ACT #2022 - 289

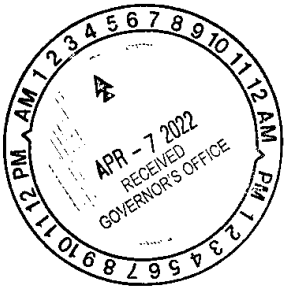
SB184

216600-4

By Senators Shelnutt and Allen

RFD: Healthcare

First Read: 03-FEB-22



Doe Pls' Trial Ex.

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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

Mac McCutcheon

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

Kay Ivey

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 Judy 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)

PL010542

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

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

[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

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

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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,

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

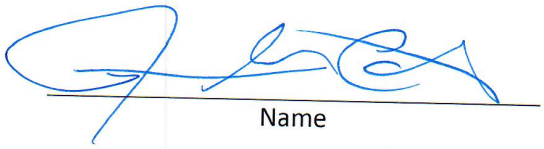
Peer-reviewed article:

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.



Name

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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
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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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7. Cantor, J. M. (2012). The errors of Karen Franklin's *Pretextuality* [Commentary]. *International Journal of Forensic Mental Health, 11,* 59–62. doi: 10.1080/14999013.2012.672945
8. Cantor, J. M., & Blanchard, R. (2012). White matter volumes in pedophiles, hebephiles, and teleiophiles [Letter to the Editor]. *Archives of Sexual Behavior, 41, 749–752.* doi: 10.1007/s10508-012-9954-2
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.

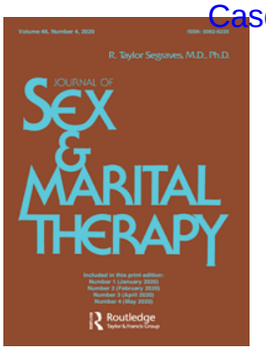
Appearances and Interviews

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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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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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

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2006	Tercica MS301-	study completed 2008
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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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Associate Professor of Pediatrics, Endocrinology and Diabetes
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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
16. Hertel J, Struthers H, Horj CB, Hruz PW. A structural basis for the acute effects of HIV protease inhibitors on GLUT4 intrinsic activity. *J Biol Chem*. 2004;279(53):55147-52. doi:10.1074/jbc.M410826200 PMCID:PMC1403823 PMID:15496402
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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26. Gazit V, Weymann A, Hartman E, Finck BN, Hruz PW, Tzekov A, Rudnick DA. Liver regeneration is impaired in lipodystrophic fatty liver dystrophy mice. *Hepatology*. 2010;52(6):2109-17. doi:10.1002/hep.23920 PMCID:PMC2991544 PMID:20967828
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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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)

[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

[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

[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

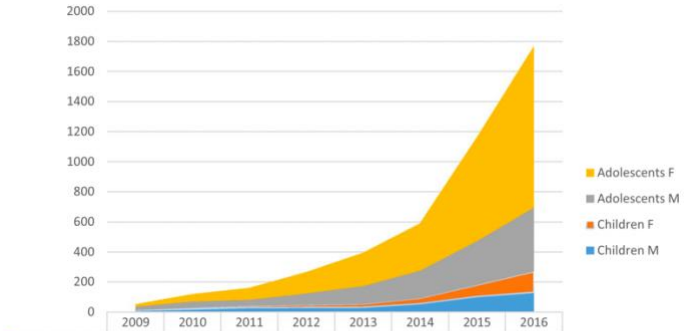
[47] Kaltiala-Heino R, Lindberg N. Gender identities in adolescent population: Methodological issues and prevalence across age groups. *Eur psychiatr*. 2019;55:61-66. doi:10.1016/j.eurpsy.2018.09.003

[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, 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.

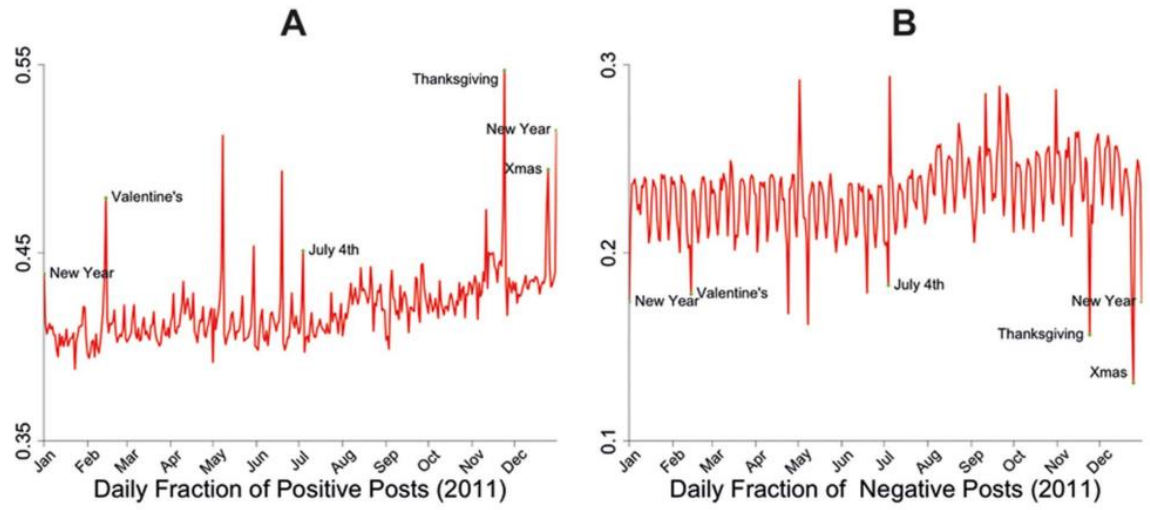

Figure 1

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.

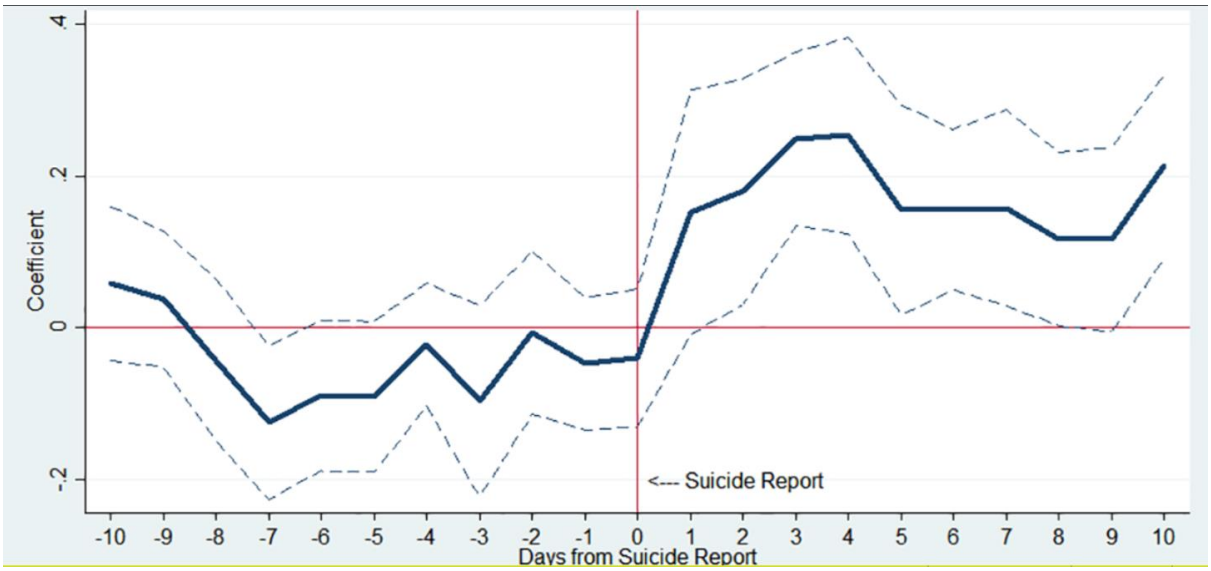

Figure 2[7] Suicide trends before and after reporting of a celebrity suicide

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

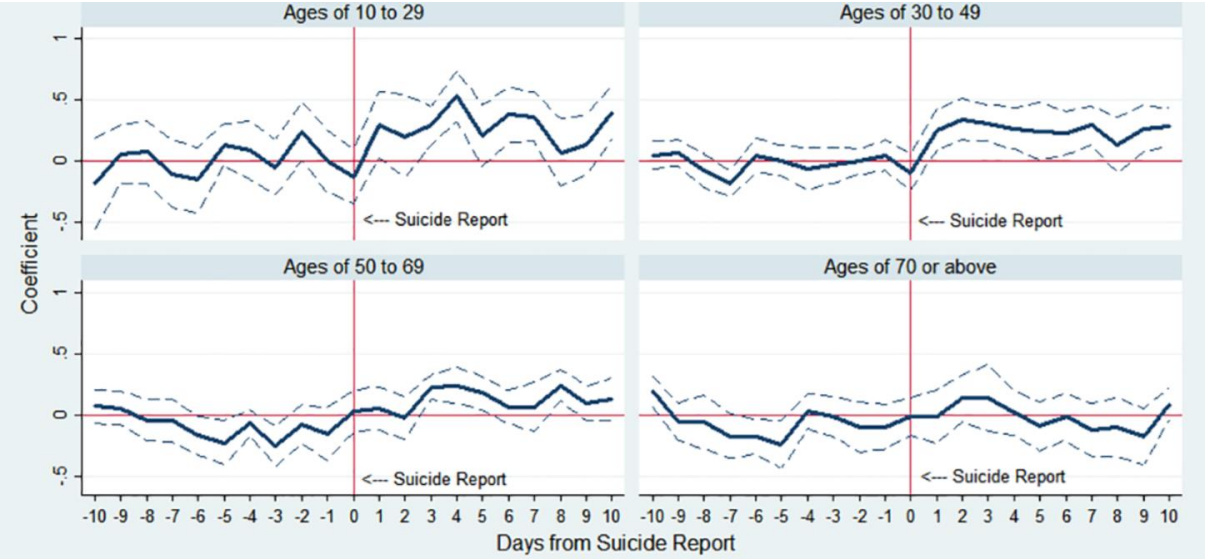

Figure 3 Suicide trends by age group

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?

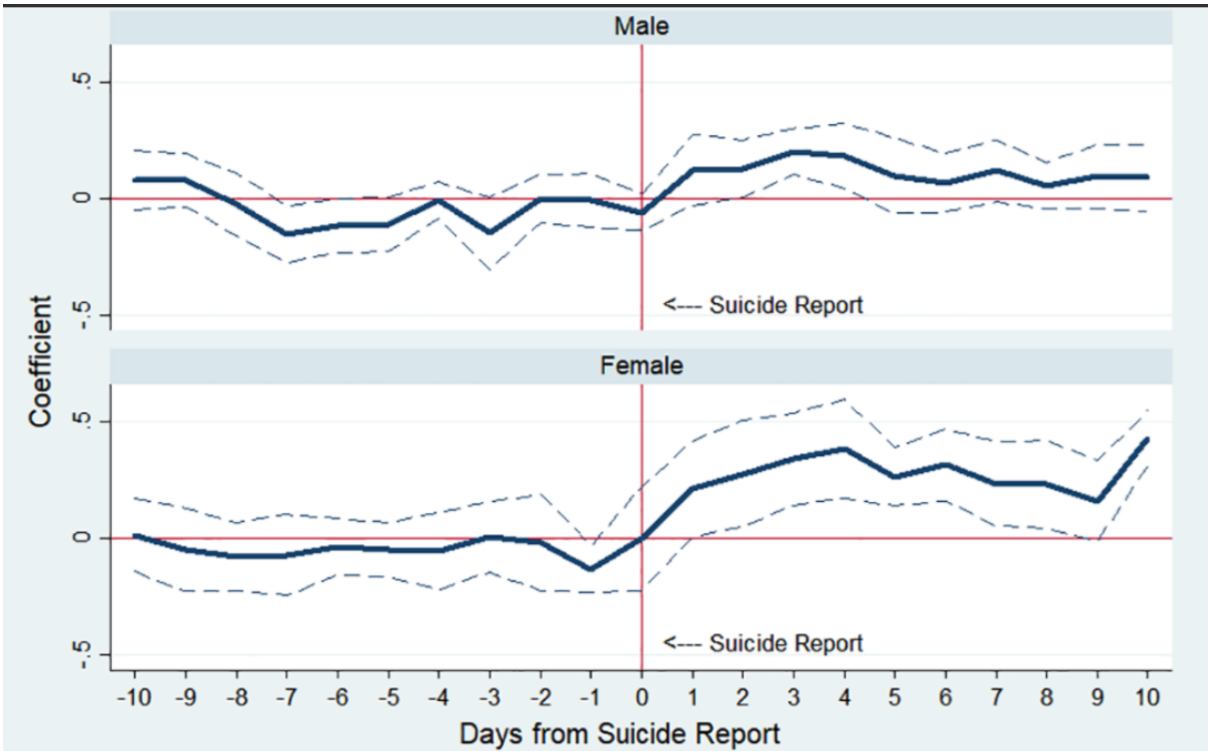

Figure 4 Suicide trends by sex

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/.

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.

[14] Aitken, M., Steensma, T. D., Blanchard, R., VanderLaan, D. P., Wood, H., Fuentes, A. … Zucker, K. J. (2015). Evidence for an altered sex ratio in clinic-referred adolescents with gender dysphoria. *Journal of Sexual Medicine, 12,* 756–763.

Ashley, F. (2019). Shifts in assigned sex ratios at gender identity clinics likely reflect changes in referral patterns [Letter to the Editor]. *Journal of Sexual Medicine, 16,* 948–949.

Becker, I., Gjergji-Lama, V., Romer G., & Möller, B. (2014). Characteristics of children and adolescents with gender dysphoria referred to the Hamburg Gender Identity Clinic [German]. *Prax Kinderpsychol Kinderpsychiatr, 63,* 486–509.

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.

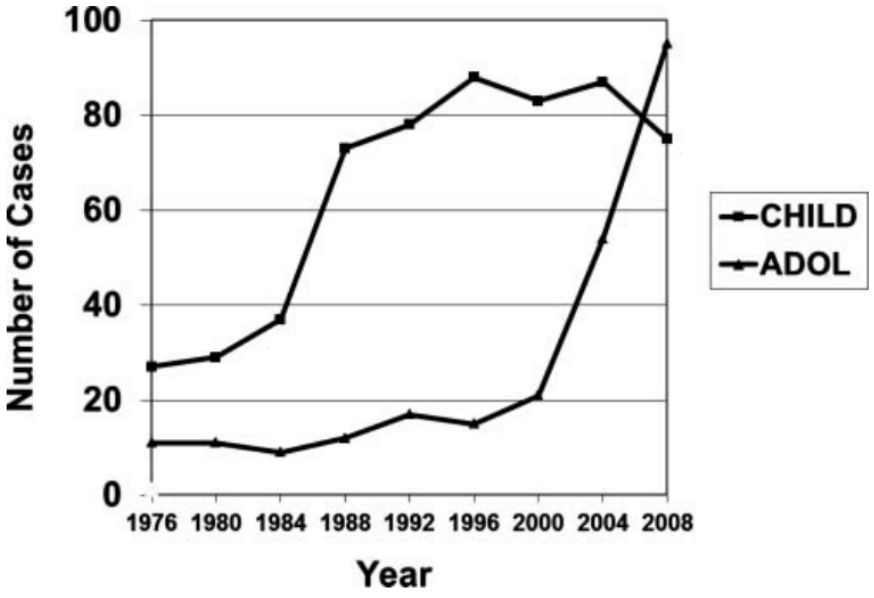

Figure 5 Number of children and adolescents referred to gender clinics 1976-2011)

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).

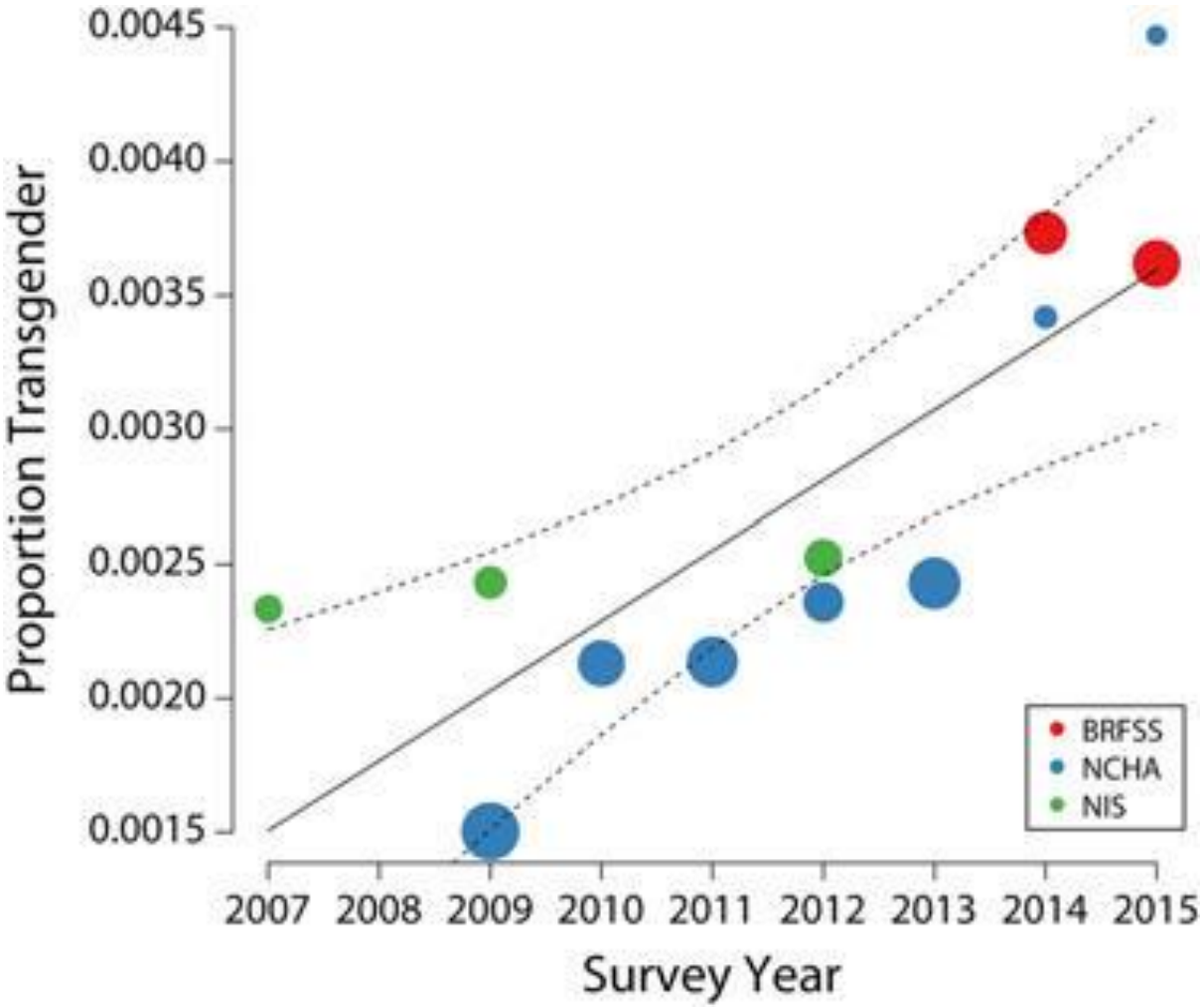

Figure 6[17] [Source: Meerwijk & Sevelius (2017)]

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

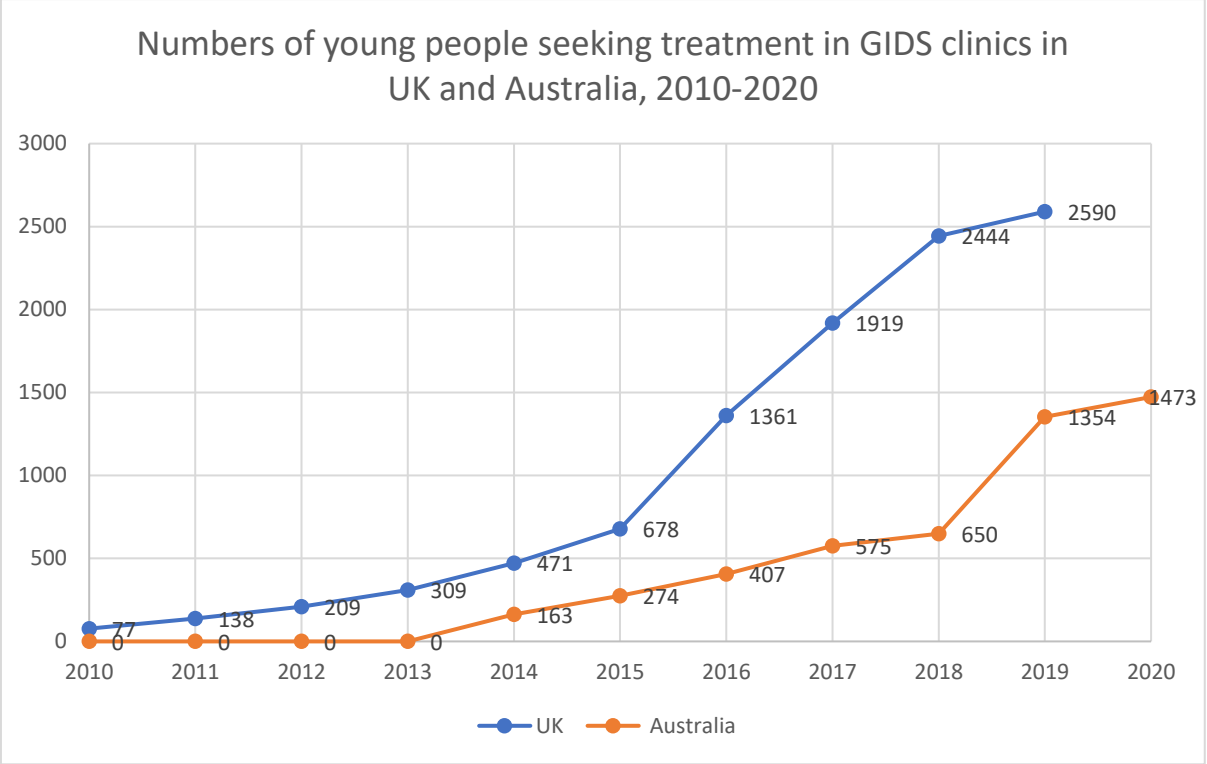

Figure 7

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.

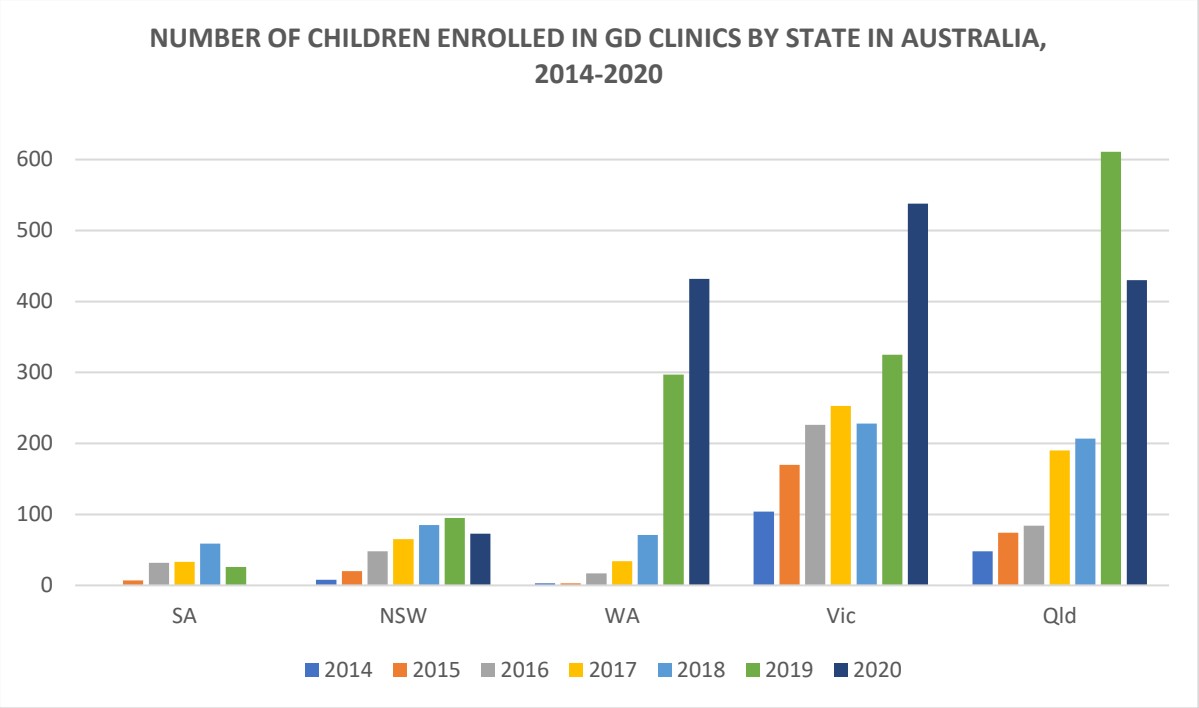

Figure 8

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.

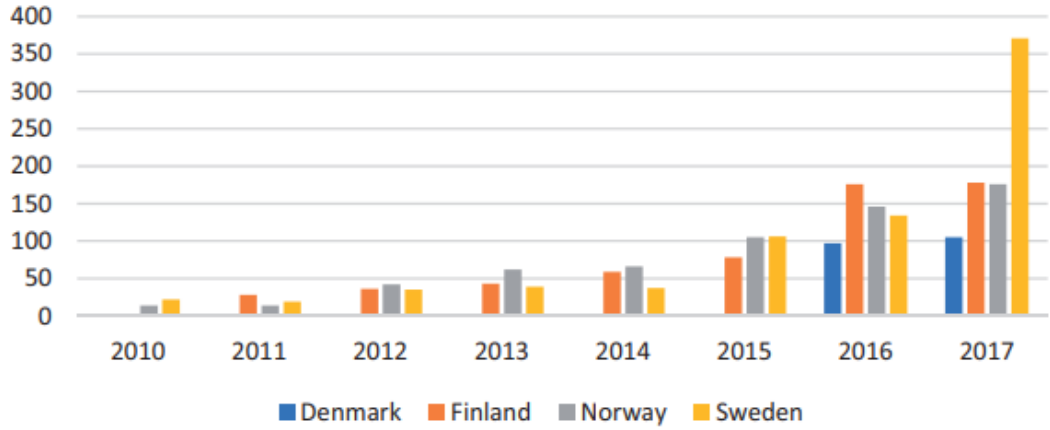

Figure 1. Referrals to child and adolescent gender identity services 2010–2017 in four Nordic countries.

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,

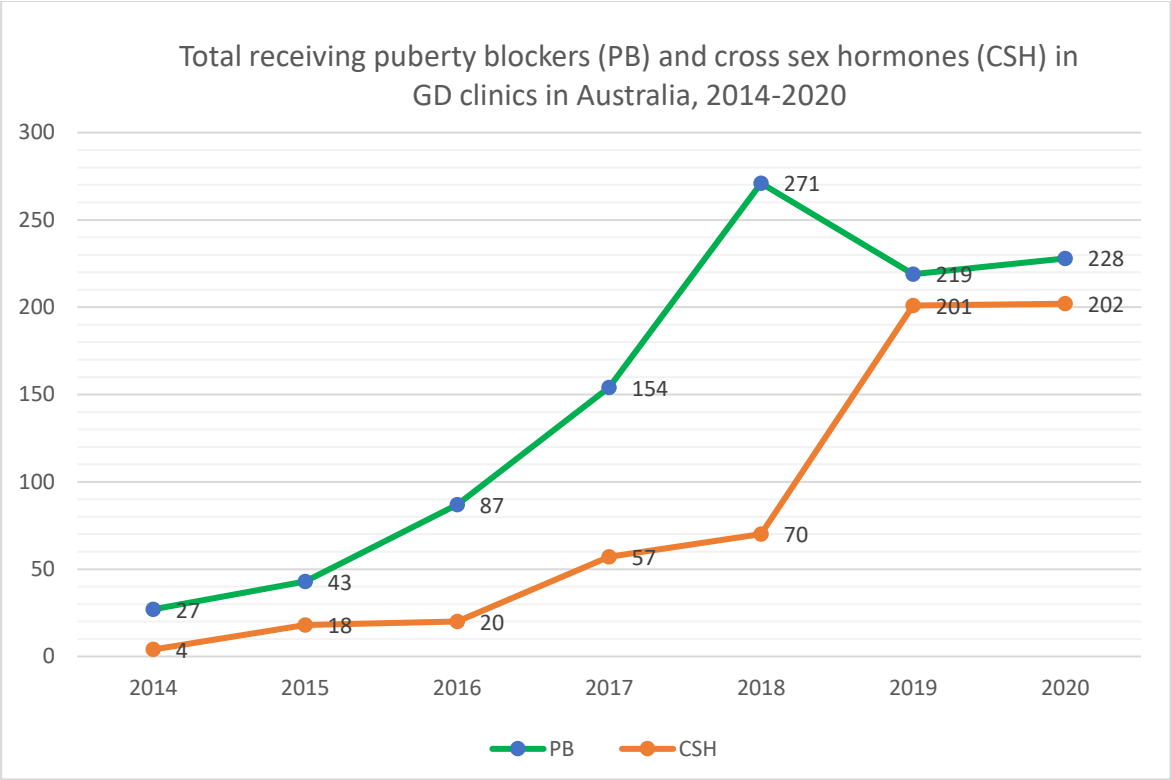

Figure 10

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".

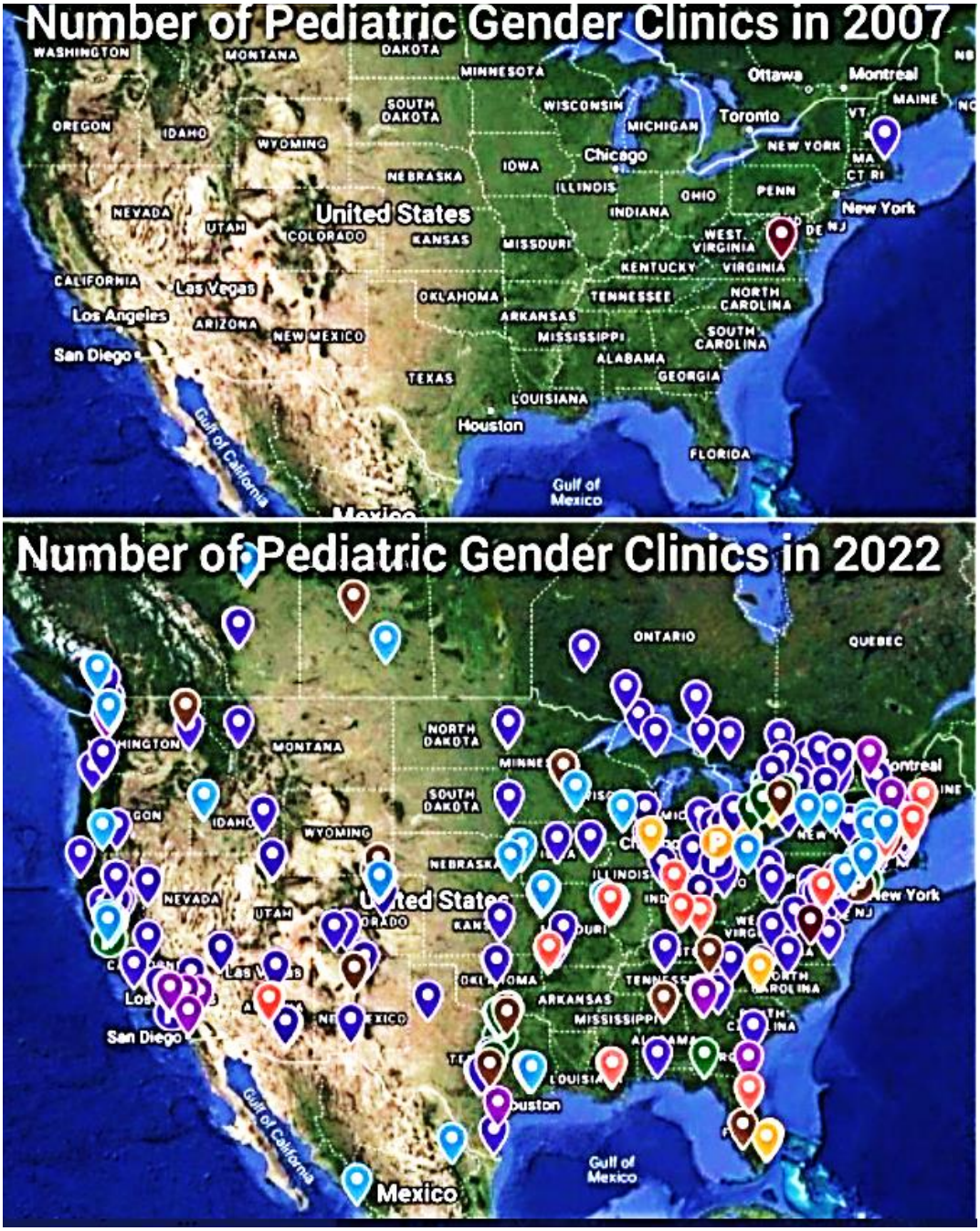

Figure 11 Number of gender clinics in USA and Canada in 2007 and 2022.

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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-

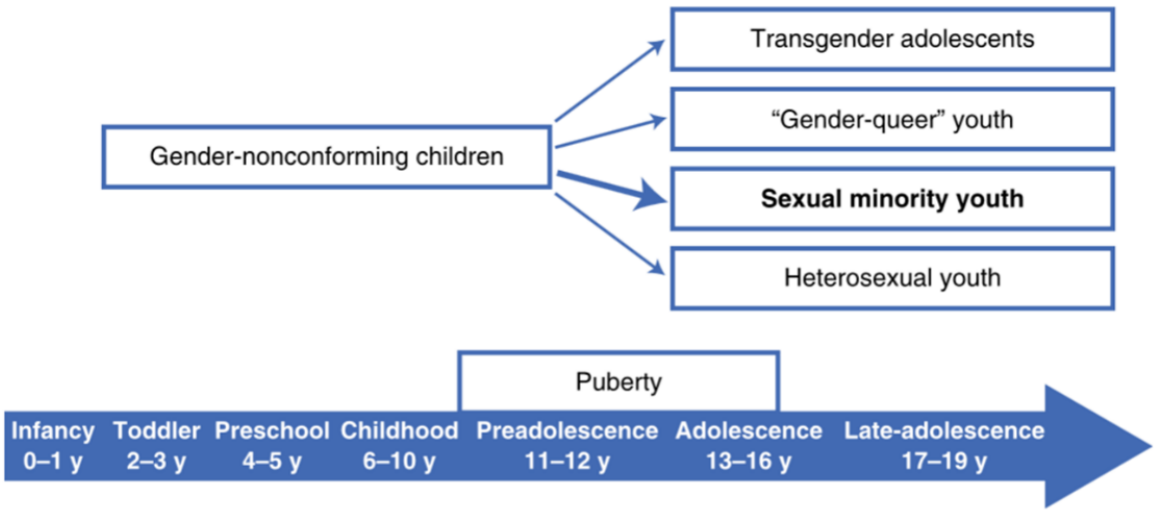
hatred against their bodies. Affirming clinicians collude with the patient's own attacks on the traumatized self by "traumatizing" their young patients' bodies with cross-sex hormones and mutilating surgery. In the hope that transition will restore the young person to an ideal state, medics become omnipotent 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%20Diana%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.

Kenny, D.T. (1989). The effect of grade repetition on the academic performance and social/emotional adjustment of infant and primary students. In Luszcz M. and Nettlebeck T. (Eds). *Psychological development: Perspectives across the lifespan*, pp 261-271. North Holland: Elsevier Science Publisher B.V.

(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.

Kenny, D.T. & Lennings, C. (2007). *Provisional sentencing of serious young offenders.* NSW Sentencing Council. Department of the Attorney General.

Kenny, D.T., Nelson, P., Butler, T., Lennings, C., Allerton, M., & Champion, U. (2006). *Young people on community orders health survey: Key findings report.* Sydney, Australia: University of Sydney ISBN: 1 86487 845 2

Allerton, M., Champion, U., Kenny, D.T., Butler, T. et al (2003). 2003 *Young people in custody health survey.* NSW Department of Juvenile Justice ISBN 0 7347 6518 5

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.

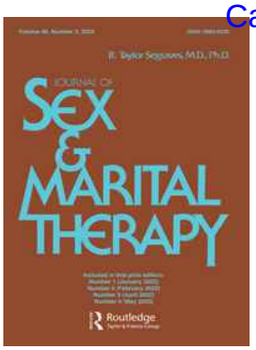
Kenny, D.T. (2005). Impact of violence classification on its relationship to psychological factors and mental health. *Prisoner Health Research Symposium*, JusticeHealth (18 February). Sydney, Australia.

Kenny, D.T., Vecchiato, C., Allerton, M., Kenny, D.T. (2003). Young People in Custody Health Survey: Mental health. *Australian Institute of Criminology Conference* (1-2 December). Sydney, Australia.

Kenny, D.T. (2002). Predictors of recidivism in juvenile sex offenders: Lessons for prevention. *Jocelyn Wale Distinguished Scholar Series* (23 June). James Cook University, Queensland.

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.



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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.

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DEFENDANT'S EXHIBIT 9

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>
</table>

<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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#4 [mh ^transsexualism] 27
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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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#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 69476
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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,ab696
#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
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#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
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#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
#129 {or #33-#128} 6844
#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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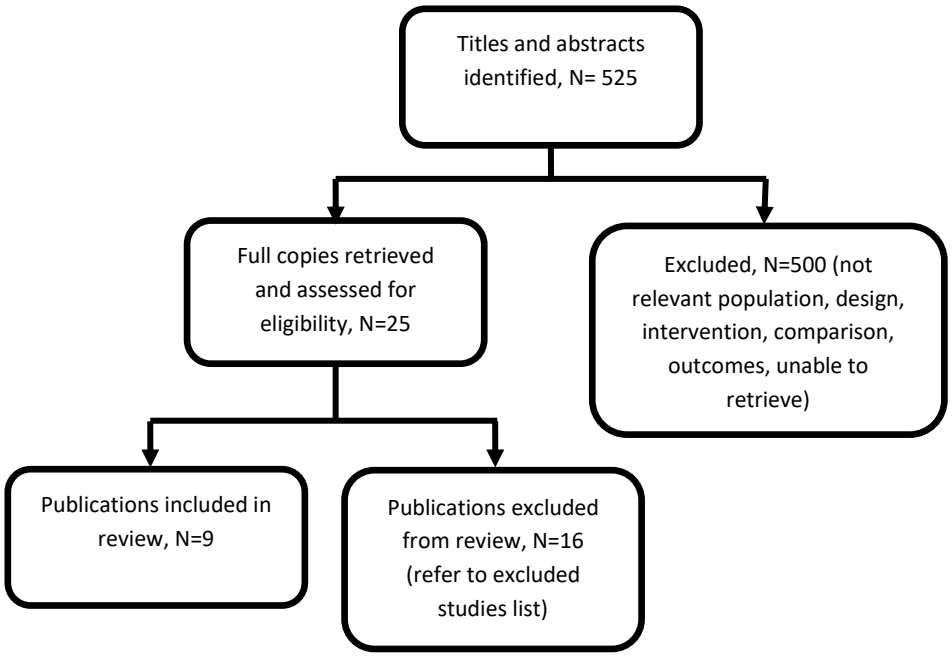
85 ("76932-60-0" or "76932600").ti,ab. (0)
86 ("86220-42-0" or "86220420").ti,ab. (0)
87 ("rs 94991 298" or rs94991298).ti,ab. (0)
88 synarel.ti,ab. (0)
89 deslorelin.ti,ab. (8)
90 gonadorelin.ti,ab. (3)
91 ("33515-09-2" or "33515092").ti,ab. (0)
92 ("51952-41-1" or "51952411").ti,ab. (0)
93 ("52699-48-6" 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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DEFENDANT'S EXHIBIT 10

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).

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[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**