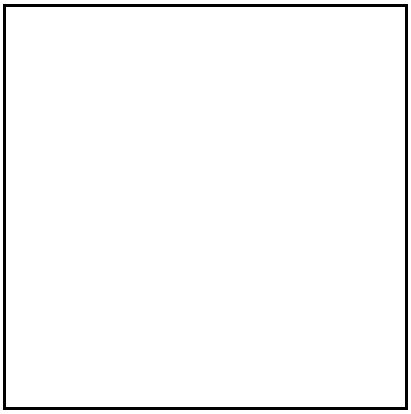
One other thing I should have mentioned. I spoke with counsel for the Walker plaintiffs, and they consent to consolidation. So you probably want to phrase your motion as an unopposed motion, and also put in there that counsel for the Walker plaintiffs also consent to consolidation.

Call me if questions.

Thanks,
Melody



Melody H. Eagan
Attorney



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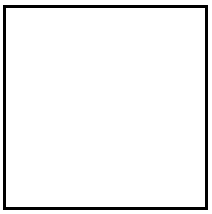

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