

**IN THE UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF ARKANSAS
CENTRAL DIVISION**

DYLAN BRANDT, et al.,

PLAINTIFFS,

v.

No. 4:21-CV-00450-JM

LESLIE RUTLEDGE, et al.,

DEFENDANTS.

DEFENDANTS' EXHIBITS

Defendants rely on the following exhibits in support of their combined brief in opposition to Plaintiffs' motion for a preliminary injunction and reply in support of Defendants' motion to dismiss:

1. **Declaration of Stephen B. Levine, M.D.**
2. **Declaration of Mark Regnerus, Ph.D.**
3. **Declaration of Paul W. Hruz, M.D., Ph.D.**
4. **Declaration of Patrick W. Lappert, M.D.**
5. **Finland Evidence Review** – "Recommendation of the Council for Choices in Health Care in Finland," PALKO / COHERE Finland (2020).
6. **Sweden Evidence Review** – "Gender Dysphoria in Children and Adolescents: An Inventory of the Literature," Swedish Agency for Health Tech. Assessment and Assessment of Social Services (Dec. 2019).
7. **Sweden – Karolinska Hospital** – "Policy Change Regarding Hormonal Treatment of Minors with Gender Dysphoria at Tema Barn – Astrid Lindgren Children's Hospital," Karolinska Hospital (2021).
8. **Sweden – Karolinska Hospital** – "Guideline Regarding Hormonal Treatment of Minors with Gender Dysphoria at Tema Barn – Astrid Lindgren Children's Hospital (ALB)," Karolinska Hospital (2021).
9. **UK – NICE Evidence Review of Puberty Blockers** – "Evidence Review: Gonadotrophin Releasing Hormone Analogues for Children and Adolescents with Gender Dysphoria," Nat. Inst. for Health and Care Excellence (Oct 2020).

10. **UK – NICE Evidence Review of Cross-Sex Hormones** – “Evidence Review: Gender-affirming Hormones for Children and Adolescents with Gender Dysphoria,” Nat. Inst. for Health and Care Excellence (Oct. 2020).
11. **Cochrane Review** – C. Haupt, et al., “Antiandrogen or Estradiol Treatment or Both during Hormone Therapy in Transitioning Transgender Women (Review),” Cochrane Database of Systematic Reviews (2020).
12. **Bränström & Pachankis** – “Correction to Bränström and Pachankis,” 177 Am. J. Psychiatry 734 (Aug. 2020).
13. **Bränström & Pachankis** – Letters to the Editor, 177 Am. J. Psychiatry 764 (Aug. 2020).
14. James M. Cantor, “Transgender and Gender Diverse Children and Adolescents: Fact-Checking of AAP Policy,” J. Sex & Marital Therapy (Dec. 2019).
15. Devita Singh, et al., “A Follow-Up Study of Boys with Gender Identity Disorder,” *Frontiers in Psychiatry* (March 2021).
16. Michael Biggs, “The Tavistock’s Experimentation with Puberty Blockers.”
17. Michael Biggs, “The Tavistock’s Experiment with Puberty Blockers” (Jul. 2019).
18. Steven H. Woolf, “Potential Benefits, Limitations, and Harms of Clinical Guidelines,” 318 British Med. J. 527 (Feb. 1999).
19. **WPATH** – Eli Coleman, et al., “Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People,” World Pro. Assoc. for Transgender Health (7th ed., 2012).
20. **WPATH** – “Position Statement on Medical Necessity of Treatment, Sex Reassignment, and Insurance Coverage in the U.S.A,” World Pro. Assoc. for Transgender Health (Dec. 2016).
21. **Endocrine Society** – Wylie C. Hembree, et al., “Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline,” 102 J. Clinical Endocrinology & Metabolism 3869 (Sep. 2017).
22. **American Psychological Association** – “Guidelines for Psychological Practice with Transgender and Gender Nonconforming People,” 70 Am. Psychologist 832 (Dec. 2015).
23. **American Academy of Pediatrics** – Jason Rafferty, “Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents,” Pediatrics (Oct. 2018).

24. **DSM-5** – “Gender Dysphoria,” *Diagnostic and Statistical Manual of Mental Disorders*, American Psychiatric Association (5th ed. 2013).
25. **Declaration of Roger Hiatt, Jr., M.D.**
26. **Declaration of Christine Cryer.**
27. **Declaration of Clifton Francis Burleigh, Jr.**
28. **Declaration of Walt Heyer.**
29. **Declaration of Laura Perry.**

Dated: July 9, 2021

Respectfully submitted,

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DECLARATION OF STEPHEN B. LEVINE, M.D.

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

I. CREDENTIALS – KNOWLEDGE, TRAINING, AND EXPERIENCE:

1. **Education - Academic Appointments - Research Grants:** I am a Clinical Professor of Psychiatry at Case Western Reserve University School of Medicine, and also maintain an active private clinical practice. I received my MD from Case Western Reserve University in 1967, and completed a psychiatric residency at the University Hospitals of Cleveland in 1973. I became an Assistant Professor of Psychiatry at Case Western in 1973, and became a Full Professor in 1985. I have been the recipient of the following grants for scientific research and/or program development:

- a. Twenty-three separate pharmaceutical company grants to study various pro-sexual medications;
- b. U.S. National Institute of Health grant for the study of sexual consequences of Systemic Lupus Erythematosus. Co-principal investigator; and
- c. Five separate grants from the private Sihler Mental Health Foundation;
 - i. to create the Program for Professionals which evaluated medical and religious leaders accused of sexual offenses;
 - ii. to establish a Center for Marital and Sexual Health;
 - iii. to create a placebo controlled research study on Clomipramine for Premature ejaculation;

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- iv. to create a follow-up study of clergy accused of sexual impropriety; and
- v. to establish a new clinical service for women with breast cancer.

2. **Medical-Psychiatric Specialty Areas of Focus - Recent Addresses:** Since July 1973 my specialties have included psychological problems and conditions relating to sexuality and sexual relations including sexual identity issues, therapies for sexual problems, and the relationship between love and intimate relationships and wider mental health. In 2005, I received the Masters and Johnson Lifetime Achievement Award from the Society of Sex Therapy and Research. I am a Distinguished Life Fellow of the American Psychiatric Association. Over the years I have lectured frequently to professional groups. During the previous two years, these lectures have included:

- a. The Mental Health Professionals' Role with the Transgendered: Making the Controversies Clear, given to Grand Rounds at the University Hospitals of Cleveland on March 12, 2021;
- b. Psychotherapeutic Approaches to Sexual Problems, an invited lecture to the American Psychiatric Association Annual Meeting on May 1, 2021 (similar lecture in May 2020);
- c. Seven years of six-hour Continuing Education Courses at the American Psychiatric Association Meetings on Love and Sexuality;
- d. Grand Rounds at Cleveland Clinic Foundation on Sexuality Education of Psychiatric Residents on June 25, 2020;
- e. Grand Rounds at Cleveland Clinic Foundation June 2019 Transgenderism: Beware! Repeated by invitation at Akron General Hospital and at National meeting of American Association of Behavioral Health in 2019 in Washington, DC

- f. Three-hour workshop at Society of Sex Therapy and Research in April 2020 on Therapy for Sexual Problems;
- g. Workshop on “Lets talk about sex!” at the American Association of Directors of Psychiatric Residency Training in March 2020 in Dallas, Texas;
- h. Three-hour continuing education seminar with Massachusetts Department of Corrections Gender Identity Staff Fall 2019 in Foxboro, MA;
- i. Also, I have been a visiting professor at Stanford University and St. Elizabeth’s Hospital in DC as well a grand rounds presenter at various departments of psychiatry over many years;
- j. I have served as a book and manuscript reviewer for numerous professional publications. I have been the Senior Editor of the first (2003), second (2010) and third (2016) editions of the Handbook of Clinical Sexuality for Mental Health Professionals. In addition to five other solo authored books, I authored Psychotherapeutic Approaches to Sexual Problems, published in 2020; it has a chapter titled “The Gender Revolution”;
- k. I am a frequent reviewer of submitted papers to the Archives Sexual Behavior, Journal of Sex & Marital Therapy, and Journal of Sexual Medicine; and
- l. I am an infrequent or occasional reviewer for 25 other journals in various medical specialties and psychological and sociologic journals on topics related to human sexuality.

3. **Founder of the Case Western Gender Identity Clinic - former WPATH Chairman of the Standards of Care Committee:** I first encountered a patient suffering what we would now call gender dysphoria in July 1973. In 1974, I founded the Case Western Reserve

University Gender Identity Clinic, and have served as Co-Director of that clinic since that time. Across the years, our Clinic evaluated and treated hundreds of patients who were experiencing a transgender identity. An occasional child was seen during this era. I was the primary psychiatric caregiver for several dozen of our patients and supervisor of the work of other therapists. I was an early member of the Harry Benjamin International Gender Dysphoria Association (later known as WPATH) and served as the *Chairman of the WPATH Standards of Care Committee* that developed the 5th version of its Standards of Care. In 1993 the Case Western Reserve University Gender Identity Clinic was renamed, moved to a new location, and became independent of Case Western Reserve University. I continue to serve as Co-Director. In 2020, the clinic was renamed the Gender Diversity Clinic.

4. **Court Appointed Expert:** In 2006, Judge Mark Wolf of the Eastern District of Massachusetts asked me to serve as an independent, court-appointed expert in a litigation involving the treatment of a transgender inmate within the Massachusetts prison system. After providing a six-hour workshop to the mental health professionals in the system, I was retained by the Massachusetts Department of Corrections in 2007 as a consultant on the treatment of transgender inmates. I have been in that role continuously since.

5. **Experience as an Expert Witness:** I was qualified as an expert and testified concerning the diagnosis, understanding, developmental paths and outcomes, and therapeutic treatment, of transgenderism and gender dysphoria, particularly as it relates to children, in 2019 in the matter of *In the Interest of J.A.D.Y. and J.U.D.Y.*, Case No. DF-15-09887-S, 255th Judicial District, Dallas County, TX (the “*Younger* litigation”). Before and particularly after that contribution, I have given testimony in:

- a. US District Court, Judge Mark L. Wolf's witness in *Michelle Kosilek vs. Massachusetts Dept. of Corrections et al.* (transsexual issue) in Boston, 2007;
- b. Deposition in the *Battista vs. Massachusetts Dept. of Corrections* case (transsexual issue) in Cleveland, October 2009;
- c. Witness for Massachusetts Dept. of Corrections in their defense of a lawsuit brought by prisoner Katheena Soneeya. March 22, 2011 Deposition in Boston and October 2018 in Cleveland and 2019 in Boston;
- d. Witness for *State of Florida vs. Reyne Keohane*, July 2017;
- e. Pennsylvania legislative testimony. Written submission and live testimony before a committee of the Pennsylvania legislature, March 2020 (Engaged by Pennsylvania Family Institute);
- f. In the Interests of the Younger Children. Expert testimony by deposition and at trial in Dallas, TX. (Engaged by Texas counsel Odeneal & Odeneal) (Dallas Cty. Dist. Ct. 2019);
- g. *Doe v. Madison Metropolitan School District*. Expert declaration submitted February 19, 2020, rebuttal declaration submitted August 14, 2020;
- h. *Hecox v. Idaho*. Expert declaration submitted June 4, 2020. (D. Idaho);
- i. *In the matter of Rhys & Lynn Crawford* (Washington State). March 30, 2021, *Tingley v. Washington State*. (W.D. Wa.);
- j. London: *Queen (Quincy Bell) vs. Tavistock and Portman Clinics and NHS* in High Court of London, Decision handed down on December 1, 2020. I was the only American to submit a report. The Court found that puberty blocking hormones could not be administered to youth and that for any 16 or 17 year old to obtain

hormonal therapy for gender dysphoria they must have court approval for its administration with each case separately;

k. London 2: In the High Court of Justice Queen's Bench Division administrative court. The Queen (on the application of) L. and Hampshire County Council. (A matter of education about transgender identities in schools; not yet decided);

l. North Carolina, *Kadal v. Folwell* (M.D.N.C)

m. Earlier this year, the District of Arizona relied on evidence I submitted regarding the guidelines for treating adolescents with gender dysphoria, in *Hennessy-Waller v. Snyder*, Case No. CV-20-00335-TUC-SHR, 2021 WL 1192842, at *5-6 & n.10 (D. Ariz. Mar. 30, 2021).

m. I have been retained by the defense in this case to serve as an expert witness. My compensation is \$400 per hour. My compensation is not dependent upon the outcome of this litigation or the substance of my opinions.

A more complete review of my professional experience, publications, and awards is provided in my curriculum vitae, a copy of which is attached hereto as Exhibit A.

7. I have reviewed the "Declaration of Deanna Adkins, MD, in Support of Plaintiffs' Motion for a Preliminary Injunction," dated June 11, 2021 ("Adkins"). In that declaration Dr. Adkins makes a variety of statements about gender dysphoria, therapies for gender dysphoria, and outcomes of therapies, which I believe to be inaccurate, or unsupported by scientific evidence. Dr. Adkins is a pediatric endocrinologist. I note with some concern that Dr. Adkins makes a number of sweeping and purportedly scientific assertions that are supported by almost no peer-reviewed articles or studies. I note also that Dr. Adkins herself has published only one peer-reviewed article relating to treatment of individuals suffering from gender dysphoria.

7A. Although Dr. Adkins does not attach her curriculum vitae, based on her declaration, Dr. Adkins' practice is focused on children and adolescents. Her declaration does not suggest substantial experience in working with adults or older young adults who are living in a transgender identity, or who suffer from gender dysphoria. (This diagnosis requires distress). The wider lifecycle view that derives from experience with these adults (and familiarity with the literature concerning them) provides an important cautionary perspective on the treatment of children and adolescents. The psychiatrist or psychologist treating a trans child or adolescent, of course seeks to make the young patient happy, but the overriding consideration is the creation of a happy, highly functional, mentally healthy person for the next 50 to 70 years of life. I refer to treatment that keeps this goal in view as the "life course" perspective.

7B. It is my opinion that a number of Dr. Adkins' assertions are inaccurate or unsupported, for reasons that I explain in this Declaration. I will provide citations to published, peer-reviewed articles that inform my judgments.

7C. I have also reviewed the "Declaration of Armand H. Matheny Antommara, MD, PhD, FAAP, HEC-C," dated June 11, 2021 ("Antommara"). In that declaration, Dr. Antommara makes assertions about medical ethics, informed consent, and the evidentiary basis supporting the use of a variety of procedures for gender transition, which I believe are inaccurate and unsupported by scientific evidence.

7D. Before I summarize my key points in the next section, I want to share my understanding of the fundamental scientific controversy embedded within this legal challenge. On one side, there is the well-intentioned compassionate treatment of dysphoric trans teenagers with hormones that has been occurring almost for one decade. On the other side, there is time-honored ethical expectation that innovated major medical and surgical treatments should be based on

well-defined methodologically sophisticated scientific studies. This matter is far from unique to Arkansas. The same matter has recently been both studied adjudicated in Europe and is being similarly challenged in various US courts. My point is that neither of Plaintiff's experts seems to be aware of three important processes during the previous two years.

7E. First are the recent objective, independent, reappraisals of the use of puberty blocking hormones and cross-sex hormones in this age group. Finland, Sweden, and the UK have each reviewed the relevant medical literature, and—contrary to the Plaintiff's expert opinions—have concluded that the scientific evidence of efficacy is at best unclear. The literature is methodologically of low quality, follow up studies are few, incomplete, and fail to show major improvements in mental health. Finland's report discouraged their use. The Swedish Karolinska Hospital's review prohibited their use except in a carefully designed research protocol. The UK's report did not make policy recommendations but similarly characterized the inadequacies of the science.

7F. Second, in a separate judicial review announced on December 1, 2020, the High Court of London banned the use of puberty blockers for those less than 16 and required any 16 or 17 year old who is being considered for puberty blockers or cross sex hormones to obtain court permission prior to administration. The High Court spoke to the lack of good scientific evidence, the immaturity of these youth to make life-altering decisions, the unexplained recent increase in incidence of youth declaring a trans identity, and the lack of adequate follow-up of those already treated at the two very busy referral clinics for gender dysphoric teens. In discussing the use of puberty blockers in minors, the High Court cited evidence I offered about how young people mature through adolescence. See *Bell v. The Tavistock & Portman NHS Foundation Trust* [2020] EWHC (Admin) 3274 [64].

7G. Third, neither of the Plaintiff's experts seem to appreciate that two separate evaluations, one from Canada and one from the UK, reviewed WPATH's Standards of Care and found them untrustworthy as scientific guidelines.¹

8. **Summary of Issues:** In this declaration, I offer information and my expert opinions concerning a number of aspects of the phenomenon of Gender Dysphoria and transgender identity (i.e., Gender Discordance, Gender Incongruity), as well as a discussion of competing views among mental health and other professionals as to the appropriate assessment and therapeutic methods-practices for patients who experience gender dysphoria. At many points in this statement, I provide citations to published, peer-reviewed articles that provide foundational or additional supporting or relevant information. The central issue in this case stems from the fact that hormonal-surgical treatments were developed for the treatment of trans-declared patients that spread internationally well in advance of the objective-reliable-scientific appraisal of its consequences. Thus, we have been listening to advocates-practitioners of unproven, experimental clinical practices vs. concerned voices about the harm to patients of ignoring scientific evidence. A summary of the key points I discuss in this statement includes:

- a. Sex as defined by biology and reproductive function cannot be changed. While hormonal and surgical procedures may enable some individuals to "pass" as the opposite gender during some or all of their lives, such procedures carry with them physical, psychological, and social risks. No procedure can enable an individual to perform the reproductive role of the opposite sex.;

¹ See 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 Apr 29;11(4):e048943. doi: 10.1136/bmjopen-2021-048943. PMID: 33926984; PMCID: PMC8094331; see also <https://genderreport.ca/bias-not-evidence-dominate-transgender-standard-of-care/>.

b. The diagnosis of “gender dysphoria” encompasses a diverse array of conditions, with widely differing pathways and characteristics depending on age of onset among other things. Data from one population (e.g. adults) cannot be assumed to be applicable to others (e.g. children);

c. Among psychiatrists and psychotherapists who practice in the area, there are currently widely varying views concerning both the causes of and appropriate therapeutic response to gender dysphoria. Existing studies do not provide a basis for a reliable scientific conclusion as to which therapeutic responses result in the best long-term outcomes for affected individuals — thus the field remains in an experimental stage;

d. A majority of young children in twelve studies (typically a large majority) who are diagnosed with gender dysphoria “desist” — that is, their gender dysphoria does not persist — by puberty or adulthood. It is not currently known how to distinguish children who will persist from those who will not — thus the majority of patients will do best with no “affirmation” (i.e., “gender transitioning”) treatments in childhood. It has not been scientifically established — we have no reliable measures to test — which patients would do better with “affirmation” treatments versus the large majority of patients who are better left alone to naturally grow out of gender dysphoria (“desist”). Social affirmation (acting as if the child were a different sex) puts children on a pathway for potential short-term subjective gains that are likely to involve life-long damage to healthy organs and natural biological processes. Such

“affirmed” or “transitioning” children and their families anticipate treatment with puberty blocking hormones which recent multinational (England, Finland, Sweden) European science/treatment reviews have opposed;

e. Some recent studies suggest that active affirmation of transgender identity in young children will substantially reduce the number of children naturally outgrowing or “desisting” from transgender identity. This raises ethical and public health concerns that “affirmation” treatments will increase the number of individuals who suffer the multiple long-term physical, mental, and social limitations that are strongly associated with living life as a transgender person;

f. Social transition of children and adolescents is itself an important intervention with profound implications for the long-term mental and physical health of the minor. When a mental health professional evaluates a child or adolescent and then recommends social transition, presumably that professional is available to help with interpersonal, familial, and psychological problems that may arise. However, many adolescents transition without mental health assessment and ongoing care, leaving themselves and their families on their own to deal with subsequent problems;

g. In most cases, parental involvement is necessary for an accurate and thorough diagnosis of a child or adolescent presenting with gender dysphoria or a desire for a transgender identity, as well as for effective psychotherapeutic treatment and support of the young person;

h. The knowledge base concerning the cause and treatment of gender dysphoria available today has been repeatedly characterized in multiple reviews as a “paucity of evidence” and of “low scientific quality.” Often statements of cause are

not correctly labeled as hypotheses about possible influences thus leading insufficiently informed practitioners to proceed with hazardous treatments far beyond what the current science ethically supports;

i. There are currently no studies that directly demonstrate that affirmation of transgender identity in young children reduces suicide, suicidal ideation, or suicide attempts or improves long-term outcomes as compared to other therapeutic approaches. Meanwhile, multiple studies show that adult individuals living transgender lives suffer much *higher* rates of suicide and *negative* physical and mental health conditions than does the general population. Thus it remains unclear how much benefit, if any, is provided by the fashionable experimental treatments commonly employed;

j. In light of what is known and not known about the impact of affirmation on the incidence of suicide, suicidal ideation, and other indicators of mental and physical health, it is *scientifically baseless and unethical* to assert that a child or adolescent who expresses an interest in a transgender identity will kill him or herself — or is more likely to do so — unless adults and peers affirm that child in a transgender identity. Physicians and psychologists have an ethical obligation to honestly represent scientific facts rather than their own beliefs;

k. Putting a child or adolescent on a pathway towards life as a transgender person puts that individual at risk of a wide range of long-term or even life-long harms, including: sterilization (whether chemical or surgical) and associated regret and sense of loss; inability to experience orgasm (for trans women); physical health risks associated with exposure to elevated levels of cross-sex hormones; surgical

complications and life-long after-care; alienation of family relationships; inability to form healthy romantic relationships and attract a desirable mate; elevated mental health risks. In my opinion, putting young children through such risks who are very likely to naturally grow out of gender dysphoria into acceptance of their biological sex and gender is an unethical practice that is experimental because long term follow does not exist and the practice did not emerge from randomized studies;

1. Informed consent is ethically required for potentially life-altering psychological or medical procedures. However, the informed consent process in such complex cases is also complex. In some cases, it may not be possible to obtain meaningful informed parental consent to place a child on a risky psychological pathway. Do parents have a right to determine their child's future sterility, for instance? A child is not competent, of course, to weigh how these potentially devastating life-long risks and issues will impact his or her lifetime happiness. Informed consent of parents is essential, although it may not be sufficient. Withholding accurate information from patients or parents about alternative approaches and the risks and benefits of transition, or misrepresenting the current state of research in this field should be viewed as a serious ethics violation. The "affirmation" treatment industry (i.e., the diverse professionals, the pharmaceutical manufacturers, private funders, hospitals and clinics that specialize in affirmative care and those who advocate for them) are, perhaps unknowingly, providing misleading information to the public and the legal system. For example, it is not the case that puberty halting hormone treatments are "easily reversed" when the psychosocial consequences are not considered and the negative bone density effects have been documented while its reversal has not;

m. Research reviews support my opinion that gender affirmation treatments remain experimental and have never been accepted by the relevant scientific community and have no known nor published error rate — meaning the rates of clinical errors as manifested by desistance, increased mental suffering, educational failure, vocational inconstancy, or social isolation have not been established.²

Within the last two years, detailed research reviews exposing multiple and serious methodological and ethical flaws in the research of Bränström, and Panchankis and Turban et al , and other “affirmation” advocates have pinpointed fundamental methodological errors in their papers which claim to support affirmation treatment. These reviews also support my opinions that gender affirmation treatments such as puberty blocking hormones and gender conforming surgeries, although common, remain experimental. Claims of their efficacy have been refuted by others in the relevant scientific community.³

² See, e.g., 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; Swedish Agency for Health Technology Assessment and Assessment of Social Services.

³ See Kalin N. H. (2020). Reassessing Mental Health Treatment Utilization Reduction in Transgender Individuals After Gender-Affirming Surgeries: A Comment by the Editor on the Process. *The American journal of psychiatry*, 177(8), 764. <https://doi.org/10.1176/appi.ajp.2020.20060803>; Biggs M. (2020). Puberty Blockers and Suicidality in Adolescents Suffering from Gender Dysphoria. *Archives of sexual behavior*, 49(7), 2227–2229. <https://doi.org/10.1007/s10508-020-01743-6>; D’Angelo, R., Syrulnik, E., Ayad, S., Marchiano, L., Kenny, D. T., & Clarke, P. (2020). One Size Does Not Fit All: In Support of Psychotherapy for Gender Dysphoria. *Archives of sexual behavior*, 10.1007/s10508-020-01844-2. Advance online publication. <https://doi.org/10.1007/s10508-020-01844-2>.

II. BACKGROUND IN THIS FIELD

A. The biological base line of sex

9. Dr. Adkins refers to the sex of an individual as “assigned at birth” or “designated at birth.” (Adkins 4, 5.) This phrasing is misleading. It is appropriate only in the (extremely rare) circumstances in which an infant is born with a disorder of sex development (or intersex characteristics). The sex of a human individual at its core structures the individual’s biological reproductive capabilities—to produce ova and bear children as a mother, or to produce semen and beget children as a father. As physicians know, sex determination occurs at the instant of conception, depending on whether a sperm’s X or Y chromosome fertilizes the egg. Medical technology can now be used to determine a fetus’s sex before birth almost as easily as after birth. It is thus not correct to assert that doctors “designate” or “assign” the sex of a child at birth. Instead, they simply recognize the existing fact of that child’s sex; barring extremely rare disorders of sexual development,⁴ anyone can identify the sex of an infant by genital inspection. What the general public may not understand, however, is that every nucleated cell of an individual’s body is chromosomally identifiably male or female—XY or XX. Claims that patients can change their sex in a biological sense misleading and scientifically impossible. In reality, the typical “transgender” patient has normal healthy sex organs but struggles with gender discordant feelings and perceived identity. Such patients can receive hormones and surgeries to make them to be socially perceived as a member of their aspired to sex, but such methods never actually “transition” a patient to “another sex.” In my opinion, these views are generally accepted by the relevant scientific community in the fields of biology, zoology, neonatology, genetics, pediatrics,

⁴ The sometimes-cited statistic that 1.7 percent of people are born intersex is incorrect. The actual figure is 0.02%. L. Sax (2002) *How common is Intersex? A response to Anne Fausto-Sterling*, J. of Sex Research DOI: 10.1080/00224490209552139

and psychiatry. They are not accepted by some in the “affirmation” treatment industry who promulgate innumerable variations in male-female sex and deny that sex, per se, is dimorphic among humans.

10. The self-reported gender of a child, in contrast, arises in part from how others label the infant: “I love you, son (daughter).” This designation occurs thousands of times in the first two years of life when a child begins to show awareness of the two possibilities. As acceptance of the designated gender corresponding to the child’s sex is the natural outcome in >99% of children everywhere, anomalous gender discordant identity formation begs for understanding. Is it biologically shaped, influenced or determined? Is it the product of how the child was privately regarded and treated? Does it stem from trauma-based rejection of maleness or femaleness, and if so flowing from what traumas? Is it a symptom of another, as of yet unrevealed emotional disturbance? Is it the result of a social contagion process — such as anorexia or bulimia may be, or from Internet involvement with trans websites? The ongoing scientific, clinical, and societal debate over such issues awaits reliable answers; while some offer authoritative opinions on these questions, they are not scientifically proven. They are merely hypotheses. In my opinion, these views are generally accepted by the relevant scientific community.

11. Under the influence of hormones secreted by the testes or ovaries, numerous additional sex-specific differences between male and female bodies continuously develop post-natally, culminating in the dramatic maturation of the primary and secondary sex characteristics with puberty. These include differences in hormone levels, height, weight, bone mass, shape and development, musculature, body fat levels and distribution, and hair patterns, as well as physiological differences such as menstruation. These are genetically programmed biological conse-

quences of sex, which also serve to influence the consolidation of gender identity during and after puberty. Of course there are variations in degrees of the parameters listed above, but these do not change the fundamental male-female variations in all living things. In my opinion, these views are generally accepted by the relevant scientific community.

12. Despite the increasing ability of hormones and various surgical procedures to refigure some male bodies to visually pass as female, or vice versa, the biology of the person remains as defined by his (XY) or her (XX) chromosomes, including cellular, anatomic, and physiologic characteristics and the particular disease vulnerabilities associated with that chromosomally-defined sex. 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 trans individual to become “a complete man” or “a complete woman,” this is not biologically attainable—that is, all anatomic and physiological features cannot be eradicated. 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.⁵ In my opinion, these views are generally accepted by the relevant scientific community.

B. Definition and diagnosis of gender dysphoria

13. Specialists have used a variety of terms over time, with somewhat shifting definitions, to identify and speak about a distressing incongruence between an individual’s sex as determined by their chromosomes and their thousands of genes, and the gender with which they eventually

⁵ See S. Levine (2018), Informed Consent for Transgendered Patients, *J. of Sex and 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. American Academy of Psychiatry and Law* 44, 236 at 238 (“Reflections”).

subjectively identify or to which they aspire. Today's American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-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 note that the DSM is based on interrater reliability rather than the "validity" of its categories. The DSM began as an attempt to create a dictionary of disorders for psychiatry. Conception of what is a mental illness and the criteria used to define them change every decade or less. Those who have participated in this process know that its product derives from consensus-seeking methodologies — such as "voting" by small committees of 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.⁶ In my opinion, these views are generally accepted by the relevant scientific community.

14. There are at least five distinct pathways to gender dysphoria: 1) early childhood onset; 2) onset near or after puberty with no prior cross gender patterns; 3) onset after homosexual lifestyle; 4) adult onset after years of heterosexual transvestism; and 5) onset in later adulthood with few or no prior indications of cross-gender tendencies or identity. The early childhood onset pathway and the more recently observed onset around puberty pathway are relevant to this

⁶ See, e.g., Lee, C., *The NIMH Withdraws Support for DSM-5: The latest development is a humiliating blow to the APA*. Psychology Today News Blog at <https://www.psychologytoday.com/us/blog/side-effects/201305/the-nimh-withdraws-support-dsm-5>: "Just two weeks before DSM-5 is due to appear, the National Institute of Mental Health, the world's largest funding agency for research into mental health, has indicated that it is withdrawing support for the APA's manual. In a humiliating blow to the American Psychiatric Association, Thomas R. Insel, M.D., Director of the NIMH, made clear the agency would no longer fund research projects that rely exclusively on DSM criteria. Henceforth, the NIMH, which had thrown its weight and funding behind earlier editions of the manual, would be "re-orienting its research away from DSM categories."

matter. Whereas the onset of cross-gender identifications in the preschool years may suggest biologically-derived temperamental and intrafamilial shaping forces, the post-pubertal onset of what is now commonly referred to as a rapid onset gender dysphoria or post-pubertal gender dysphoria seems to be heavily influenced by social and internal developmental forces. The former derive primarily from socialization via the Internet and educational environments. The vulnerability to such social contagion may stem from conspicuous or subtle mental health problems of anxiety, difficulty with friendship formation and social isolation or the child's misunderstanding of the normality of early pubertal discomfort with one's body, previous peer relationships, and despair about future gender-based social roles. The newly acquired trans identity is often passionately held, as it explains away past and current unhappiness and emotional or behavioral problems.

C. Changing complexities in young gender discordant patients

15. **The Social Contagion Hypothesis.** To avoid the methodological error of confirmation bias, clinicians and researchers generate and test alternative hypotheses. It is currently unclear how many of the new—and demographically very different—gender discordant patients have been influenced by social contagion processes. During the last 10-15 years, there have been multiple reports from multiple nations reporting a dramatic increase (over 4,000% in just a few years) in the number of gender discordant patients as well as a dramatic change in the reported sex ratio of young patients presenting to clinics with trans gender identities. In the 20th century, the biologic male to biologic female ratio was consistently 3-4:1 in most North American and European clinics. But now many clinics are reporting an inverted 7:1 ratio of girls to boys. Biological theories of gender dysphoria (e.g., “immutable,” genetic, brain structures, etc.) appear quite unlikely to explain large, rapid demographic shifts in gender discordant patients. A social contagion/social influence theory has arisen in an attempt to help explain these dramatic

demographic changes. But some advocates, denying cultural influences, seek to explain this phenomenon on the previously hidden high prevalence of unrecognized gender dysphoria. This seems unconvincing to me since courses in personality development have long recognized that one of the tumultuous tasks of adolescent development was the stabilization of sexual identity.⁷

In decades past, gender discordant children and teens with homoerotic attractions and fantasies may have typically aspired to become a member of the opposite sex only to find some other cis sexual identity. More recently, patients are increasingly likely to define themselves as “non-binary persons,” meaning that they have elements of both sexes/genders within them or they have none of these elements. Such teens often report being influenced by trans websites and trans “influencers” on Internet sources such as video blogs on YouTube. These onsite shows reportedly reach millions and teach adolescents to consider their problems, worries, discomforts, and anticipated social roles to be typical experiences of the unfolding of a biologically-determined trans self. In addition to YouTube and other Internet sources, patients reportedly have been influenced by school trans awareness training programs teaching the normality of trans current and future lives — without an accurate discussion or depiction of the known risks and benefits. I have not seen a trans adolescent who has not spent countless hours on trans Internet sites.

A multi-disciplinary analysis that includes developmental psychology and the history of psychiatry provides additional support for the social contagion/social influence hypothesis. Mental health professionals have long been familiar with adolescent females experiencing social worries that contribute to anorexia nervosa, bulimia, and self-harm such as cutting, burning, and piercings. Prof. Amanda Rose at the University of Missouri has conducted research to

⁷ See Blos, P. (1979). *The adolescent passage: developmental issues*. London. International Universities Press.

understand why adolescent girls demonstrate heightened susceptibility to a social contagion of psychiatric symptoms. She reports that “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. This is a potential — and as yet uninvestigated hypothesis — as to the reports of “clusters” and “friend groups” of teen girls who are adopting trans identity and “transitioning” together.⁸ Prof. Rose’s investigations note that adolescent girls seem more willing to adopt a friend’s pain and even suspend reality to “get on the symptom team” of their friends.⁹ This new presentation of teens who previously had no evidence of gender dysphoria has now been seen in gender clinics all over the Western world, and there has been a huge surge in the number of cases. One recent US survey found a 4000% increase (over 40-fold) since 2006, and there have been similar large increases reported in Finland, Norway, the Netherlands, Canada, and Australia. The London GIDS clinic reported a 30-fold increase in referrals over the past decade—and again they were primarily adolescent girls who report that they now identify as boys.

⁸ See L. Littman (2018), *Parent Reports of Adolescents & Young Adults Perceived to Show Signs of a Rapid Onset of Gender Dysphoria*, PLoS ONE 13(8): e0202330 at 13.

⁹ See R. Schwartz-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. Scientific research is needed to address these complex issues. See McCall, B. and Nainggolan, L., *Medscape Transgender Teens: Is the Tide Starting to Turn?*, https://www.medscape.com/viewarticle/949842#vp_1 (“The vast majority of youth now presenting with gender dysphoria are adolescents who suddenly express revulsion with their sex from birth, and 70% of them were born female. Many of them have comorbidities such as separation and social anxiety, attention deficit hyperactivity disorder, autism spectrum traits, and depression, Malone et al explains (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 Mar 27;dgab205. doi: 10.1210/clinem/dgab205. Epub ahead of print. PMID: 33772300).

It should be noted that rapid, unpredicted changes in the demographics of trans patients (i.e., from chronically discordant, early onset males to pubertal-onset biological females) calls into question the usefulness and accuracy of predictions emanating from research conducted on previous, demographically and clinically different patient groups. This enormously important epidemiological distinction has thus far been underappreciated by “affirmation” providers. This again highlights the complex, little known, and experimental practices of the “affirmation” treatment industry.¹⁰ Similar large increases have been reported in Finland,¹¹ in Norway and in the Netherlands,¹² in Canada,¹³ and in others.

16. Gender dysphoria has very different characteristics depending on age and sex at onset. Young children who are living a transgender identity commonly suffer materially fewer symptoms of concurrent mental distress than do older patients.¹⁴ The developmental and mental health patterns for each of these groups are sufficiently different that data developed in connection with one of these populations cannot be assumed to be applicable to another.

¹⁰ See National College Health Assessment: ACHA-NCHA, https://www.acha.org/NCHA/ACHA-NCHA_Data/Publications_and_Reports/NCHA/Data/Publications_and_Reports.aspx?hkey=d5fb767c-d15d-4efc-8c41-3546d92032c5.

¹¹ Kaltiala-Heino, Riittakerttu, Hannah Bergman, Marja Työläjäarvi, and Louise Frisen. “Gender Dysphoria in Adolescence: Current Perspectives.” *Adolescent Health, Medicine and Therapeutics* Volume 9 (March 2018): 31–41, <https://doi.org/10.2147/AHMT.S135432>

¹² De Vries, Annelou L.C. de. “Challenges in Timing Puberty Suppression for Gender-Nonconforming Adolescents.” *Pediatrics* 146, no. 4 (October 2020): e2020010611. <https://doi.org/10.1542/peds.2020-010611>

¹³ Zucker, Kenneth J. “Adolescents with Gender Dysphoria: Reflections on Some Contemporary Clinical and Research Issues.” *Archives of Sexual Behavior* 48, no. 7 (October 2019): 1983–92. <https://doi.org/10.1007/s10508-019-01518-8>

¹⁴ See K. Zucker (2018), The Myth of Persistence: Response to “A Critical Commentary on Follow-Up Studies & ‘Desistance’ Theories about Transgender & Gender Non-Conforming Children” by Temple Newhook et al., *Int’l J. of Transgenderism* at 10, DOI: 10.1080/15532739.2018.1468293 (“Myth of Persistence”).

17. The criteria used in DSM-5 to identify Gender Dysphoria (“Gender Incongruence” is another term used) include a number of signs of discomfort with one’s natal sex and vary somewhat depending on the age of the patient, but in all cases require “clinically significant distress or impairment in important areas of functioning” such as social, school, or occupational settings. When these criteria in children (or adolescents, or adults) are not met, two other diagnoses may be given. These are Other Specified Gender Dysphoria and Unspecified Gender Dysphoria. Specialists sometimes refer to children who do not meet criteria as being “subthreshold.”

18. In a complex, experimental, and little understood field such as transgender medicine, generating and exploring alternative hypotheses is essential to our efforts to help alleviate the tragic suffering of our patients. One such alternative is to teach coping and resilience skills to gender discordant children. It is able to identify and work with past adversities to help the child appreciate and processes what has happened around and to them. Such training could include a realization that a wide range of behaviors are available within their biologically concordant gender roles. Acquiring a broader perspective on the patient’s natal sex roles might be a better solution for some than permanent damage to healthy sex organs via hormone and surgical “transitioning” procedures. Children who conclude that they are transgender are often unaware of a vast array of adaptive possibilities for how to live life as a man or a woman—possibilities that become increasingly apparent over time to both males and females. A boy or a girl who claims or expresses interest in pursuing a transgender identity often does so based on stereotypical notions of femaleness and maleness that are based on constrictive notions of what men and women can be.¹⁵ A young child’s, even an adolescent’s, understanding of this topic is quite limited. Nor

¹⁵ See S. Levine (2017), Ethical Concerns About Emerging Treatment Paradigms for Gender Dysphoria, *J. of Sex & Marital Therapy* at 7, DOI: 10.1080/0092623X.2017.1309482 (“Ethical Concerns”).

do they have the perspective that discomfort with the body and perceived social role is not new to civilization. What *is* new is the option to become a trans person.

With most complex behavioral problems of child and adolescents, patients and families receive psychiatric attention that includes a thorough developmental history from parents, prolonged interviews with the patient, and a therapeutic approach that involves to some extent the parents, the patient, and the three together with or without medication assistance. Tragically, in too many transgender clinics, young patients are not treated with the standard of care—a complex, multi-disciplinary, evidence-based approach. Children are often quickly referred to gender “specialists”—which generally means therapists who deeply believe (based on clinical-political ideology and ignorance of the science being discussed here) that every young person who is questioning his or her gender identity or declaring a trans identity should be quickly “affirmed” and supported in their atypical identity. Moreover, the ideological fashions of these therapists and the organizations that support them have effectively convinced many—contrary to the relevant science—that any other approach to these youth is dangerous, harmful, and might even lead to suicide. The “psychotherapy” that they have been educated to provide is support and encouragement for continuing and providing labels for others as transphobic. Other evidence-based, more methodologically sound approaches are denigrated and ideologically labeled as “conversion therapy.” Tragically, such ideological restrictions are institutionalizing malpractice via confirmation bias, the failure to generate and test alternative hypotheses. Children suffering from psychiatric dysfunctions manifesting as depression or anxiety and those suffering with autistic spectrum characteristics are mistreated by inducting them into the “affirmation” system. Arkansas’s SAFE Act protects children from such improper, unproven experimentation, just as Finland, Sweden, and England have also done.

The ideologically based indoctrination efforts to ban evidence based alternative treatments as “conversion therapy” can have harmful effects on our vulnerable patients. For example, many traditional therapists claim to not know how to take care of these gender discordant patients, as though they are not children who are suffering. This rationalization may only be a reflection of the fear of being attacked for performing dreaded, and now in some locations, illegal, “conversion therapy.” In this way, qualified mental health professionals have failed to develop a robust experience with alternative ways of investigating patients’ and their families’ lives as they do with all other child and adolescent psychiatric problems.

The recently released national guidelines for gender dysphoric patients from Sweden and Finland are moving towards a much greater emphasis on alternative methods including psycho-social support, therapy, and long-term psycho-social evaluations—perhaps for years—prior to engaging in any “affirmative” medical interventions.

External pressures on providers who have been cautious about affirmative care of children and rapid use of hormones for early pubertal teens should not be underestimated. Leaders in the field of gender dysphoria have been attacked, placed on administrative leave, have been summarily fired, and have had their reputations sullied by activists who believe they know best how other people’s children should be treated. The fact that science has not yet established the ideal treatment approaches to the diversity of situations does not seem to matter to these passionate persons. Thus, the court needs to be informed about how political processes have frightened many competent child and adolescent professionals from working with this population. Instead they refer them to gender specialists.

19. Confirmation bias is a hazardous cognitive error that can beset any field of medicine or science. Confirmation bias is the methodologically defective tendency to process information

by only looking for, and interpreting, evidence consistent with existing beliefs, favorite theories, and pre-conceived notions. This bias can cause a person or a field to ignore information that is contrary to what is common, fashionable, popular, or “politically correct.” It is often associated with a weak understanding of how science establishes the legitimacy of a therapy and the belief that because a therapeutic approach has been long employed or is supported by powerful forces, reliable and valid science must have previously established the approach. Both of the essential concepts of “gender affirmative treatment” and “conversion therapy” are based on such misunderstandings. Everyone must remain vigilant about confirmation bias in constructing their arguments.

20. The expected initial evaluation of a trans person typically begins with the patient who tells the evaluator, “I am trans.” The patient relates his or her symptoms of discomfort that may or may not fulfill DSM-5 criteria for Gender Dysphoria. Ideally, a developmental history is taken from the parents and the patient to consider what is known as a differential diagnostic process to determine what other conditions may underlie these symptoms. The extent to which this latter process is undertaken depends upon the therapist’s beliefs about the origin of trans identities and the long-term effectiveness of affirmative responses. To the extent that life-changing affirmative treatment programs are believed to be already scientifically established, the differential diagnosis process tends to be glibly superficial. The patient is typically pleased with the rapid affirmation recommendation, although the parents are often horrified by the failure to consider previous struggles the child and family have undergone. Two professional assumptions facilitate quick affirmation: first is the belief that trans phenomena are determined biologically, making most post-natal influences moot; second is that trans identity is fixed for life. Alternative treatment approaches or hypotheses are given short shrift (i.e., a product of confirmation

bias). When one grasps the fact that the scientific process underlying affirmation is inadequate because of “weak evidence” based on often defective research, one can begin to see that confirmation bias can create an unethical process that places patient futures in jeopardy.

D. The inequitable impact of gender dysphoria on minority and vulnerable groups

21. In considering the appropriate response to gender dysphoria, it is important to know that certain groups of children have an increased prevalence and incidence of trans identities. These include: children of color, children with mental developmental disabilities, including children on the autistic spectrum (at a rate more than 7x the general population), children residing in foster care homes, adopted children (at a rate more than 3x the general population), children with a prior history of psychiatric illness, and more recently adolescent girls (in a large recent study, at a rate more than 2x that of boys).¹⁶ These data are consistent with Littman’s research.¹⁷

¹⁶ G. Rider at 4; See 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. (In a large sample, non-white youth made up 41% of the set who claimed a transgender or gender-nonconforming identity, but only 29% of the set who had a gender identity consistent with their sex.); see D. Shumer & A. Tishelman (2015), *The Role of Asperger in the Treatment of Transgender Adolescents*, Int. J. Transgenderism at 1, DOI: 10.1080/15532739.2015.1075929; D. Shumer et al. (2016), Evaluation of Asperger Syndrome in Youth Presenting to a Gender Dysphoria Clinic, LGBT Health, 3(5) 387 at 387; Shumer et al. (2017), Overrepresentation of Adopted Adolescents at a Hospital-Based Gender Dysphoria Clinic, Transgender Health, Vol. 2(1) 76 at 77; L. Edwards-Leeper et al. (2017), Psychological Profile of the First Sample of Transgender Youth Presenting for Medical Intervention in a U.S. Pediatric Gender Center, Psychology of Sexual Orientation and Gender Diversity, 4(3) 374 at 375 (“Psychological Profile”); R. Kaltiala-Heino et al. (2015), *Two Years of Gender Identity Service for Minors: Overrepresentation of Natal Girls with Severe Problems in Adolescent Development*, Child and Adolescent Psychiatry & Mental Health, 9(9) 1 at 5 (in the 2015 Finland gender identity service statistics, 75% of adolescents assessed “had been or were currently undergoing child and adolescent psychiatric treatment for reasons other than gender dysphoria.”).

¹⁷ See L. Littman (2018), *Parent Reports of Adolescents & Young Adults Perceived to Show Signs of a Rapid Onset of Gender Dysphoria*, PLoS ONE 13(8): e0202330 at 13 (Parental survey concerning adolescents exhibiting Rapid Onset Gender Dysphoria reported that 62.5% of gender dysphoric adolescents had “a psychiatric disorder or neurodevelopmental disability preceding the onset of gender dysphoria.”).

Properly protecting vulnerable, marginalized patients from experimental, potentially dangerous treatments should be an essential concern to trans gender treatment industry but has not been.

E. Three competing conceptual models of gender dysphoria and transgender identity

22. Discussions about appropriate responses by mental health professionals (“MHPs”) to actual or sub-threshold gender dysphoria are complicated by the fact that various speakers and advocates (or a single speaker at different times) view transgenderism through at least three very different paradigms, often without being aware of, or at least without acknowledging, the distinctions. I attempt to summarize these three as though they are equally valid. I do not actually consider this to be true.

23. Gender dysphoria is conceptualized and described by some professionals and laypersons as though it were a serious, physical illness that causes suffering, comparable, for example, to prostate cancer, a disease that is curable before it spreads. Within this paradigm, whatever is causing distress associated with gender dysphoria—whether secondary sex characteristics such as facial hair, nose and jaw shape, presence or absence of breasts, or the primary anatomical sex organs of testes, ovaries, penis, or vagina—should be removed to alleviate the illness. The promise of these interventions is the cure of the gender dysphoria. Frequently, the underlying assumption is that all types of gender dysphoria have their ultimate origin in “brain structures,” often determined embryonically. Although numerous studies have been undertaken to attempt to demonstrate a distinctive physical “brain structure” associated with transgender identity, as of yet there is no credible scientific evidence that these patients have any defining abnormality in

brain structure that precedes the onset of gender dysphoria.¹⁸ More recent studies demonstrating diverse MRI patterns seem to be adding to the hypothesis that brain may be different in these groups but whether the differences are caused by the identity or themselves cause the identity is unclear. Most authorities in the field are clear such data are used to build an etiological hypothesis and do not justify statements such as gender dysphoria is a biological illness.¹⁹

Gender dysphoria is a *psychiatric* rather than a *medical* diagnosis. Since its inception in DSM-III, it has always and only been specified in the psychiatric DSM manuals. Notably, *gender dysphoria is the only psychiatric condition to be treated by surgery*, even though no endocrine or surgical intervention package corrects any identified biological abnormality (cf. body integrity identity disorder (BIID) (See Levine, *Reflections*, at 240.)) In my opinion, the “affirmation” treatment protocols using endocrine and surgical “treatments” to change a psychiatric condition are not accepted by the relevant scientific community, are supported by only “weak evidence” from methodologically defective research studies, and have no known, nor published error rates. For example, in the Bränström., et.al., study, an enormous part of the sample was “lost” and never followed up. The authors failed to explore available data to see how many of these patients have de-transitioned, died via suicide, etc. One has to wonder why the suicide rate is reportedly so very high for patients who received trans genital surgery. In sum, these “treatments” remain experimental and poorly studied and we’ll need much more and much higher

¹⁸ See Mueller, De Cuypere & T’Sjoen. Transgender research in the 21st century: A selective critical review from a neurocognitive perspective. *American Journal of Psychiatry* 174: 12, 2017.

¹⁹ See Mueller SC, et al The Neuroanatomy of Transgender Identity: Mega-Analytic Findings From the ENIGMA Transgender Persons Working Group. *J Sex Med.* 2021 Jun;18(6):1122-1129. doi: 10.1016/j.jsxm.2021.03.079. Epub 2021 May 22. PMID: 34030966

quality scientific research before we will know if such “treatments” are actually helping or injuring patients. I note hormonal and surgical treatments for gender discordant patients have been increasingly done over a 50-year period and yet no reliable, valid protocols for evaluation or treatment have been properly researched, nor generally accepted by the relevant scientific community, nor published with methodologically sound error rates. For decades, vulnerable patients struggling with gender identity issues have deserved better, more clearly effective, less hazardous, less ideologically tainted, and properly researched interventions—they are still waiting.

24. The second way gender dysphoria can be effectively and alternatively conceptualized is in developmental terms, as an adaptation to a psychological problem that was first manifested as a failure to establish a comfortable conventional sense of self in early childhood. This paradigm starts from the premise that all human lives are influenced by past processes and events. Trans lives are not exceptions to this axiom. (Levine, *Reflections*, at 238.) MHPs who think of gender dysphoria through this paradigm may work both to identify and address causes of the basic problem of the deeply uncomfortable self, and also to ameliorate suffering when the underlying problem cannot be solved. They work with the patient and (ideally) family to inquire what forces may have led to the trans person repudiating the gender associated with his sex. The developmental paradigm is mindful of biologically induced temperamental, parental bonding, psychological, sexual, and physical trauma influences, and the fact that young children work out their psychological issues through fantasy and play. A developmental perspective grasps that children and teens show considerable discontinuities in their interests and capacities over time. Few things are predictable about a six year old over the next decade.

24A. The developmental paradigm recognizes that, with the important exception of genetic sex, essentially all aspects of an individual’s identity evolve—often markedly—across the

individual's lifetime. This includes gender. Some advocates assert that a transgender identity is biologically caused, fixed from early life, and present in an unchanging manner. Taking this line, Dr. Adkins asserts that gender identity is "fixed." (Adkins 4.) This assertion, however, is not supported by science.²⁰ In contrast, the developmental paradigm points to the sudden enormous increase in incidence of child and adolescent gender dysphoria over the last twenty years in North America and Europe. This points to sociological-psychological processes rather than a biological one. From the beginning of epidemiological research into this arena, there have always been some countries, Poland and Australia, for example, where the sex ratios were reversed as compared to North America and Europe. This, too, points to the powerful effect of cultural influences.²¹

25. In recent years, for adolescent patients, intense involvement with online transgender communities and virtual friends who have never been seen in person is reportedly the rule rather than the exception. The developmental paradigm does not preclude such external social influences.

26. The third paradigm through which gender dysphoria is alternatively conceptualized is political, from a sexual minority rights perspective. Under this paradigm, any response other than medical and societal affirmation and implementation of a patient's claim to be the opposite gender or a non-binary person is a violation of the individual's civil right to self-expression. Any effort to ask "why" questions about the patient's condition, or to address underlying causes, is viewed as a violation of autonomy and civil rights. In the last few years, this paradigm has

²⁰ Even the advocacy organization The Human Rights Campaign asserts that a person can have "a fluid or unfixed gender identity." <https://www.hrc.org/resources/glossary-of-terms>.

²¹ See Levine, Ethical Concerns, at 8 (citing M. Aitken, T. D. Steensma, et al. (2015), Evidence for an Altered Sex Ratio in Clinic-Referred Adolescents with Gender Dysphoria, *J. of Sexual Medicine* J. 12(3) 756 at 756-63).

been successful in influencing public policy, the education of pediatricians, endocrinologists, and many mental health professionals, and local ordinances prohibiting “conversion therapy.” Activists, legal professionals, and politicians should note that this political hypothesis—as powerful as it has become—has never been *scientifically* validated and might, in the end, be far more damaging than helpful to suffering, vulnerable gender discordant patients.

Mental health diagnoses are influenced by political process (voting by committee), as illustrated by a great deal of political effort that went into the European classification system called ICD-11 to reclassify the label Gender Incongruence not as a mental illness (similar to the DSM-5’s classification of Gender Dysphoria as a disorder) but as merely a condition affecting sexual health.²² Clearly, political sensibilities can sway the thinking of professionals in ways unsupported by the evidence.

F. Competing models of therapy of minors

27. Because of the complexity of the human psyche and the avoidance of running controlled experiments in this area, substantial disagreements among professionals about the causes of psychological disorders and the appropriate therapeutic responses are not unusual. When we add to this the very different paradigms for understanding transgender phenomena, it is not surprising that such disagreements also exist with regard to appropriate therapies for patients experiencing gender-related distress. I summarize below the leading approaches, and offer certain observations and opinions concerning them.

²² See Reed GM, Drescher J, Krueger RB, Atalla E, Cochran SD, First MB, Cohen-Kettenis PT, Arango-de Montis I, Parish SJ, Cottler S, Briken P, Saxena S. Disorders related to sexuality and gender identity in the ICD-11: revising the ICD-10 classification based on current scientific evidence, best clinical practices, and human rights considerations. *World Psychiatry*. 2016 Oct;15(3):205-221. doi: 10.1002/wps.20354. Erratum in: *World Psychiatry*. 2017 Jun;16(2):220. PMID: 27717275; PMCID: PMC5032510.

1. The “watchful waiting” therapy model

28. I review below the uniform finding of follow-up studies that the large majority of children who present with gender dysphoria will desist from desiring a transgender identity by adulthood if left untreated. (See *infra* ¶ 60.)

29. When a pre-adolescent child presents with gender dysphoria, a “watchful waiting” approach avoids hormonal treatments to allow for the developmental nature of gender identity in children to naturally resolve—that is, take its course from forces within and surrounding the child. Watchful waiting has two versions:

- a. **Model 1.** Treating any other psychological co-morbidities—that is, other mental illnesses as defined by the DSM-5—that the child may exhibit (separation anxiety, bedwetting, attention deficit disorder, obsessive-compulsive disorder, depression) without a focus on gender; and
- b. **Model 2.** No medical intervention, but regular follow-up. This might be labeled a “hands off” approach.

2. The psychotherapy model: Alleviate distress by identifying and addressing causes

30. One of the foundational principles of psychotherapy has long been to work with a patient to identify the causes of observed psychological distress and then to address those causes as a means of alleviating the distress. The National Institute of Mental Health has promulgated the idea that 75% of adult psychopathology has its origins in childhood experience.

31. Many experienced practitioners in the field of gender dysphoria, including myself, have believed that it makes sense to employ these long-standing tools of psychotherapy for patients suffering gender dysphoria, asking the question as to what factors in the patient’s life are the determinants of the patient’s repudiation of his or her natal sex. (Levine, *Ethical Concerns*,

at 8.) I and others have reported success in alleviating distress in this way for at least some patients, whether or not the patient's sense of discomfort or incongruence with his or her natal sex entirely disappeared. Relieving accompanying psychological co-morbidities leaves the patient freer to consider the pros and cons of transition as he or she matures.

32. Among other things, the psychotherapist who is applying traditional methods of psychotherapy may help—for example—the male patient appreciate the wide range of masculine emotional and behavioral patterns as he grows older. He may discuss with his patient, for example, that one does not have to become a “woman” in order to be kind, compassionate, caring, noncompetitive, and devoted to others' feelings and needs. Many biologically male trans individuals, from childhood to older ages, speak of their perceptions of femaleness as enabling them to discuss their feelings openly, whereas they perceive boys and men to be constrained from emotional expression within the family and larger culture. Men, of course, can be emotionally expressive, just as they can wear pink. Converse examples can be given for girls and women. These types of ideas regularly arise during psychotherapies.

33. Many gender-nonconforming children and adolescents in recent years derive from minority and vulnerable groups who have reasons to feel isolated and have an uncomfortable sense of self. A trans identity may be a hopeful attempt to redefine the self in a manner that increases their comfort and decreases their anxiety. The clinician who uses traditional methods of psychotherapy may not focus on their gender identity, but instead work to help them to address the actual sources of their discomfort. Success in this effort may remove or reduce the desire for

a redefined identity. This often involves a focus on disruptions in their attachment to parents in vulnerable children, for instance, those in the foster care system.²³

34. Because “watchful waiting” can include treatment of accompanying psychological co-morbidities, and the psychotherapist who hopes to relieve gender dysphoria may focus on potentially causal sources of psychological distress rather than on the gender dysphoria itself, there is no sharp line between “watchful waiting” and the psychotherapy model in the case of prepubescent children. The goals of psychotherapy are improved mental health and improved social, educational, and intrafamilial functioning; it is not to convert a minor’s gender identity. The fact that parents almost always prefer that the child desist from their current identity should not blind the court about the actually goals of the long-term relation-based psychotherapeutic intervention.

35. To my knowledge, there is no credible scientific evidence beyond anecdotal reports that psychotherapy can enable a return to male identification for genetically male boys, adolescents, and men, or return to female identification for genetically female girls, adolescents and women. Controlled studies have never been attempted. On the other hand, anecdotal case report evidence of such outcomes does exist; I and other clinicians have witnessed reinvestment in the patient’s biological sex in some individual patients who are undergoing psychotherapy. The Internet contains many such reports, and I published a paper recently on a patient who sought my therapeutic assistance to reclaim his male gender identity after 30 years living as a woman and is in fact living as a man today. (Levine, *Transitioning*, at 1.) I have seen children desist even before puberty in response to thoughtful parental interactions and a few meetings of the child with

²³ See S. Levine (2017), *Transitioning Back to Maleness*, Arch of Sexual Behavior at 7, DOI: 10.1007/s10508-017-1136-9) (“*Transitioning*”).

a therapist. Recently, a paper reviewing the phenomenon of de-transition has been published in which the authors claims to have identified 16,000 case reports world wide on the Internet.²⁴

3. The affirmation therapy model for minors and adolescents

36. While it is widely agreed that the therapist should not directly challenge a claimed transgender identity in a child, some advocates and practitioners go much further and recommend that any expression of transgender identity should be immediately accepted and thoroughly affirmed by means of consistent use of clothing, toys, pronouns, etc. associated with transgender identity. These advocates treat any question about the causes of the child's transgender identification as inappropriate. They assume that observed psychological co-morbidities in the children or their families are unrelated or will get better with transition and need not be addressed by the MHP who is primarily providing supportive guidance concerning the child's gender identity.

37. Some advocates, indeed, assert that unquestioning affirmation of any claim of transgender identity in children is essential, and that the child will otherwise face a high risk of suicide or severe psychological damage. Dr. Adkins appears to follow this line, asserting that "gender-affirming medical care can be lifesaving treatment and can improve . . . health outcomes." (Adkins 16.) I address claims about suicide and health outcomes below.

38. Dr. Adkins asserts that fully supported social transition is the "only treatment for pre-pubertal children." (Adkins 7) As my discussion indicates, this is not correct. Some advocates also assert that this "affirmation therapy" model is accepted and agreed with by the overwhelming majority of mental health professionals. It may be true for those practicing in the "affirma-

²⁴ See Expósito-Campos P. A Typology of Gender Detransition and Its Implications for Healthcare Providers. *J Sex Marital Ther.* 2021;47(3):270-280. doi: 10.1080/0092623X.2020.1869126. Epub 2021 Jan 10. PMID: 33427094

tion” treatment industry and those who know little of the science being discussed here. One respected academic in the field has recently written that, on the contrary, “almost all clinics and professional associations in the world” do *not* use “gender affirmation” for prepubescent children and instead “delay any transitions after the onset of puberty.”²⁵

39. Even the current guidelines published by the World Professional Association for Transgender Health (WPATH), an organization which in general leans strongly towards affirmation in the case of adults, does not specify affirmation of transgender identity as the indicated therapeutic response for young children. Instead, WPATH guidelines recognize that social transition in early childhood “is a controversial issue, and divergent views are held by health professionals”; state that “[t]he current evidence base is insufficient to predict the long-term outcomes of completing a gender role transition during early childhood”; and acknowledge that “previously described relatively low persistence rates of childhood gender dysphoria” are “relevant” to the wisdom of social transition in childhood.²⁶ Given that the majority of such children naturally grow out of the problem even WPATH calls for a careful process of discernment and decision by the family in consultation with the MHP.

39. Dr. Adkins cites a statement published by the American Academy of Pediatrics (Rafferty 2018) as asserting that “gender transition” “is safe, effective, and medically necessary treatment for the health and wellbeing of children and adolescents suffering from gender dysphoria.” (Adkins 6 & n.6.) Dr. Adkins neglects to mention that a detailed and peer-reviewed review of

²⁵ See J. Cantor (2019), Transgender and Gender Diverse Children and Adolescents: Fact-Checking of AAP Policy, *J. of Sex & Marital Therapy* at 1, DOI: 10.1080.0092623X.2019.1698481

²⁶ See Eli Coleman, et al., *Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People*, 7th ed., 13 *Int’l J. of Transgenderism* 165 (2012); WPATH, *Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People* (7th ed.) (2012), at 17, <https://www.wpath.org/publications/soc>.

that AAP statement by prominent researcher James Cantor concluded that “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,” and described Rafferty 2018 as “a systematic exclusion and misrepresentation of entire literatures.” (See Cantor, *Fact-Checking of AAP Policy*) Based on my professional expertise and my review of the literature, I agree with Dr. Cantor’s evaluation of Rafferty 2018. It also should be noted that subcommittee reports from larger organizations pass through other committees for approval of policy recommendations. Readers may erroneously assume this is a scientific process when in fact it is a political voting process. Organizational committee processes review the literature in very different ways that peer review of journal articles which have to pass through several reviewers and the editor’s sensibilities of publication worthiness.

40. The DSM-5 added—for both children and adolescents—a requirement that a sense of incongruence between biological and felt gender must last at least six months as a precondition for a diagnosis of gender dysphoria, precisely because of the risk of “transitory” symptoms and “hasty” diagnosis that might lead to “inappropriate” treatments.²⁷

41. I do not know what proportion of practitioners are using which model. However, in my opinion, in the case of young children, prompt and thorough affirmation of a transgender identity disregards the principles of child development and family dynamics, and is not supported by credible, reliable-valid scientific evidence. Rather, the MHP must focus attention on the child’s underlying internal and familial issues. Ongoing relationships among the MHP, the

²⁷ See K. Zucker (2015), *The DSM-5 Diagnostic Criteria for Gender Dysphoria*, in C. Trombetta et al. (eds.), *Management of Gender Dysphoria: Multidisciplinary Approach*, DOI 10.1007/978-88-470-5696-1_4 (Springer-Verlag Italia 2015).

parents, and the child are vital to help the parents, child, other family members, and the MHP to understand the issues that need to be dealt with over time by each of them.

42. Likewise, since the child's sense of gender develops in interaction with his parents and their own gender roles and relationships, the responsible MHP will almost certainly need to delve into family and marital dynamics.

G. Gender dysphoria does not have a single developmental pathway

43. In my opinion, it is not possible to make a single, categorical statement about the proper treatment of children presenting with gender dysphoria or other gender-related issues. There is no single pathway of development and outcomes governing transgender identity, nor one that predominates over the large majority of cases. Instead, as individuals grow up and age, depending on their differing psychological, social, familial, and life experiences, their outcomes differ widely. But I can categorically opine that unproven, experimental affirmation "treatments" should not be used on uninformed or misinformed patients and families.

44. As to causes in children, details about the onset of gender dysphoria may be found in an understanding of family relationship dynamics. In particular, the relationship between the parents themselves, between each of the parents and the child, and between each of the siblings and the child should be well understood by the MHP. A disturbingly large proportion of children who seek professional care in connection with gender issues have a wider history of psychiatric co-morbidities.²⁸ As a 2017 study from the Boston Children's Hospital Gender Management Service program reported, "Consistent with the data reported from other sites, this investigation

²⁸ See Becerra-Culqui TA, Liu Y, Nash R, Cromwell L, Flanders WD, Getahun D, Giammattei SV, Hunkeler EM, Lash TL, Millman A, Quinn VP, Robinson B, Roblin D, Sandberg DE, Silverberg MJ, Tangpricha V, Goodman M. Mental Health of Transgender and Gender Nonconforming Youth Compared With Their Peers. *Pediatrics*. 2018 May; 141(5):e20173845. doi: 10.1542/peds.2017-3845. Epub 2018 Apr 16. PMID: 29661941; PMCID: PMC5914494

documented that 43.3% of patients presenting for services had significant psychiatric history, with 37.1% having been prescribed psychotropic medications, 20.6% with a history of self-injurious behavior, 9.3% with a prior psychiatric hospitalization, and 9.3% with a history of suicide attempts.”²⁹ It seems likely that an even higher proportion will have had prior undiagnosed psychiatric conditions. So a slow, comprehensive, trust building process between therapist and family members is the ideal standard of care for gender dysphoric minors.

H. Understanding WPATH and its “Standards of Care”

45. Dr. Adkins notes that she is a member of the World Professional Association for Transgender Health (WPATH), invokes the guidelines that that organization publishes, and asserts that those guidelines are “widely accepted.” (Adkins 2, 6.) I previously have noted two independent reviews of the WPATH guidelines that contradict Dr. Adkin’s belief in their trustworthiness. Accordingly, I provide some context concerning that private organization and its guidelines.

46. I was a member of the Harry Benjamin International Gender Dysphoria Association from 1974 until 2001. From 1997 through 1998, I served as the Chairman of the eight-person International Standards of Care Committee that issued the fifth version of the Standards of Care. I resigned my membership in 2002 due to my regretful conclusion that the organization and its recommendations had become dominated by politics and ideology, rather than by proper, reliable scientific methodologies, as was its mission years earlier. In approximately 2007, the Henry

²⁹ See Perez-Brumer A, Day JK, Russell ST, Hatzenbuehler ML. Prevalence and Correlates of Suicidal Ideation Among Transgender Youth in California: Findings From a Representative, Population-Based Sample of High School Students. *J Am Acad Child Adolesc Psychiatry*. 2017 Sep;56(9):739-746. doi: 10.1016/j.jaac.2017.06.010. Epub 2017 Jul 5. PMID: 28838578; PMCID: PMC5695881. L. Edwards-Leeper, *Psychological Profile*.

Benjamin International Gender Dysphoria Association changed its name to the World Professional Association for Transgender Health.

47. WPATH is a voluntary membership, activist advocacy organization. Since at least 2002, attendance at its biennial meetings has been open to trans individuals who are *not licensed professionals*. While this ensures taking patients' perceived needs, values, and sensibilities into consideration, it limits the ability for honest, methodologically competent scientific debate. It also means that WPATH can no longer be reasonably considered a purely professional or scientific organization.

48. WPATH takes a very narrow and ideologically driven view on increasingly controversial issues as to which there is a wide range of opinion among professionals. WPATH explicitly views itself as not merely a scientific organization, but also as an advocacy organization. These are obviously incompatible goals. (Levine, *Reflections*, at 240.) WPATH is supportive to those who want sex reassignment surgery ("SRS") even though such surgery is not supported by credible, reliable-valid scientific research, not accepted by the relevant scientific community, and has no known error rates, and no careful systematic follow-up using agreed upon criteria to even assess multifaceted failure rates. Skepticism as to the benefits of SRS to patients, and strong alternate views, are not well tolerated in discussions within the organization. Such views have been literally shouted down and effectively silenced by the large numbers of nonprofessional adults who attend the organization's biennial meetings. Such "mob rule" is quite incompatible with appropriate, competent methodological discussions. Skepticism about hormones and surgeries that have been done for 50 years also is not warmly welcomed by those whose careers and expertise are based on their continued use.

49. The Standards of Care (“SOC) are the product of an enormous effort, but the document is not a politically neutral one. The most serious limitations and defects of the Standards of Care, however, are caused by the decades-long and continuing lack of credible, rigorous research in the field, which allows room for passionate convictions and ongoing controversies on how to care for the transgendered.³⁰

50. In recent years, WPATH has fully adopted—in the absence of reliable, valid scientific research—some mix of the medical and civil rights paradigms discussed above. It has downgraded the role of counseling or psychotherapy as a requirement for these life-changing processes. WPATH no longer considers preoperative psychotherapy to be a requirement. It is important to WPATH that the person has gender dysphoria; but the pathway to the development of this state is not. (Levine, *Reflections*, at 240.) The trans person is assumed to have thoughtfully considered his or her options before seeking hormones, for instance. In clear violation of ethics rules, licensing regulations, and legal requirements, informed consent is neither standardized nor reasonably complete. The informed consent process is essential to protect the fundamental right of all patients to control their health care with informed choices. Informed consent documentation is needed to protect the doctor and the patient by verifying that the patient understands the potential benefits and the risk of specific harms including the risks of proceeding with such experimental gender affirmation treatments in the face of the ongoing lack of scientific evidence that might demonstrate these treatments are safe and effective. Additional risks include the lack of any credible long-term scientific follow-up studies showing the safety and effectiveness of such experimental treatments over time. Finally, informed consent documents should verify a

³⁰ See, e.g., Vrouenraets et al, *Early Medical Treatment of Children and Adolescents With Gender Dysphoria: An Empirical Ethical Study*, *Journal of Adolescent Health* 57 (2015) 367e373.

patient has been presented with and thoughtfully considered alternative treatments including no treatment. Many of my older adolescent patients who have received hormones signed an informed consent document on the first or second visit to a professional who knew little about them other than their self-reporting, “I am trans.”

51. Most psychiatrists and psychologists who treat patients suffering sufficiently severe distress from gender dysphoria to seek inpatient psychiatric care are *not* members of WPATH. Many psychiatrists and psychologists who treat some patients suffering gender dysphoria on an outpatient basis are not members of WPATH. WPATH represents a self-selected subset of the profession along with its many non-professional members; it does not capture the clinical experiences of others. WPATH claims to speak for the medical profession; however, it does not welcome skepticism nor competent scientific debate and analysis and therefore, deviates from the philosophical core of medical science.

52. For example, in 2010 the WPATH Board of Directors voted (note this is a consensus-seeking and not a reliable-valid scientific methodology) to issue a statement advocating that incongruence between sex and felt gender identity should cease to be identified in the DSM as a pathology. This position was debated but voted down by the (much larger) American Psychiatric Association, which maintained the definitions and diagnoses of gender dysphoria as a pathology in the DSM-5 manual, issued in 2013. By declaring that all forms of gender identity (some list over 120 different labels) are normal, the WPATH voting process involved fiat and not a proper-

rigorous scientific analysis and consideration of alternate ways of defining mental abnormalities. The WPATH voting process was done to bolster the self-esteem of patients and to decrease social discrimination. It was not based on evidence.³¹

53. In my experience some WPATH members practicing in gender affirmative clinics have little ongoing experience with the mentally ill and are not deeply experienced with recognizing and treating frequently associated psychiatric co-morbidities. Because the 7th version of the WPATH Standards of Care recommendations deleted the requirement for psychotherapy, trans care facilities that consider these standards sufficient are permitting patients to be counseled to transition by means of social presentation, hormones, and surgery by professionals inexperienced with ongoing psychotherapy rather than those with medical or PhD degrees who are more likely during their careers to have considered the developmental forces shaping identity and behavior.

As a result of the downgrading of the role of the psychiatric assessment of patients, new “gender affirming” clinics have arisen in many urban settings that quickly (sometimes within an hour’s time) recommend transition. Patients and their families are not told they are entering an experimental and potentially dangerous process. Concerned parents who brought their child or teen to a professional office expecting to learn what is going on with their child instead often leave feeling overwhelmed, disoriented, and fearful for the future health and safety of that child. Some report being treated as if they are the enemy of the child because they are not immediately supportive of the clinics’ “affirmative” responses. I am concerned that such defective

³¹ See WPATH *De-Psychopathologisation Statement* (May 26, 2010), available at wpath.org/policies (last accessed January 21, 2020).

practices are increasingly wide-spread. Such practices are the result of political advocacy and are not based on credible, reliable, valid science.

Medical subspecialty sets of guidelines are expected to be offered every five years because of the advances in the field. WPATH's eighth's SOC is two years overdue presumably because of the controversies involving minor children and teens discussed above. A recent review of twelve guidelines related to the care of the transgendered gave WPATH's SOC low marks based on numerous criteria including the scientific foundation of its recommendations and conflicts of interest.³²

III. SOCIAL TRANSITION OF PRE-PUBERTAL CHILDREN IS AN EXPERIMENTAL INTERVENTION THAT SUBSTANTIALLY CHANGES OUTCOMES

54. A distinctive and critical characteristic of juvenile gender dysphoria is that multiple studies from separate groups and at different times have reported that in the large majority of patients, absent a substantial intervention such as social transition and/or hormone therapy, gender dysphoria does *not* persist through puberty. A recent article reviewed 11 existing follow-up studies and reported that “every follow-up study found the same thing: By puberty, the majority of GD children ceased to want to transition.”³³ Another article summarized the existing data as showing that “Symptoms of GID [i.e., gender identity disorder] at prepubertal ages decrease or

³² 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 Apr 29;11(4):e048943. doi: 10.1136/bmjopen-2021-048943. PMID: 33926984; PMCID: PMC8094331

³³ See Cantor JM. Transgender and Gender Diverse Children and Adolescents: Fact-Checking of AAP Policy. *J Sex Marital Ther*. 2020;46(4):307-313. doi:10.1080/0092623X.2019.1698481. Epub 2019 Dec 14. PMID: 31838960; see also S. Adelson & American Academy of Child & Adolescent Psychiatry (2012), Practice Parameter on Gay, Lesbian, or Bisexual Sexual Orientation, Gender Nonconformity, and Gender Discordance in Children and Adolescents, *J. Am. Acad Child Adolescent Psychiatry* 51(9) 957 at, 963 (“Practice Parameter”) (“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.”).

disappear in a considerable percentage of children (estimates range from 80-95%).” A 2021 publication found that only 12% of previously evaluated grade school-aged children persisted in their trans identities many years later. (Singh, Bradley, and Zucker, *Frontiers of Psychiatry*.³⁴

55. It is not yet known how to distinguish those children who will desist from that small minority whose trans identity will persist.³⁵ Further, it is apparent in the adolescent phenomenon of rapid onset of gender dysphoria following a gender normative childhood that gender identity is not inherently stable. Some desist and others evolve dramatically to become more comfortable with a more expansive gender role.

56. Desistance (a patients’ willing reacceptance of their biological sex through normal developmental processes) within a relatively short period may also be a common outcome for post-pubertal youths who exhibit rapid onset gender disorder. I observe an increasingly vocal online community of young women who have reclaimed a female identity after claiming a male gender identity at some point during their teen years. Reliable, valid scientific data on outcomes for this age group with and without therapeutic interventions is not yet available. A recent review of de-transitioning claimed to have identified 16,000 case histories in a search of proliferating websites devoted to this topic.³⁶ In the past WPATH has simply declined to discuss this vital topic, another example of WPATH’s political consensus-seeking, increasingly anti-science methodology.

³⁴ See P. T. Cohen-Kettenis, H. A. Delemarre-van de Waal et al. (2008), *The Treatment of Adolescent Transsexuals: Changing Insights*, *J. Sexual Medicine* 5(8) 1892 at 1895.

³⁵ Zucker, *Gender Dysphoria in Children and Adolescents*, in *Principles and Practices of Sex Therapy* 6th edition, Guilford Press, 2020; Levine, *Ethical Concerns*, at 9.

³⁶ Pablo Exposito-Campos. A typology of gender detransition and its implications for health care providers *J Sex & Marital Therapy* 2020 <https://doi.org/10.1080/0092623x.2020.1869126>

57. In contrast, there is now data that suggests that encouraging social transition dramatically changes outcomes and often “locks in” a patient’s journey into a life course of dependence on experimental hormone “treatments.” A prominent group of authors has written that “[t]he gender identity affirmed during puberty appears to predict the gender identity that will persist into adulthood.” Similarly, a comparison of recent and older studies suggests that when an “affirming” methodology is used with young children, a substantial proportion of children who would otherwise have desisted by adolescence—that is, achieved comfort identifying with their natal sex—instead persist in a transgender identity.³⁷

58. Indeed, a review of multiple studies of boys treated for gender dysphoria across the last three decades found that early social transition to living as the opposite sex severely reduces the likelihood that the child will revert to identifying with the child’s natal sex. That is, while studies that began before the widespread use of social transition for young children reported desistance rates in the range of 80-98%, a more recent study reported that fewer than 20% of boys who engaged in a partial or complete transition prior to puberty desisted when surveyed at age 15.³⁸ Another study found that social transition by the child was found to be strongly correlated with persistence for natal boys, but not for girls.³⁹

³⁷ Zucker KJ (2018) The myth of persistence. *International Journal of Transgenderism* 19, 231-245.

³⁸ See T.D. Steensma, J.K. McGuire et al. (2013), *Factors Associated with Desistance & Persistence of Childhood Gender Dysphoria: A Qualitative Follow-up Study*, *J. of the Am. Academy of Child and Adolescent Psychiatry*. 52, 582; see also C. Guss et al. (2015), *Transgender and Gender Nonconforming Adolescent Care: Psychosocial and Medical Considerations*, *Curr. Opin. Pediatrics* 26(4) 421 at 421 (“TGN Adolescent Care”).

³⁹ Zucker, *Myth of Persistence* (citing T.D. Steensma, J.K. McGuire et al. (2013), *Factors Associated with Desistance & Persistence of Childhood Gender Dysphoria: A Qualitative Follow-up Study*, *J. of the Am. Academy of Child and Adolescent Psychiatry*. 52, 582.

Some vocal practitioners of prompt affirmation and social transition claim that essentially *no* children who come to their clinics exhibiting gender dysphoria or cross-gender identification desist in that identification and return to a gender identity consistent with their biological sex. This is a very large change as compared to the desistance rates documented apart from social transition. Some researchers who generally advocate prompt affirmation and social transition also acknowledge a causal connection between social transition and this change in outcomes.⁴⁰

59. Accordingly, I agree with Zucker, a noted researcher in the field, that social transition in children must be considered “a form of psychosocial treatment.” (Zucker, *Debate*, at 1.)

59A. Dr. Adkins speaks of the use of puberty blockers as though this major hormonal disruption of some of the most basic aspects of ordinary human development were a small thing, and entirely benign. (Adkins 8.) It should be understood that puberty blockers are usually administered to early-stage adolescents as part of a path that includes social transition. Maintaining young teens in a childlike physical prepubertal state while their peers and undergoing puberty with its cognitive, physical, social, and sexual changes cannot be considered a mere time out or pause. It further separates the patients from their peers inducing many subtle changes that are not apparent to a medical professional who is primarily monitoring endocrine function. Puberty blockade has psycho-social-sexual implications. Without studies of the long term effects of puberty blockers, minimizing their potential harm by declaring their effects as reversible does not

⁴⁰ See Guss, *TGN Adolescent Care*, at 2 (“The gender identity affirmed during puberty appears to predict the gender identity that will persist into adulthood.” “Youth with persistent TNG [transgender, nonbinary, or gender-nonconforming] identity into adulthood . . . are more likely to have experienced social transition, such as using a different name . . . which is stereotypically associated with another gender at some point during childhood.”)

put one on firm ethical grounds. That puberty may resume when these agents are stopped does not detract from the above unknowns. Plaintiff's experts suggest that these agents relieve gender dysphoria but this was not apparent in the reviews done by Finland, Sweden, and UK. Similarly, a recent study found no changes in mental health and social functioning on those on puberty blockade.⁴¹

60. So far as I am aware, no study yet reveals whether the life-course mental and physical health outcomes for this relatively new class of “persisters” are more similar to the non-transgender population, or to the notably worse outcomes exhibited by the transgender population generally.⁴²

61. However, I agree with Zucker who has written, “we cannot rule out the possibility that early successful treatment of childhood GID will diminish the role of a continuation of GID into adulthood. If so, successful treatment would also reduce the need for the long and difficult process of sex reassignment which includes hormonal and surgical procedures with substantial medical risks and complications.”⁴³

By the same token, a therapeutic methodology for children that *increases* the likelihood that the child will continue to identify as the opposite gender into adulthood will *increase* the

⁴¹ See Carmichael P, Butler G, Masic U, Cole TJ, De Stavola BL, Davidson S, Skageberg EM, Khadr S, Viner RM. 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. PLoS One. 2021 Feb 2;16(2):e0243894. doi: 10.1371/journal.pone.0243894. PMID: 33529227; PMCID: PMC7853497.

⁴² See, e.g., B. Ehrensaft (2015), *Listening and Learning from Gender-Nonconforming Children*, The Psychoanalytic Study of the Child 68(1) 28 at 34 (“In my own clinical practice . . . of those children who are carefully assessed as transgender and who are allowed to transition to their affirmed gender, we have no documentation of a child who has ‘desisted’ and asked to return to his or her assigned gender.”)

⁴³ See Zucker, *Myth of Persistence*, at 8 (citing H. Meyer-Bahlburg (2002), *Gender Identity Disorder in Young Boys: A Parent- & Peer-Based Treatment Protocol*, Clinical Child Psychology & Psychiatry 7, 360 at 362).

need for the long and potentially problematic processes of hormonal and genital and cosmetic surgical procedures.

62. Given these facts, encouraging social transition in children remains controversial. Supporters of such transition acknowledge that “Controversies among providers in the mental health and medical fields are abundant . . . These include differing assumptions regarding . . . the age at which children . . . should be encouraged or permitted to socially transition These are complex and providers in the field continue to be at odds in their efforts to work in the best interests of the youth they serve.”⁴⁴ Transition then, should be undertaken only subject to standards, protocols, and reviews appropriate to actual clinical experiments, which involve time-honored careful processes supervised by an Institutional Review Board with a predetermined method of evaluation, primary and secondary endpoints and safeguards to protect the rights of patients to truly informed consent. These protections are not present in the “affirmation” treatment industry, where vulnerable patients are receiving “treatments” that lack sufficient proof of efficacy and safety.

63. In sum, therapy for young children that encourages transition cannot be considered to be neutral, but instead is an experimental procedure that has a high likelihood of altering the life path of the child, with highly unpredictable effects on mental and physical health, suicidality, and life expectancy. Claims that a civil right is at stake do not change the fact that what is proposed is a social and medical experiment on vulnerable patients. (Levine, *Reflections*, at 241.)

⁴⁴ See A. Tishelman et al. (2015), *Serving Transgender Youth: Challenges, Dilemmas and Clinical Examples*, Prof. Psychol. Res. PR. at 11, DOI: 10.1037/a0037490 (“*Serving TG Youth*”).

IV. “AFFIRMATION” HAS NOT BEEN SHOWN TO REDUCE SUICIDE OR GENERALLY RESULT IN BETTER OUTCOMES

64. I am aware that organizations including the American Academy of Pediatrics and Parents, Families and Friends of Lesbians and Gays (PFLAG)) have published statements that suggest that all children who express a desire for a transgender identity should be promptly supported in that claimed identity. This position appears to rest on the belief—pushed by advocacy organizations—that science has already established that prompt “affirmation” is best for all patients, including all children, who present with a transgender identity. Dr. Adkins appears to hold this belief. (*See, e.g.*, Adkins 5, 16.) But it is scientifically unsupported. It ignores both what is known and what is unknown.

A. The knowledge base concerning the causes and treatment of gender dysphoria has low scientific quality.

66. In 2009 the Endocrine Society published clinical guidelines for the treatment of patients with persistent gender dysphoria.⁴⁵ 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. This guideline used the GRADE (Recommendations, Assessment, Development, and Evaluation) system for rating clinical recommendations. The publication stated, “the strength of recommendations and the quality of evidence was low or very low.” Low recommendations indicate, “Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to

⁴⁵ 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).

change the estimate.” Very low recommendations mean that “any estimate of effect is very uncertain.” These guidelines were updated eight years later.⁴⁶ The low quality of evidence persists to the current day as the controversy over these “treatments” is accelerating in recent years. Scientific progress has not been made even though the treatments have greatly expanded.

A 2020 Cochrane review of hormonal treatment outcomes for male-to-female transitioners older than 16 years found “insufficient evidence to determine the efficacy or safety of hormonal treatment approaches.” It is remarkable that decades after the first transitioned male-to-female patient, quality evidence for the benefit of transition is still lacking.⁴⁷

Two systematic reviews commissioned by the Endocrine Society in 2017 concur with the finding of the weak evidence base, stating that the finding of benefits of hormonal interventions in terms of “psychological functioning and overall quality of life” comes from “low-quality evidence (i.e., which translates into low confidence in the balance of risk and benefits).” Despite this sober assessment, the Endocrine Society instructed clinicians to proceed with treating gender-dysphoric youth with hormonal interventions in its guidelines, which have now been broadly adopted by a number of medical societies.

In the Society for Evidence-Based Gender Medicine (SEGM)’s view, the “low confidence in the balance of risks and benefits” of hormonal interventions calls for extreme caution when working with gender-dysphoric youth, who are in the midst of a developmentally-appropriate phase of identity exploration and consolidation. While there may be short-term psychological

⁴⁶ 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).

⁴⁷ 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. <https://doi.org/10.1002/14651858.CD013138.pub2>, at <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013138.pub2/full>

benefits associated with the administration of hormonal interventions to youth, they must be weighed against the long-term risks to bone health, fertility, and other as yet-unknown risks of life-long hormonal supplementation.

Further, the irreversible nature of the effects of cross-sex hormones, and the potential for puberty blockers to alter the natural course of identity formation should give pause to all ethical clinicians. Studies consistently show that the vast majority of patients with childhood-onset gender distress who are not treated with “gender-affirmative” social transition or medical interventions grow up to be LGB adults. However, socially-transitioned and puberty-suppressed children have much higher rates of persistence of transgender identification (96%), necessitating future invasive and risky treatments. The trajectory of the novel, and currently the most common presentation of gender dysphoria, which emerges for the first time in adolescence following a gender-normative childhood, is unknown. The number of desisters and detransitioners suggest the rate of regret within this novel cohort will not be as rare as previously estimated.

SEGM’s position is that the significant uncertainties regarding the long-term risk/benefit profile of hormonal interventions call for noninvasive approaches (e.g. psychotherapy, social support, coping and resilience training), as the first line of treatment for youth. If pursued, invasive and potentially irreversible interventions for youth should only be administered in clinical trial settings with rigorous study designs capable of determining whether these interventions are beneficial. In addition to undergoing rigorous psychological and psychiatric evaluations, patients and their families should participate in a valid informed consent process. This process

must accurately disclose the many uncertainties regarding the long-term mental and physical health outcomes of these experimental interventions.⁴⁸

67. Recently, several countries reviewed existent relevant scientific data and concluded that “gender-affirming” medical interventions in young people must be halted.

a. Finland suggested that clinicians wait until age 26 to administer hormones and surgical treatments for trans individuals and recommended psychotherapeutic approaches instead of puberty blockers and hormones

b. The Swedish review found no scientific studies that explain the increase in incidence in children and adolescents who seek the health care because of gender dysphoria. It found no 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. It found 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. It found 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.⁴⁹

⁴⁸ See 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, 3914–3923, <https://doi.org/10.1210/jc.2017-01643>

⁴⁹ See Swedish Agency for Health Technology Assessment and Assessment of Social Services, “Gender dysphoria in children and adolescents: an inventory of the literature: A systematic scoping review at <https://www.sbu.se/307e>

c. The National Institute of Health and Care Excellence (NICE) reviewed the treatments offered for Gender Dysphoria in Great Britain in 2020. NICE undertook two systematic evidence reviews of the use of GnRH agonists (“puberty blockers”) and cross-sex hormones as treatments for gender dysphoric patients <18 years old. These reviews were led by Dr. Hilary Cass and published in March 2021. It found the evidence for using puberty blocking drugs to treat young people struggling with gender identity is “very low quality.” The studies were small and “subject to bias and confounding.” It found “[t]he quality of evidence for these outcomes was assessed as very low certainty.” When the clinical effectiveness of GnRH analogues was compared with psychological support, social transitioning but no medication or no intervention, NICE could not draw conclusions because of the defective way the studies had been designed. The studies were “all small” and lacked control groups. There was “very little data” on any additional interventions—such as counseling or whether other medications were provided along with taking puberty blockers. The review found no evidence of cost-effectiveness of treatment.⁵⁰

The NICE review of cross-sex hormones after age 16 looked at improved mental health, quality of life and body image. The evidence was of “very low” quality. It found “[a]ny potential benefits of gender-affirming hormones must be weighed

⁵⁰ See National Institute for Health and Care Excellence - NICE, Evidence review: Gonadotrophin releasing hormone analogues for children and adolescents with gender dysphoria, 11 March 2021, at <https://www.evidence.nhs.uk/document?id=2334888&returnUrl=search%3fq%3dtransgender%26s%3dDate>

against the largely unknown long-term safety profile of these treatments in children and adolescents with gender dysphoria.”⁵¹

d. A review by Professor Carl Heneghan and editor of British Medical Journal Findings echo what has just been stated but also emphasized the exponential rise in referrals to Gender Identity Service since 2011. This has been noted by many others.⁵²

67. The knowledge base concerning the causes and treatment of gender dysphoria has low scientific quality.

68. In evaluating claims of scientific or medical knowledge, it is important to understand that it is axiomatic in science that no knowledge is absolute, and to recognize the widely accepted hierarchy of reliability when it comes to “knowledge” about medical or psychiatric phenomena and treatments. Unfortunately, in this field opinion and ideological fervor are too often confused with reliable knowledge, rather than clearly locating what exactly is scientifically known. In order of increasing confidence, such “knowledge” may be based upon data comprising of:

a. Expert opinion—it is perhaps surprising to educated laypersons that expert opinion standing alone is the lowest form of knowledge, the least likely to be proven

⁵¹ See National Institute for Health and Care Excellence - NICE, Evidence review: Gender-affirming hormones for children and adolescents with gender dysphoria, 11 March 2021, at <https://www.evidence.nhs.uk/document?id=2334889&returnUrl=search%3ffrom%3d2021-03-10%26q%3dEvidence%2bReview%26to%3d2021-04-01>

⁵² See Arch Dis Child 2018;103:631–6. doi:10.1136/archdischild-2018-314992; see also Gender-affirming hormone in children and adolescents, British Medical Journal, 25th February 2019 at <https://blogs.bmj.com/bmjebmspotlight/2019/02/25/gender-affirming-hormone-in-children-and-adolescents-evidence-review/>

correct in the future, and therefore does not garner as much respect from professionals as what follows.

b. A single case or series of cases (what could be called anecdotal evidence);
(Levine, *Reflections*, at 239.)

c. A series of cases with a control group;

d. A cohort study;

e. A randomized double-blind clinical trial;

f. A review of multiple trials;

g. A meta-analysis of multiple trials that maximizes the number of patients treated despite their methodological differences to detect trends from larger data sets. The current status of the field of gender affirmation treatments has been labeled “low quality” science by multiple reviews with existing studies suffering from numerous methodological defects and misreporting of data thus the field is still at the experimental stage lacking in general acceptance and without known error rates.

68. Before the recent reviews discussed above were published, prominent voices in the field have emphasized the severe lack of scientific knowledge in this field. The American Academy of Child and Adolescent Psychiatry has recognized that “[d]ifferent clinical approaches have been advocated for childhood gender discordance. . . . There have been no randomized controlled trials of any treatment. . . . [T]he proposed benefits of treatment to eliminate gender discordance... must be carefully weighed against... possible deleterious effects.” (Adelson et al., *Practice Parameter*, at 968–69.) Similarly, the American Psychological Association has stated, “because no approach to working with [transgender and gender nonconforming] children

has been adequately, empirically validated, consensus does not exist regarding best practice with pre-pubertal children.”⁵³

69. Critically, “there are no randomized control trials with regard to treatment of children with gender dysphoria.” (Zucker, *Myth of Persistence*, at 8.) On numerous critical questions relating to cause, developmental path if untreated, and the effect of alternative treatments, the knowledge base remains primarily at the level of the practitioner’s exposure to individual cases, or multiple individual cases. As a result, claims to certainty are not justifiable.⁵⁴

70. Large gaps exist in the medical community’s knowledge regarding the long-term effects of sex reassignment surgery and other gender identity disorder treatments in relation to their positive or negative correlation to suicidal ideation, attempts, and completion. What is known, however, is not encouraging.

B. Effective Criticism of Recently Published Research

71. In 2020, Bränström and Panchankis, published a study claiming that “the longitudinal association between gender-affirming surgery and reduced likelihood of mental health treatment lends support to the decision to provide gender-affirming surgeries to transgender individuals who seek them.”⁵⁵ They claimed their research provided the first empirical evidence (sic) that gender transition surgeries had long-term benefits. Nine letters were submitted to the editor from

⁵³ See American Psychological Association, Guidelines for Psychological Practice with Transgender & Gender Nonconforming People (2015), Am. Psychologist 70(9) 832 at 842.

⁵⁴ Levine, *Reflections*, at 239; see American Psychological Association, Guidelines for Psychological Practice with Transgender & Gender Nonconforming People (2015), Am. Psychologist 70(9) 832 at 842.

⁵⁵ See Bränström R, Pachankis JE: Reduction in mental health treatment utilization among transgender individuals after gender-affirming surgeries: a total population study. Am J Psychiatry 2020; 177: 727–734.

MDs, PhDs, and other methodologists that clarified methodological blunders and/or what appear to be potentially manipulative deceptions. These were published in August 2020.

The writers concluded that, “These methodological shortcomings preclude any statement on the suitability of early surgery in persons seeking treatment for gender non-congruence based on the results presented in this article.” They noted evidence supporting the theory that these “errors” could well be purposeful and designed to support an ideological perspective when they noted, “people diagnosed with gender incongruence have a dramatically worse overall mental health outcome” after “transitioning” treatments than the general population, which is, in fact, the answer to their stated aim and research question, but this essential finding is not even referred to in the title or in the conclusions section of the article.⁵⁶

Other serious flaws were highlighted: “For those whose last surgery was 10 or more years earlier, how many completed suicide, died of other causes, or left Sweden prior to study initiation?” The authors failed to find out. “A drop in hospitalizations for suicide attempts *alone* provides a very incomplete picture. When the data for such findings are accessible in the Swedish national registers, this omission is glaring. The lack of control subjects, the limited 1-year time frame, and the avoidance of examining completed suicides and psychiatric hospitalizations are substantial study shortfalls.” “The study supports only weak conclusions about psychiatric medication usage and nothing decisive about suicidality. In overlooking so much available data, this

⁵⁶ Kalin, N.H., Reassessing Mental Health Treatment Utilization Reduction in Transgender Individuals After Gender-Affirming Surgeries: A Comment by the Editor on the Process by the Editor-in-Chief The American Journal of Psychiatry, *Am J Psychiatry* 2020; 177:764; doi: 10.1176/appi.ajp.2020.20060803; see also Anckarsäter, H., and Gillberg, C., Methodological Shortcomings Undercut Statement in Support of Gender-Affirming Surgery, *Am J Psychiatry* 2020; 177:764–765; doi: 10.1176/appi.ajp.2020.19111117

study lacks the evidence to support its pro gender-affirmation surgery conclusion.”⁵⁷ Still others noted more serious flaws.⁵⁸

Taken together, these nine separate criticisms and the editor’s decision to publish each of them in less than a year after e-publication, constitutes an illustration of the dangers of confirmation bias. The authors admitted their conclusions were in error and that “more research” is needed to answer the questions they raised.⁵⁹

Like Bränström and Pachankis, too many ideologically tainted and methodologically defective research studies suffer from these kinds of serious errors, improper analyses and deceptive conclusions. Such poorly designed and improperly analyzed research studies continue to prevent gender transition “affirmation” treatments from being generally accepted by the relevant scientific community.

⁵⁷ See Van Mol, A., Laidlaw, M. K., Grossman, M., McHugh, P., Gender-Affirmation Surgery Conclusion Lacks Evidence, *Am J Psychiatry* 177:8, August 2020 ajp.psychiatryonline.org 765.

⁵⁸ See Curtis, D., Study of Transgender Patients: Conclusions Are Not Supported by Findings, *Am J Psychiatry* 2020; 177:766; doi: 10.1176/appi.ajp.2020.19111131; Malone, W. and Roman, S., Calling Into Question Whether Gender-Affirming Surgery Relieves Psychological Distress, *Am J Psychiatry* 2020; 177:766–767; doi: 10.1176/appi.ajp.2020.19111149; Landén, M. The Effect of Gender-Affirming Treatment on Psychiatric Morbidity Is Still Undecided, *Am J Psychiatry* 2020; 177:767–768; doi: 10.1176/appi.ajp.2020.19111165; Wold, A. Gender-Corrective Surgery Promoting Mental Health in Persons With Gender Dysphoria Not Supported by Data Presented in Article, *Am J Psychiatry* 2020; 177:768; doi: 10.1176/appi.ajp.2020.19111170; Ring, A. and Malone, W., Confounding Effects on Mental Health Observations After Sex Reassignment Surgery, *Am J Psychiatry* 2020; 177:768–769; doi: 10.1176/appi.ajp.2020.19111169 (“Therefore, accounting for the increase in mental health issues from 2005, together with an assumption of *increased* mental health treatment due to this surgery, fits the data in the article and *overturns* the authors’ stated conclusions, suggesting that sex reassignment surgery is in fact associated with increased mental health treatment.”).

⁵⁹ See Bränström, R. and Pachankis, J. , Toward Rigorous Methodologies for Strengthening Causal Inference in the Association Between Gender-Affirming Care and Transgender Individuals’ Mental Health: Response to Letters, *Am J Psychiatry* 2020; 177:769–772; doi: 10.1176/appi.ajp.2020.20050599.

72. The Carmichael, et al, study of 2020 looked at 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. The authors “*identified no changes in psychological function but noted that*” changes in bone density were consistent with suppression of growth.” Most importantly, the authors noted the lack of research support for such treatments, stating “Larger and longer-term prospective studies using a range of designs are needed to more fully quantify the benefits and harms” of pubertal suppression in gender dysphoria.⁶⁰

73. Olson-Kennedy has at times been an advocate for social transitioning of grade school youth and the employment of puberty blockers and is currently studying five-year outcomes supported by an NIMH grant. This provides some hope that science will clarify some of the issues stated in this report. Along with other researchers she summarized a number of the ongoing serious defects in the field’s understanding of transgender patients. “Clinically useful information for predicting individual psychosexual development pathways is lacking.”⁶¹

C. Suicide, suicidal ideation, suicide attempts, suicidal manipulations

74. With respect to suicide risks, individuals with gender dysphoria are well known to have a higher risk of committing suicide or otherwise suffering increased mortality before and

⁶⁰ See Polly Carmichael, Gary Butler, Una Masic, Tim J Cole, Bianca L DeStavola , Sarah Davidson, Elin M. Skageberg, Sophie Khadr, Russell Viner. 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> and <https://www.medrxiv.org/content/10.1101/2020.12.01.20241653v1>; see also Schumm, WR and Crawford, DW, Is Research on Transgender Children What It Seems? Comments on Recent Research on Transgender Children with High Levels of Parental Support, Linacre Quarterly, 2020, Vol. 87(1) 9-24. DOI: 10.1177/0024363919884799

⁶¹ See Olson-Kennedy, J, Cohen-Kettenis, P., et al., Research priorities for gender non-conforming/transgender youth gender identity development and biopsychosocial outcomes, Current Opinion in Endocrinology & Diabetes and Obesity: April 2016 - Volume 23 - Issue 2 - p 172-179, doi: 10.1097/MED.0000000000000236

after not only social transition, but also before and after sex reassignment surgery. (Levine, *Reflections*, at 242.) For example, in the United States, the death rates of trans veterans are *comparable to those with schizophrenia and bipolar diagnoses but 20 years earlier* than expected.

These crude death rates include significantly elevated suicide rates. (Levine, *Ethical Concerns*, at 10.) Similarly, researchers in Sweden and Denmark have reported on almost all individuals who underwent sex-reassignment surgery over a 30-year period. The Swedish follow-up study found a suicide rate in the post-sex reassignment surgery population *19.1 times greater than that of the controls after affirmation treatment*; both studies demonstrated elevated mortality rates from *medical and psychiatric conditions*.⁶²

75. Advocates of immediate and unquestioning affirmation of social transition in children who indicate a desire for a transgender identity sometimes assert that any other course will result in a high risk of suicide in the affected children and young people. Parents report that they have been told that their choice may come down to having a trans child or a dead child. Based on current knowledge, this is a highly unethical statement to make. Dr. Adkins raises the specter of suicide and claims that “[t]he only effective treatment to avoid this serious harm is . . . to affirm gender identity.” (Adkins 5.) Apparently, she has dismissed *psychiatric* care for suicidal ideation, gestures, and attempts—conditions that MHPs are trained to deal with effectively. Contrary to these assertions, no reliable, valid scientific studies show that affirmation of children (or any-

⁶² Levine, *Ethical Concerns*, at 10; see C. Dhejne et al. (2011), Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden, PLOS ONE 6(2) e16885 (“Long Term”); R. K. Simonsen et al. (2016), Long-Term Follow-Up of Individuals Undergoing Sex Reassignment Surgery: Psychiatric Morbidity & Mortality, Nordic J. of Psychiatry 70(4).

one else) reduces suicide, prevents suicidal ideation, or improves long-term outcomes, as compared to either a “watchful waiting” or a psychotherapeutic model of response, as I have described. (See the reviews from Finland, England, and Sweden discussed herein).

A 2020 article, by Turban, et al.⁶³ has been incorrectly and misleadingly described in some press reports and professional articles as demonstrating that administration of puberty suppressing hormones to transgender adolescents reduces suicide or suicidal ideation. The paper itself does not directly make that claim, nor permit that conclusion. It has been rigorously criticized for not emphasizing that both those treated and not treated with puberty blockers had high suicidal ideation rates and more children on these drugs were hospitalized for suicidal plans than the untreated.⁶⁴

76. Any discussion of suicide when considering younger children involves very long-range and *very uncertain, inaccurate* predictions. Suicide in pre-pubescent children is very rare and the existing studies of gender identity issues in pre-pubescent children do *not* report significant incidents of suicide. *The current estimated suicide rate of trans adolescents is the same as teenagers who are in treatment for serious mental illness.* What trans teenagers do demonstrate is more suicidal ideation and attempts (however serious) than other teenagers.⁶⁵

77. Claims that “affirmation” will reduce the risk of suicide for children are not based on credible science. Such claims overlook the lack of even short-term supporting data as well as the

⁶³ J. Turban et al., *Puberty Suppression for Transgender Youth and Risk of Suicidal Ideation*, Pediatrics 145(2), DOI: 10.1542/peds.2019-1725

⁶⁴ See, e.g., Hruz, Mayer and Schumm January 26m 2020, and M.Biggs Puberty Blockers and Suicidality in Adolescents Suffering from Gender Dysphoria. Arch Sex Behav. 2020 Oct; 49(7): 2227-2229. doi: 10.1007/s10508-020-01743-6. Epub 2020 Jun 3.

⁶⁵ See A. Perez-Brumer, J. K. Day et al. (2017), Prevalence & Correlates of Suicidal Ideation Among Transgender Youth in Cal.: Findings from a Representative, Population-Based Sample of High Sch. Students, J. Am. Acad Child Adolescent Psychiatry 56(9), 739.

lack of studies of long-term outcomes resulting from the affirmation or lack of affirmation of transgender identity in children. It also overlooks the other tools that the profession does have for addressing depression and suicidal thoughts in a patient once that risk is identified including cognitive behavioral therapy and other proven interventions. Psychiatry, of course, has a long history of striving to prevent suicide in those who seek our care.

A number of data sets have also indicated significant concerns about wider indicators of physical and mental health, including ongoing functional limitations including: abuse, depression, and psychiatric hospitalizations and increased cardiovascular disease, cancer, asthma, and COPD. Worldwide estimates of HIV infection among transgendered individuals are up to 17-fold higher than the cisgender population. Looking at such data may provide an indirect explanation for the high prevalence of suicidality both before and after transition from adolescence to older age among trans populations.⁶⁶

78. Similarly, no scientific studies show that affirmation of pre-pubescent children leads to more positive outcomes (mental, physical, social, or romantic) by, e.g., age 25 than does “watchful waiting” or ordinary psychotherapy. Because childrens’ affirmation, social transition, and the use of puberty blockers for transgender children are a recent phenomenon, it could hardly be otherwise.

79. Thus, given the lack of credible science evidence for suicide reduction, transition of any sort must be justified, if at all, as a *life-enhancing* measure, not a *lifesaving* measure—although there is no credible to support either hypothesis. (Levine, *Reflections*, at 242.) In my

⁶⁶ Levine, *Informed Consent*, at 6; see also G. Zeluf, C. Dhejne et al. (2016), *Health, Disability and Quality of Life Among Trans People in Sweden—A Web-Based Survey*, BMC Public Health 16(903), DOI: 10.1186/s12889-016-3560-5. See C. Dhejne, R. Van Vlerken et al. (2016), *Mental Health & Gender Dysphoria: A Review of the Literature*, Int’l Rev. of Psychiatry 28(1) 44.

opinion, this is an important fact that patients, parents, and even many MHPs fail to understand. They also often do not understand that the current gender affirmation “treatment” data for life saving or enhancement are so weak, sparse, and poorly gathered that they do not permit us to know if gender affirmation interventions will increase or decrease a patient’s risk of suicide or reduced depression or even an improved life. How many years will go by before such research is competently completed?⁶⁷

V. KNOWN, LIKELY, OR POSSIBLE DOWNSIDE RISKS ATTENDANT ON MOVING QUICKLY TO “AFFIRM” TRANSGENDER IDENTITY IN CHILDREN

80. As some research has already demonstrated, enabling and affirming social transition in a prepubescent child appears to be highly likely to increase the odds that the child will in time pursue pubertal suppression and persist in a transgender identity into adulthood. This means the MHP, pediatrician, and parent must consider long-term as well as short-term implications of life as a transgender individual when deciding whether to permit or encourage a child to socially transition.

81. Dr. Adkins asserts without citation to peer-reviewed literature that social transition and hormone therapy are “safe, effective and essential” for young people. (Adkins 6, 11.) A great deal of data point in the opposite direction. The multiple studies from different nations that have documented the increased vulnerability of the adult transgender population to substance abuse, mood and anxiety disorders, suicidal ideation, and other health problems stand as a warning: Given these well-documented data, assisting a child down the road to becoming a transgender adult is an ominous decision. Data about trans adults remind all concerned that a

⁶⁷ See C. Dragon, P. Guerino, et al. (2017), *Transgender Medicare Beneficiaries & Chronic Conditions: Exploring Fee-for-Service Claims Data*, LGBT Health 4(6) 404, DOI: 10.1089/lgbt.2016.0208

casual assumption that transition will improve the child's life is not justified beyond his or her short term happiness about gender expression. The possibility that steps along this pathway, while lessening the relatively minor pain of gender dysphoria, could lead to additional future sources of crippling emotional and psychological pain, are too often not properly considered by advocates of social transition and not considered at all by the trans child. (Levine, *Reflections*, at 243.). The informed consent process for parents considering this option ethically should spell out short-term gains and long-term risks (beginning at early puberty risks). What follows is a discussion of the medical, social, and psychological risks of affirmation interventions ("transition").

A. Physical risks associated with transition

82. Sterilization. Dr. Adkins rightly notes that many patients who begin down the path defined by puberty blockers and social transition end up feeling the need to undergo "surgical treatment to alleviate gender dysphoria." (Adkins 11.) As I have noted, there is not good scientific evidence that Sex Reassignment Surgery (SRS) results in better long-term mental health outcomes. What is certain, however, is that SRS that removes testes, ovaries, or the uterus and is *inevitably sterilizing and irreversible*. While by no means all transgender adults elect SRS, many patients do ultimately feel compelled to take this serious step in their effort to "live fully as the opposite sex." More immediately, practitioners recognize that the administration of cross-sex hormones, which is often viewed as a less radical measure, and is now increasingly done to minors, creates a risk of irreversible sterility. These risks have never been properly studied nor quantified in a systematic manner. Dr. Adkins implicitly acknowledges this risk when she cites anecdotes about "[m]any people" undergoing "fertility preservation" before proceeding with transition. (Adkins 14.) This is just another example of how putting children on a pathway to trans adulthood keeps them tethered to medical care. As a result, even when treating a child, the

MHP, patient, and parents must consider permanent loss of reproductive capacity (sterilization) to be one of the major risks of starting down the road. The risk that supporting social transition may put the child on a pathway that leads to intentional or unintentional permanent sterilization is particularly concerning given the disproportionate representation of minority and other vulnerable groups among children reporting a transgender or gender-nonconforming identity.⁶⁸ (*See supra* ¶ 21.)

83. Loss of sexual response. Puberty-blockers prevent maturation of the sexual organs and response. Some and perhaps many transgender individuals who transitioned as children and thus did not go through puberty consistent with their sex face significantly diminished sexual response as they enter adulthood, and *are unable ever to experience orgasm*. Additionally, they will also experience the social, psychological, and interpersonal impact of not being in puberty for 4-5 years while their peers are challenged by the normative processes of maturing bodies and minds. Dr. Adkins does not acknowledge these effects of puberty blockers. To my knowledge, data quantifying this impact has not been published. In the case of males, the cross-sex administration of estrogen limits penile genital function. Much has been written about the negative psychological and relational consequences of anorgasmia among non-transgender individuals that is ultimately applicable to the transgendered.⁶⁹

84. Other effects of hormone administration. While it is commonly said that the effects of puberty blockers are reversible after cessation (Dr. Adkins describes the effect of puberty

⁶⁸ See C. Guss et al., *TGN Adolescent Care* at 4 (“a side effect [of cross-sex hormones] may be infertility”) and 5 (“cross-sex hormones . . . may have irreversible effects”); Tishelman et al., *Serving TG Youth* at 8 (cross-sex hormones are “irreversible interventions” with “significant ramifications for fertility”).

⁶⁹ Levine, *Informed Consent*, at 6; see Perelman and Watters, 2016, *Delayed Ejaculation in Handbook of Clinical Sexuality for Mental Health Professionals* 3rd edition, New York, Routledge.

blockers as just a “pause” (Adkins 12)), in fact controlled research studies have never been done as to how completely this is true. However, it is well known that many effects of cross-sex hormones cannot be reversed should the patient later regret his transition. This is dramatically evident among females’ deeper voice quality after testosterone administration and the loss of muscle mass among males on estrogen for long periods of time. After puberty, the individual who wishes to live as the opposite sex will in most cases have to take cross-sex hormones for life.

85. The long-term health risks of this major alteration of hormonal levels have not yet been quantified in terms of exact risk thus appropriate, ethical, complete informed consent is not yet possible for such experimental “treatments.” However, a recent study found greatly elevated levels of strokes and other acute cardiovascular events among male-to-female transgender individuals taking estrogen. Those authors concluded, “it is critical to keep in mind that the risk for these cardiovascular events in this population must be weighed against the benefits of hormone treatment.”⁷⁰

Others similarly noted that administration of cross-sex hormones creates “an additional risk of thromboembolic events”—which is to say blood clots (Guss et al., *TGN Adolescent Care* at 5), which are associated with strokes, heart attack, and lung and liver failure. The young patient may feel, “I don’t care if I die young, just as long I get to live as a woman.” The mature adult may take a different view of such risks including the risk of reduced life expectancy.⁷¹

⁷⁰ See Tishelman et al., *Serving TG Youth* at 6-7 (Long-term effect of cross-sex hormones “is an area where we currently have little research to guide us”; see also D. Getahun et al. (2018), *Cross-Sex Hormones and Acute Cardiovascular Events in Transgender Persons: A Cohort Study*, *Annals of Internal Medicine* at 8, DOI:10.7326/M17-2785.

⁷¹ See Blosnich, J. R., Brown, G. R., Wojcio, S., Jones, K. T., & Bossarte, R. M. (2014). Mortality among veterans with transgender-related diagnoses in the Veterans Health Administration, FY2000–2009. *LGBT Health*, 1, 269–276. doi:[10.1089/lgbt.2014.0050](https://doi.org/10.1089/lgbt.2014.0050)

86. Health risks inherent in complex surgery. Complications of surgery exist for each procedure, and complications in surgery affecting the reproductive organs and urinary tract can have significant anatomical and functional complications for the patient's quality of life. In a famous Dutch study, 1 of the 30 teens died in surgery.

87. Disease and mortality generally. The MHP, the patient, and in the case of a child the parent, must also be aware of the wide sweep of strongly negative health outcomes among transgender individuals. Shortened life expectancy has been repeatedly documented in Sweden, the US, and Denmark.⁷²

B. Social risks associated with transition

88. Family and friendship relationships. Gender transition routinely leads to isolation from at least a significant portion of one's family in adulthood. In the case of a juvenile transition, this will be less dramatic while the child is young, but commonly increases over time as siblings who marry and have children of their own often do not wish the transgender individual to be in contact with those children. By adulthood, the friendships of transgender individuals tend to be confined to other transgender individuals (often "virtual" friends known only online) and the generally limited set of others who are comfortable interacting with transgender individuals. (Levine, *Ethical Concerns*, at 5.) While friendship in general is highly desirable, many trans teens and older individuals want to interact more fully and extensively with the ordinary population of cis individuals.

89. Long term psychological and social impact of medically induced sterility. The life-long negative emotional impact of infertility on both men and women has been well studied.

⁷² See Levine, *Informed Consent*, at 5 (citing T. van de Grift, G. Pigot et al. (2017), A Longitudinal Study of Motivations Before & Psychosexual Outcomes After Genital Gender-Confirming Surgery in Transmen, *J. Sexual Medicine* 14(12) 1621.

While this impact has not been studied specifically within the transgender population, the opportunity to be a parent is likely a human, emotional need, and so should be considered an important risk factor when considering gender transition for any patient. However, it is particularly difficult for parents of a young child to seriously contemplate that child's potential as a future parent and grandparent. This makes it all the more critical that the MHP spend substantial and repeated time with parents to help them see the implications of what they are considering. The percentage of transitioned patients who will become increasingly suicidal as they fully realize the meaning of permanent sterility and the loss of the possibility of being a biological parent has never been studied and is thus unknown.

90. Sexual-romantic risks associated with transition. After adolescence, transgender individuals find the pool of individuals willing to develop a romantic and intimate relationship with them to be greatly diminished. When a trans person who passes well reveals his or her natal sex, many potential cisgender mates lose interest. When a trans person does not pass well, he discovers that the pool of those interested consists largely of individuals looking for exotic sexual experiences rather than genuinely loving relationships. (Archives Sexual Behavior April 2021; Levine, *Ethical Concerns*, at 5, 13.) Nor is the problem all on the other side; transgender individuals commonly become strongly narcissistic, unable to give the level of attention to the needs of another that is necessary to sustain a loving relationship.⁷³ The percentage of transitioned patients

⁷³ See S. Levine, *Barriers to Loving: A Clinician's Perspective*, at 40 (Routledge, New York 2013).

who will become increasingly suicidal as they fully realize the depth of the social isolation experienced by many transgender patients has never been studied and is thus unknown. A recently published article whose title explains the finding is relevant.⁷⁴

91. Social risks associated with delayed puberty. The social and psychological impact of remaining puerile (not growing) for, e.g., three years while one's peers are undergoing puberty, and of undergoing puberty at a substantially older age, have not been systematically studied (see Sweden, England, and Finland reviews and other research cited above), although clinical MHPs often hear of distress and social awkwardness in those who naturally have a delayed onset of puberty. In my opinion, individuals in whom puberty is delayed multiple years are likely to suffer at least subtle negative psychosocial and self-confidence effects as they stand on the sidelines while their peers are developing the social relationships (and attendant painful social learning experiences) that come with adolescence. (Levine, Informed Consent, at 9.) We should recall that puberty introduces sexual desire, changes socialization patterns, and enables teens to enter into early romantic relationships all of which can lead to maturation, self-confidence, and an understanding of the complexity of partner relationship. Delaying puberty can reasonably be assumed to increase the adolescent's sense of isolation, otherness, and being an outsider.

C. Mental health costs or risks

92. One would expect the negative physical and social impacts reviewed above to adversely affect the mental health of individuals who have transitioned. In addition, adult transi-

⁷⁴ See Anzani A, Lindley L, Tognasso G, Galupo MP, Prunas A. "Being Talked to Like I Was a Sex Toy, Like Being Transgender Was Simply for the Enjoyment of Someone Else: Fetishization and Sexualization of Transgender and Nonbinary Individuals." Arch Sex Behav. 2021 Apr. 50(3):897-911. doi: 10.1007/s10508-021-01935-8. Epub 2021 Mar 24. PMID: 33763803; PMCID: PMC8035091

tioned individuals find that living as the other (or, in a manner that is consistent with the stereotypes of the other as the individual perceives them) is a continual challenge and stressor, and many find that they continue to struggle with a sense of inauthenticity in their transgender identity and bear consequent chronic uneasiness. (Levine, *Informed Consent*, at 9.) In addition, individuals often pin excessive hope in transition, believing that transition will solve what are in fact ordinary social stresses associated with puberty. Thus, transition can result in deflection from mastering personal challenges at the appropriate time, or addressing underlying psychiatric conditions that require treatment. The percentage of transitioned patients who will become increasingly suicidal due to deflection from mastering personal challenges at the appropriate time, has never been studied and is thus unknown.

93. Whatever the reason, transgender individuals including transgender youth certainly experience greatly increased rates of mental health problems. I have detailed this above with respect to adults living under a transgender identity. Indeed, Swedish researchers in a long-term study (up to 30 years since Sex Reassignment Surgery (SRS), with a median time since SRS of >10 years) concluded that individuals who have SRS should have postoperative *lifelong* psychiatric care. (Dhejne, Long Term, at 6-7.) With respect to youths a cohort study found that transgender youth had an elevated risk of depression (50.6% vs. 20.6%) and anxiety (26.7% vs. 10.0%); a higher risk of suicidal ideation (31.1% vs. 11.1%), suicide attempts (17.2% vs. 6.1%), and self-harm without lethal intent (16.7% vs. 4.4%) relative to the matched controls; and a significantly greater proportion of transgender youth accessed inpatient mental health care (22.8% vs. 11.1%) and outpatient mental health care (45.6% vs. 16.1%) services.⁷⁵

⁷⁵ Reisner, S. L., Veters, R., Leclerc, M., Zaslow, S., Wolfrum, S., Shumer, D., & Mimiaga, M. J. (2015). Mental health of transgender youth in care at an adolescent urban community health center: a matched retrospective cohort study. *The Journal of adolescent health: official*

93A. Dr. Adkins asserts that “when appropriately treated”—by which she apparently means social and ultimately hormonal transition—“gender dysphoria is easily managed.” (Adkins 5.) I am not aware of any such studies. Instead, based on the long-term data discussed above, the responsible MHP cannot focus narrowly on the short-term happiness of the patient, but must instead consider the happiness and health of the patient from a “life course” perspective. The many studies that I have cited here warn us that as we look ahead to the patient’s life as a young adult and adult, the prognosis for the physical health, mental health, and social well-being of the child or adolescent who transitions to live in a transgender identity is not good. Gender dysphoria is not easily managed except when it naturally desists. A recent study in the *American Journal of Psychiatry* reported the high mental health utilization patterns of adults for ten years after surgery for approximately 35% of patients.⁷⁶ This is not “easy” management.

D. Regret following transition is not an infrequent phenomenon.

94. The large numbers of children and young adults who have desisted as documented in both group and case studies each represent “regret” over the initial choice in some sense.

95. The phenomenon of desistance or regret experienced later than adolescence or young adulthood, or among older transgender individuals, has to my knowledge not been quantified or well-studied. However, it is a real phenomenon. I myself have worked with multiple individuals who have abandoned trans female identity after living in that identity for years, and who would describe their experiences as “regret.”

publication of the Society for Adolescent Medicine, 56(3), 274–279. <https://doi.org/10.1016/j.jadohealth.2014.10.264>

⁷⁶ Bränström & Pachankis, (2019), *Reduction in Mental Health Treatment Utilization Among Transgender Individuals After Gender-Affirming Surgeries*, *Am. J. of Psychiatry*. 4:Appi-ajp201919010080. Doi: 10.1176/Appi.Ajp.2019.19010080

96. I have seen several Massachusetts inmates and trans individuals in the community abandon their [trans] female identity after several years. (Levine, *Reflections*, at 239.) In the gender clinic which I founded in 1974 and am still part of, we have seen many instances of individuals who claimed a transgender identity for a time, but ultimately changed their minds and re-claimed the gender identity congruent with their sex.

97. More dramatically, a surgical group prominently active in the SRS field has published a report on a series of seven male-to-female patients requesting surgery to transform their surgically constructed female genitalia back to their original male form.⁷⁷

98. I noted above an increasingly visible online community of young women who have desisted after claiming a male gender identity at some point during their teen years. Given the rapid increase in the number of girls presenting to gender clinics within the last few years, the phenomena of regret and desistance by young women deserves careful attention and study by MHPs. As reported by one author in 2021, 16,000 testimonies of personal de-transition can be found on the Internet.⁷⁸

99. Regret for post-surgical patients is claimed to be quite low but credible long-term research has never been done (e.g. the Bränström 2020 study cited above in detail and others fail to follow-up very large percentages of patients in the study – many or all of these “lost subjects” could be patients with profound regrets. Regardless of the currently unknown percentage of patients suffering regret following transitioning, those making suicide attempts, suffering from new

⁷⁷ See Djordjevic ML, Bizic MR, Duisin D, Bouman MB, Buncamper M. Reversal Surgery in Regretful Male-to-Female Transsexuals After Sex Reassignment Surgery. *J Sex Med*. 2016 Jun;13(6):1000-7. doi: 10.1016/j.jsxm.2016.02.173. Epub 2016 May 4. PMID: 27156012

⁷⁸ See Pablo Expos-ito-Campos. A typology of gender detransition and its implications for health care providers *J Sex & Marital Therapy* 2020 <https://doi.org/10.1080/0092623x.2020.1869126>

post transition depression and anxiety states, those who develop substance abuse patterns, those who have died at their own hands, and those on disability must be at least considered to have regret. Regret statistics in this field have long been self-serving to ITT professionals and not in keeping with an in-depth knowledge of individual patients.

VI. MEDICAL ETHICS AND INFORMED CONSENT

A. The obligation of the mental health professional to enable and obtain informed consent

100. I have reviewed above the knowledge and experience that, in my view, a MHP should have before undertaking the responsibility to counsel or treat a child who is experiencing gender dysphoria or transgender identification. The MHP who undertakes this type of responsibility must also be guided by the ethical principles that apply to all health care professionals. One of the oldest and most fundamental principles guiding medical and psychological care—part of the Hippocratic Oath—is that the physician must “do no harm.” This states an ethical responsibility that cannot be delegated to the patient. Physicians themselves must weigh the risks of treatment against the harm of not treating. If the risks of treatment outweigh the benefits, ethics prohibit the treatment.

101. A distinct ethical responsibility of physicians, when a significant risk exists of adverse consequences to any procedure or therapy, is to ensure that the patient understands and is legally able to consent to these unproven, experimental, high risk, often irreversible, potentially harmful “treatments”, and does consent. To achieve informed consent, the MHP, pediatrician, or other physician must do at least the following:

- a. Must reasonably inform him- or herself regarding the particular situation of his patient;

b. Must reasonably inform him- or herself concerning the state of knowledge concerning the relevant methodologies and outcomes and the unproven, experimental nature of these “treatments”;

c. Must honestly inform the patient concerning not only the benefits of treatment, but also the risks and downsides of treatment, and alternative treatments including no treatment at all as well as the lack of competent scientific study to determine accurate predictions of risks and benefits in this experimental field.

d. Must conclude that the patient (or the decision maker, such as parent or healthcare power of attorney) has comprehended what he or she has been told and possesses a cognitive capacity to make a decision based on an adequate understanding of his or her unique life circumstances.

102. Perfunctory “consent” is inadequate to fulfill the professional’s ethical obligation to obtain truly informed consent. At the very least, a patient (or parent) considering the life-altering choice of transition should be helped or indeed required by their clinicians to grapple with four relevant questions:

a. “What benefits do you expect that the consolidation of this identity, gender transition, hormones, or surgery will provide?

b. “What do you understand of the social, educational, vocational, and psychological risks of this identity consolidation and gender role transition?

c. “What do you understand about the common and rare, short- and long-term medical and health risks of hormone and surgical interventions?

d. “What have you considered the nature of your life will be in 10 to 20 years?” (Levine, *Informed Consent*, at 3.)

e. “Are you fully aware that national science reviews done in England, Sweden, Finland and the US have all noted the lack of credible scientific evidence supporting these experimental treatments? Are you fully aware that the few long-term research studies done in this field support the hypothesis that patients, in the long run, may be more harmed than helped by these experimental “treatments”?”

103. The answers of the patient will enable the professional to make a judgment about how realistic he or she is being. For example, the biological boy who envisions himself as a happy, attractive, socially accepted 21-year-old girl in future college years has probably not been adequately informed of—or has mentally blocked—hard data concerning the mental health and social wellbeing of the transgender population in their 20s, and is failing to consider the material risk that he, as a transgender individual, will not be perceived as attractive to either sex, and the impact that this may have on his future well-being.

104. Most commonly, meaningful engagement with difficult and painful questions such as those above requires a process that will consist of multiple discussions in a psychotherapeutic or counseling context, not merely “disclosure” of facts. In my experience, a too-rapid or too-eager attachment to some outcome is a warning that the patient is not able to tolerate knowledge of the risks and alternative approaches.

105. In my experience, in the area of transgender therapy, rather than the type of information and engagement that I have described, even mental health professionals too often encourage or permit decisions based on a great deal of patient and professional blind optimism about the future that is not grounded in competent, peer reviewed published, reliable-valid scientific research. (Levine, *Ethical Concerns*, at 3-4.) In understanding how the medical and psychological profession is taught how to deal with these patient/ family problems, it is quite clear that

knowledge of the scientific limitations of affirmative therapy is not emphasized. Thus, many practitioners passionately, but erroneously, negligently, and unethically, believe that controlled studies with adequate follow-up are the basis for what they have been taught. It is difficult to provide informed consent if the professional is not informed or ideologically driven to be misinformed. Consumer fraud in health care can take place via gross negligence.

B. The interests of the patient, as well as necessary disclosures and consent, must be considered from a life course perspective.

106. The psychiatrist, pediatrician, or psychologist treating a child must have in view not merely (or not even primarily) making the child “happy” now, but making him or her as healthy and happy as possible across the entire trajectory of life, to the extent that is predictable. Certainly, avoiding suicide is one important aspect of a “life course” analysis, and recognizes that “today” is not the only goal. But as we have demonstrated above, there is no credible scientifically reliable-valid evidence that these experimental treatments actually reduce life-time risk of suicide in these patients. There are many more factors across the future decades of the patient’s life that also need to be taken into account.

107. Further, in my opinion, a patient can meaningfully be said to know what will make him “happy” over the long term, prior to receiving, understanding, and usually discussing the type of information that I have described above in connection with informed consent. With respect to (most) children who are not equipped to understand, evaluate, and feel the life implications of such information, it is doubtful that there is any meaningful way in which they can be said to “know” what will make them happy over the long term. It is for similar reasons that parents ordinarily make a great many decisions, both large and small, for their young children.

108. Of particular relevance to the life course perspective, when gender-typical men and women undergo elective sterilization, there is a distinct likelihood of eventual regret, in some patients to the point of suicidal despondency. It has been documented that the younger the age of sterilization, the greater incidence of regret and increased numbers of requests to reverse the sterilized state. Thus, the medical profession and the courts are quite clear about sterilization: the adult patient must be cognitively able to prudently consider the future consequences in terms of his or her life circumstances. In minors sterilization should be done only to save a life.⁷⁹ This observation has implications for facilitating or even permitting children or adolescents to embark on a path of social transition that within a few years may psychologically steer that individual towards sterilizing chemical or surgical procedures.⁸⁰

C. Special concerns and ethical rules governing experimentation on patients

109. When psychiatric or medical research is done on subjects the informed consent process is far more rigorous than in ordinary medical and psychiatric procedures. For example, in a recent study of an agent to assist women who are distressed by their lack of sexual desire that I was a part of, the Informed Consent document was 19 pages long.

110. As reported in multiple national science reviews of this field, the absence of competently designed, long-term outcome research studies demonstrating more benefits than damages

⁷⁹ See A. Burgart et al. (2017), *Ethical Controversy About Hysterectomy for a Minor*, Pediatrics 139(6), DOI:10.1542/peds.2016-3992.

⁸⁰ See S. D. Hillis et al. (1999), *Post-sterilization Regret: Findings from the United States Collaborative Review of Sterilization*, Obstetrics & Gyn 93(6) 889; A. Burgart et al. (2017), *Ethical Controversy About Hysterectomy for a Minor*, Pediatrics 139(6), DOI:10.1542/peds.2016-3992; K. Curtis et al. (2006), *Regret Following Female Sterilization at a Young Age: A Systematic Review*, Contraception 73, 205, DOI:10.1016/j.contraception.2005.08.006; A. Tamar-Mattis (2009), *Exploring Gray Areas in the Law About DSD and Sterilization*, Endocrine Today, October ed., <https://www.healio.com/endocrinology/reproduction-androgen-disorders/news/print/endocrine-today/%7Bc6029f85-28ac-43f4-9e7e-0fc897f6313f%7D/exploring-gray-areas-in-the-law-about-dsd-and-sterilization>.

for gender affirmation interventions (“transitioning treatments”) means that the claimed therapeutic interventions for these conditions are still at a primitive stage of development, and should be considered to be experimental, rendering adequately informed consent all the more essential, all the more required by ethical and licensing rules-regulations and all the more difficult to obtain. Claims that a civil right is at stake for differently gender identifying people do not change the fact that informed consent is an internationally recognized fundamental human right and that what is proposed is a social and medical experiment.⁸¹

111. Informed consent is often defined as the willing acceptance of a medical intervention by a patient after adequate disclosure by the physician of the A) nature of the intervention, its risks, and benefits, as well as B) the risks and benefits of alternative treatments and C) the risks and benefits of no treatment.

112. 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. The infamous Tuskegee experimental studies, the Nazi and Imperial Japanese wartime experimental research on prisoners, the use of lobotomies, the recovered memory therapy movement, the “multiple personality disorder” therapy movement, and the rebirthing therapy movement, all invite comparisons with what is happening to too many gender discordant children and adolescents. In my opinion, health care professionals have ethical, professional, and moral responsibilities to protect the rights of patients and their families to be fully and accurately informed about the risks, benefits,

⁸¹ Levine, *Reflections*, at 241; see Nuremberg Code, Informed Consent Laws in each state, and The Joint Commission on Accreditation of Healthcare Organizations, or JCAHO (an organization based in the United States that accredits over 20,000 healthcare organizations and programs in the country), as well as the relevant Health Care Profession Licensing Rules and Regulations in each state.

natural history, alternatives, and state of science for the full range of experimental gender affirmation “treatments.”⁸² Properly accomplished informed consent is not controversial. 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.⁸³

D. Ethical principles do not permit using patients as “change agents”

113. Some advocates assert that various mental health pathologies commonly observed in patients who have transitioned result from societal prejudice, and would not occur if society were different. This is, of course, a hypothesis rather than demonstrated fact, and it is in any case ethically irrelevant to the treatment of an individual patient. If a therapy or life course under consideration for a child will predictably lead to social and family isolation and unemployment later in life given society as it exists, for a MHP or other advisor to recommend or encourage that path nonetheless seems to lose sight of the welfare of the patient. To do so appears to be intentionally using the child as not merely an experiment, but as a change-agent—potentially at great personal cost—rather than seeking the lifetime best interests of that child. (Levine, *Ethical Concerns*, at 9.) It seem audacious of advocates whose primary qualification is being trans oneself to tell parents how their child should be treated.

E. The inability of children to understand major life issues and risks complicates informed consent.

114. Obviously, most children cannot give legally valid consent to a medical procedure. This is not a mere legal technicality. Instead, it is a legal reflection of a reality of human

⁸² See <https://www.nobelprize.org/prizes/medicine/1949/moniz/article/>

⁸³ See Jonson AR, Siegler M, Winslade, WJ: *Clinical Ethics*, New York: McGraw Hill, 1998.

development that is highly relevant to the ethical requirement of informed consent quite apart from law. The argument that the child is consenting to the transition by his happiness ignores the fact just described.

115. Each age group poses different questions about risk comprehension. (Levine, *Informed Consent*, at 3.) While the older patient is perhaps more likely to be formally mental ill and be unrealistic sometimes to the point of being delusional, the young child is chronically unable to comprehend large and complex issues such as the meaning of biological sex, the meaning of gender, and the risks and life implications attendant on social, hormonal, and ultimately surgical transition.

116. In my experience, when clinicians actually attempt to understand patients' motives for the repudiation of their natal gender, the developmental lack of sophistication underlying their reasons can become apparent. What must a 12-year-old, for example, understand about masculinity and femininity that enables the conviction that "I can never be happy in my body?" (Levine, *Ethical Concerns*, at 8.) Obviously, this unavoidable gap in comprehension and ability to foresee must be still larger for younger children.

117. Similarly, one cannot expect a 17-year-old to grasp the complexity of married life with children when 38. One cannot expect a ten-year-old to understand the emotional growth that comes from a first long term love relationship including sexual behavior. One cannot expect a six-year-old to comprehend the changes in his psyche that may come about as the result of puberty. In some States or under some circumstances "mature minors" may be legally empowered to grant consent to certain medical procedures. Arguments have been made that minor adolescents are capable of providing legal informed consent if the physician thinks the patient is rea-

sonable.⁸⁴ Such thinking makes use of the idea that trans people including trans youth are special cases and do not have to follow cultural and scientific truths. This is an argument that I profoundly reject.

118. For this reason, it is my opinion that asking a child whether he or she wishes to transition to living as the opposite sex, or giving large weight to the child's expressed wishes, by no means satisfies the MHP's ethical obligation to obtain informed consent before assisting that child to transition to living as the opposite sex.

119. In light of the profound uncertainties in the field, and the many highly predictable or probable lifetime costs to the child if he or she persists in a transgender identity into adulthood, in my opinion it is not consistent with principles of medical ethics for physicians or other MHPs to suggest that parents should not or have no right to explore possible therapeutic options to assist their child to achieve comfort with the gender corresponding to his or her sex. The use of the label "reparative therapy" or "conversion therapy" by some advocates to lump all such possible therapies together and disparage them does not change this equation. (Levine, *Informed Consent*, at 7).

120. The transgender clinical arena is growing increasingly uncertain as more attention has been paid to the lack of fundamental studies to support the current widespread fashions of professional recommendations and confirmation bias has been identified in recent highly acclaimed but deeply flawed work. While the general public is now accustomed to reading about trans culture wars, my opinion is that of a clinician who respects scientific methods of ascertaining best

⁸⁴ See Clark BA, Virani A. This Wasn't a Split-Second Decision": An Empirical Ethical Analysis of Transgender Youth Capacity, Rights, and Authority to Consent to Hormone Therapy. *J Bioeth Inq*. 2021 Mar;18(1):151-164. doi: 10.1007/s11673-020-10086-9. Epub 2021 Jan 27. PMID: 33502682; PMCID: PMC8043901

treatments. More caution is indicated when the consequences are greater. It has been repeatedly demonstrated in medicine that one size does not fit all. One must reject the idea that if a young person is trans, nothing else matters—the treatment should be immediate affirmation and endocrine support. All must realize that 50 years after trans treatment began to spread across the world, despite more than 10,000 publications, it is not known whether the burgeoning transgender treatment industry is helping or damaging most gender dysphoric patients.

121. It is my opinion that the scientific community finds the following matters to be uncertain, controversial, or incorrect.

- Gender dysphoria is a serious, physical, brain based medical illness that causes suffering that must be treated by hormones and surgery if patients seek such treatments.

- All patients who label themselves as transgendered should be offered physical body-changing treatments, if they so desire.

- Hormones and surgery improve the lives of the transgendered in the long run.

- “Above all do no harm” principle can be sidestepped when administering hormones and removing healthy breast and genital tissues in the case of trans persons because it is “medically necessary,” that is, these patients represent a special exception to 2500 years of medical ethics.

- The uncertain long-term adjustments of trans adults, the rates of detransition, disappointment, and chronic depressive, anxiety, and substance abuse disorders do not need to be calculated nor should what is known about high psychiatric morbidity following hormonal and/or surgical treatment should not slow the affirmative treatment policy of trans youth.

- Civil rights considerations are more important than unanswered relevant scientific questions.

VII. BASES FOR EXPERT OPINIONS AND REVIEW-OPINIONS REGARDING THE PLAINTIFFS' EXPERT DECLARATIONS IN THIS CASE

122. I have reviewed dozens of scientific articles, science reviews from Sweden, Finland, and the UK (N.I.C.E.), three reviews of institutional guidelines, two of which focused on WPATH guidelines, a Cochrane Review paper, as well as the political endorsements of various professional associations, the Complaint in this case, and all expert declarations. I have formulated opinions regarding the reports by plaintiffs' experts, Drs. Adkins and Antommaria. I note that plaintiffs' experts failed to properly disclose and discuss the ongoing international debates and uncertainties whether their recommended treatment methods and procedures are helpful in significant ways and how they are not helpful and whether in balance they are more harmful than helpful.

123. The plaintiffs' experts failed to discuss the Bränström & Panchankis study, which was an effort to demonstrate that "affirmative" interventions led to mental health improvement over the long term. But published letters from 13 highly credentialed reviewers compelled the *American Journal of Psychiatry* to issue a correction and the authors to retract their conclusion. The plaintiffs' experts also failed to discuss the recent reviews documenting significant methodological failures and flaws in "transitioning" treatments (including the national review of Finland, the national review of Sweden, the national review of England (NICE) and the Cochrane Review).

124. Any State that reviews the safety and efficacy of life-altering "affirmative" treatments should consider measures like Arkansas' SAFE Act to protect their vulnerable minors and their families. Such "treatments" have been politicized, rationalized, and initiated before studies have adequately investigated the medical, social, psychological, educational, interpersonal, and

vocational outcomes. Thus, I characterize these “fashionable” rationalized interventions as experimental, because even advocates should agree that they have not been scientifically proven to be safe and effective.

125. The plaintiffs’ experts’ stunning failure to report or discuss the most salient evidence in this controversial field represents their putting the cart before the horse. Indeed, their ability to acknowledge the actual, peer-reviewed science is made difficult by a highly politicized environment where claims about civil rights to self-expression confuse the issue.

126. Finland, Sweden, and England have made historic changes in “transitioning” treatments — even banning surgery for minors and focusing on psychotherapy and social support rather than transitioning, just as Arkansas has now done. Plaintiff’s experts surely were aware when writing their selective reports that the studies done in Sweden and Denmark demonstrated many negative outcomes and dramatic numbers of completed suicides after receiving surgical and hormonal transitioning treatments. They must similarly be aware of the London High Court finding such treatments “experimental” and potentially dangerous. Should not the court be properly informed of these major and historic international science, policy, and ethics developments in transgender medicine?⁸⁵

⁸⁵ See Griffin, L., Clyde, K., Byng, R., Bewley, S., Sex, gender and gender identity: a re-evaluation of the evidence. *British Journal of Psychiatry Bulletin* (2020) doi:10.1192/bjb.2020.73, Cambridge University Press, 21 July 2020; Carmichael P, Butler G, Masic U, et al., Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old people with persistent gender dysphoria in the UK. *medRxiv* 2020.12.01.20241653; doi:https://doi.org/10.1101/2020.12.01.20241653; 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); Dyer, C. *Puberty blockers: children under 16 should not be referred without court order, says NHS* *BMJ*2020;371:m4717.doi:10.1136/bmj.m4717 pmid:33268453; Expert review for the British National Health Service <https://arms.nice.org.uk/resources/hub/1070905/attachment>; Cohen, D. and Barnes, H. BBC, “Evidence for puberty blockers use very low, says NICE,”

127. In sum, after 50 years of hormonal and surgical support for trans people, the rate of new or exacerbated mental health problems after these interventions is not clearly known. Neither the rate of patients stopping hormones due to medical injury or emotional disappointment nor the rate of substance abuse are known. Substance abuse in trans communities is known to be significantly elevated. The problem of suicidal ideation, suicide attempts, and completed suicide after these treatments continues to be elevated even though these concerns are one of the justifications for initiating the treatment in the first place.

128. Given all of the above factors, it seems reasonable to protect patients and their families from these practices. Energies of the “affirmation” treatment industry should be redirected to treating newly appearing minors in scientific protocols rather than to continue to be informed by flawed WPATH guidelines. Such scientific protocols will enable professionals either to medically and surgically support transition or to withdraw from hormonally and surgically treating minors based on their findings. The field then can decide whether current approaches are or are not similar to previous medical misadventures, such as lobotomies, aversive treatments of gay men, and fallacious diagnoses and treatments for repressed memory syndrome.

<https://www.bbc.com/news/health-56601386>; UK NICE Report, <https://www.evidence.nhs.uk/search?q=gender+affirming+hormones>; 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>); Sweden’s Karolinska Hospital 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; Finland Guidelines, https://genderreport.ca/wp-content/uploads/2021/04/Finland_Guidelines_Gender_Variance_In_Minors.pdf; See also One Year Since Finland Broke with WPATH “Standards of Care.” https://segm.org/Finland_devotes_from_WPATH_prioritizing_psychotherapy_no_surgery_for_minors.

VIII. SUMMARY OPINIONS

129. There are no long-term, peer-reviewed published, credible, reliable and valid, re-search studies documenting or establishing the follow six matters:

- a. The percentage of patients receiving gender transition procedures who are helped by such procedures according to well known criteria;
- b. The percentage of patients receiving gender transition procedures who are harmed by such procedures according to well known criteria;
- c. The reliability and validity of assessing gender identity by relying solely upon the expressed desires of a patient;
- d. The mental health outcomes of trans-behaving children who are either affirmed or not affirmed in childhood;
- e. The percentage of various types of childhood functional challenges and psychiatric diagnoses of trans identified children; and
- f. The percentage of patients whose new trans identity has been created by involvement in social media.

130. These six issues can stimulate new research whose results may shape future trans care. In the meantime, those with gender dysphoria or a trans identity have a right to be more fully informed about what is known, as do their physicians. Physicians, psychologists, parents, and patients have a right to be protected from these current experimental, politically tainted, fashionable “treatments.”

131. Informed consent is designed to protect the rights of patients and families, the cognitive and ethical processes of physicians, and the ethical and legal duties of health care institutions. The need for credible, reliable-valid science is also essential to protect each of these entities. The informed consent document for affirmative treatments of youth should specify that up

to 88% of children without affirmation will desist (heal naturally without treatment) from their childhood-onset trans preoccupations. Physicians always need to know the patient's original sex because while gender identity can dramatically change, biological sex and its unique susceptibilities to disease does not.

132. The transgender treatment industry's MHPs, endocrinologists, plastic and urological surgeons, should not be viewed as speaking for all of medicine on these highly controversial issues.

133. Science, not politics, needs to drive trans care. The medical profession has many tragic examples of when political sensibilities drive medical treatments. When policy is made by voting in the face of low quality science, claims that treatments are evidence-based should be considered misleading and deceptive.

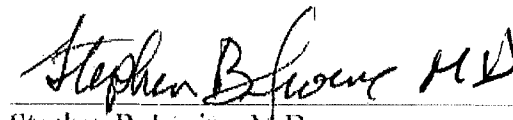
134. No medical, surgical, or psychiatric treatment is invariably successful in producing an agreed-upon outcome. In other branches of medicine and psychiatry risks and benefits, outcomes and error rates are better known, far less controversial, and much better proven by credible, reliable, and valid scientific research. Error rates for gender affirmation diagnoses, error rates for predictions of effective vs. harmful affirmation treatments, and error rates for increases or decreases in suicidal risk following affirmation treatments remain unknown. In the "gender affirmation" intervention field there has been a rush to treat and a remarkable absence of ethical concern based on obvious scientific limitations, as outlined in this report.

135. Expert Witness Report Methodological Limitations: My opinions and hypotheses in this matter are—as in all expert witness 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 July 8, 2021.



Stephen B. Levine, M.D.

Curriculum Vita
Stephen B. Levine, M.D.

I) Brief Introduction

Dr. Levine is Clinical Professor of Psychiatry at Case Western Reserve University School of Medicine. He is the solo author of five books, Sex Is Not Simple in 1989 (translated to German in 1992 and reissued in English in 1997 as Solving Common Sexual Problems); Sexual Life: A clinician's guide in 1992; Sexuality in Midlife in 1998 and Demystifying Love: Plain talk for the mental health professional in 2006; Barriers to Loving: A clinician's perspective in 2013; Psychotherapeutic Approaches to Sexual Problems: An Essential Guide for Mental Health Professionals in 2020. He is the Senior Editor of the first (2003), second (2010) and third (2016) editions of the Handbook of Clinical Sexuality for Mental Health Professionals. He has been teaching, providing clinical care, and writing since 1973 and has generated original research, invited papers, commentaries, chapters, and book reviews. He has served as a journal manuscript and book prospectus reviewer for many years. He was co-director of the Center for Marital and Sexual Health/ Levine, Risen & Associates, Inc. in Beachwood, Ohio from 1992-2017. He and two colleagues received a lifetime achievement Masters and Johnson's Award from the Society for Sex Therapy and Research in March 2005.

II) Personal Information

- A) Date of birth 1/14/42, Married 1963
- B) Medical license no. Ohio 35-03-0234-L
- C) Board Certification 6/76 American Board of Neurology and Psychiatry
- D) Office-23425 Commerce Park, Beachwood, Ohio 44122-5402 phone 216-831-2900 x 13 fax 216-831-4306
- E) Home-6415 Gates Mills Boulevard, Mayfield Heights, Oh 44124 440-442-2622; fax 216-831-4306

III) Education

- A) 1963 BA Washington and Jefferson College
- B) 1967 MD Case Western Reserve University School of Medicine
- C) 1967-68 internship in Internal Medicine University Hospitals of Cleveland
- D) 1968-70 Research associate, National Institute of Arthritis and Metabolic Diseases, Epidemiology Field Studies Unit, Phoenix, Arizona, United States Public Health Service
- E) 1970-73 Psychiatric Residency, University Hospitals of Cleveland
- F) 1974-77 Robert Wood Johnson Foundation Clinical Scholar

IV) Appointments at Case Western Reserve University School of Medicine

- A) 1973- Assistant Professor of Psychiatry
- B) 1979-Associate Professor
- C) 1982-Tenure

- D) 1985-Full Professor
- E) 1993-Clinical Professor

V) **Honors**

- A) Summa Cum Laude, Washington & Jefferson
- B) Teaching Excellence Award-1990 and 2010 (residency program)
- C) Visiting Professorships
 - 1) Stanford University-Pfizer Professorship program (3 days)–1995
 - 2) St. Elizabeth’s Hospital, Washington, DC –1998
 - 3) St. Elizabeth’s Hospital, Washington, DC--2002
- D) Named to America’s Top Doctors consecutively since 2001
- E) Masters and Johnson Lifetime Achievement Award from the Society of Sex Therapy and Research, April 2005 along with Candace Risen and Stanley Althof
- F) 2006 SSTAR Book Award for The Handbook of Clinical Sexuality for Mental Health Professionals: Exceptional Merit
- G) 2018—Albert Marquis Lifetime Achievement Award from Marquis Who’s Who. (excelling in one’s field for at least twenty years)
- H) Invitations to present various Grand Rounds at Departments of Psychiatry and Continuing Education Lectures and Workshops during 2019-2021
 - 1) March 12, 2021-The Mental Health Professionals’ Role with the Transgendered: Making the Controversies Clear Grand Rounds University Hospitals of Cleveland
 - 2) May 1, 2021 Psychotherapeutic Approaches to Sexual Problems Invited lecture to the American Psychiatric Association Annual Meeting (similar lecture in May 2020)
 - 3) Seven years of Continuing Education Courses at the American Psychiatric Association Meetings on Love and Sexuality
 - 4) Grand Rounds at Cleveland Clinic Foundation on Sexuality Education of Psychiatric Residents June 25, 2020
 - 5) Grand Rounds at Cleveland Clinic Foundation June 2019 Transgenderism: Beware! Repeated by invitation at Akron General Hospital and at National meeting of American Association of Partial Hospitalization in 2019
 - 6) Three-hour workshop at Society of Sex Therapy and Research in 2020 on Therapy for Sexual Problems
 - 7) Workshop on Teaching Sexuality to residents at the American Association of Residency Training Directors 2020 annual meeting
 - 8) Three-hour continuing education seminar with Massachusetts Department of Corrections Gender Identity Staff Fall 2019

VI) **Professional Societies**

- A) 1971- American Psychiatric Association; fellow; #19909
- B) 2005-American Psychiatric Association- **Distinguished Life Fellow**
- C) 1973- Cleveland Psychiatric Society

- D) 1973-Cleveland Medical Library Association
 - 1) 1985-Life Fellow
 - 2) 2003 Distinguished Life Fellow
- E) 1974-Society for Sex Therapy and Research
 - 1) 1987-89-President
- F) 1983- International Academy of Sex Research
- G) 1983- Harry Benjamin International Gender Dysphoria Association
 - 1) 1997-8 Chairman, Standards of Care Committee
- H) 1994- 1999 Society for Scientific Study of Sex

VII) **Community Boards**

- A) 1999-2002Case Western Reserve University Medical Alumni Association
- B) 1996-2001 Bellefaire Jewish Children's Bureau
- C) 1999-2001 Physicians' Advisory Committee, The Gathering Place (cancer rehabilitation)

VIII) **Editorial Boards**

- A) 1978-80 Book Review Editor Journal Sex and Marital Therapy
- B) Manuscript Reviewer for
 - 1) Archives of Sexual Behavior*
 - 2) Annals of Internal Medicine
 - 3) British Journal of Obstetrics and Gynecology
 - 4) JAMA
 - 5) Diabetes Care
 - 6) American Journal of Psychiatry
 - 7) Maturitas
 - 8) Psychosomatic Medicine
 - 9) Sexuality and Disability
 - 10) Journal of Nervous and Mental Diseases
 - 11) Journal of Neuropsychiatry and Clinical Neurosciences
 - 12) Neurology
 - 13) Journal Sex and Marital Therapy*
 - 14) Journal Sex Education and Therapy
 - 15) Social Behavior and Personality: an international journal (New Zealand)
 - 16) International Journal of Psychoanalysis
 - 17) International Journal of Transgenderism
 - 18) Journal of Urology
 - 19) Journal of Sexual Medicine*
 - 20) Current Psychiatry
 - 21) International Journal of Impotence Research
 - 22) Postgraduate medical journal
 - 23) Academic Psychiatry
 - 24) Expert Opinion on Drug Safety

- 25) Clinical Psychology Reviews
- 26) Heliyon
- 27) Andrologia
- 28) Children and Youth Services Review
- 29) Women and Criminal Justice
- *frequent

- C) Book Prospectus Reviewer
 - 1) Guilford
 - 2) Oxford University Press
 - 3) Brunner/Routledge
 - 4) Routledge

IX) **Administrative Responsibilities**

- A) Co-director, Center for Marital and Sexual Health/ Levine, Risen & Associates, Inc. until June 30, 2017
- B) Principal Investigator of approximately 70 separate studies involving pharmacological interventions for sexual dysfunction since 1989.
- C) Co-leader of case conferences at DELR. LLC.com
- D) **Expert Witness Appearances**
 - 1) US District Court, Judge Mark L. Wolf's witness in Michelle Kosilek vs. Massachusetts Dept of Corrections et al. case (transsexual issue) in Boston 2007
 - 2) Deposition in the Battista vs. Massachusetts Dept of Corrections case (transsexual issue) in Cleveland October 2009
 - 3) Witness for Massachusetts Dept. of Corrections in their defense of a lawsuit brought by prisoner Katheena Soneeya. March 22, 2011 Deposition in Boston and October 2018 in Cleveland and 2019 in Boston.
 - 4) Witness for State of Florida vs. Reyne Keohane July 2017

X) **Consultancy**

- A) Massachusetts Department of Corrections—evaluation of 12 transsexual prisoners and the development of a Gender Identity Disorders Program for the state prison system. Monthly consultation with the GID treatment team since February 2009 and the GID policy committee since February 2010
- B) California Department of Corrections and Rehabilitation; 2012-2015; education, inmate evaluation, commentary on inmate circumstances, suggestions on future policies
- C) Virginia Department of Corrections –evaluation of an inmate
- D) New Jersey Department of Corrections—evaluation of an inmate
- E) Idaho Department of Corrections—workshop 2016
- F) Expert Witness reports to lawsuits in Idaho, Wisconsin, and the UK in 2020
- G) Testimony to Subcommittee on Health to Pennsylvania legislature in March 2020

XI) Expert Witness Activities

- A) Pennsylvania legislative testimony. Written submission and live testimony before a committee of the Pennsylvania legislature. March 2020. (Engaged by Pennsylvania Family Institute.)
- B) In the Interests of the Younger Children. Expert testimony by deposition and at trial in Dallas, TX. (Engaged by Texas counsel Odeneal & Odeneal.) (Dallas Cty. Dist. Ct. 2019)
- C) Doe v. Madison Metropolitan School District. Expert declaration submitted February 19, 2020, rebuttal declaration submitted August 14, 2020.
- D) Hecox v. Idaho. Expert declaration submitted June 4, 2020. (D. Idaho)
- E) In the matter of Rhys & Lynn Crawford (Washington State). 3/30/2021 Tingley v. Washington State.. (W.D. Wa.)
- F) Queen (Quincy Bell) vs. Tavistock and Portman Clinics and NHS in High Court of London, Decision handed down on December 1, 2020.
- G) IN THE HIGH COURT OF JUSTICE QUEEN’S BENCH DIVISION ADMINISTRATIVE COURT
B E T W E E N: THE QUEEN (on the application of) L and Hampshire County Council
- H) *Hennessy-Waller v. Snyder, Case No. CV-20-00335-TUC-SHR, 2021 WL [1192842](#), at *5-6 & n.10 (D. Ariz. Mar. 30, 2021*

XII) Grant Support/Research Studies

- A) TAP—studies of Apomorphine sublingual in treatment of erectile dysfunction
- B) Pfizer—Sertraline for premature ejaculation
- C) Pfizer—Viagra and depression; Viagra and female sexual dysfunction; Viagra as a treatment for SSRI-induced erectile dysfunction
- D) NIH- Systemic lupus erythematosus and sexuality in women
- E) Sihler Mental Health Foundation
 - 1) Program for Professionals
 - 2) Setting up of Center for Marital and Sexual Health
 - 3) Clomipramine and Premature ejaculation
 - 4) Follow-up study of clergy accused of sexual impropriety
 - 5) Establishment of services for women with breast cancer
- F) Alza—controlled study of a novel SSRI for rapid ejaculation
- G) Pfizer—Viagra and self-esteem
- H) Pfizer- double-blind placebo control studies of a compound for premature ejaculation
- I) Johnson & Johnson – controlled studies of Dapoxetine for rapid ejaculation
- J) Proctor and Gamble: multiple studies to test testosterone patch for post menopausal sexual dysfunction for women on and off estrogen replacement
- K) Lilly-Icos—study of Cialis for erectile dysfunction
- L) VIVUS – study for premenopausal women with FSAD
- M) Palatin Technologies- studies of bremelanotide in female sexual dysfunction—first intranasal then subcutaneous administration
- N) Medtap – interview validation questionnaire studies
- O) HRA- quantitative debriefing study for Female partners os men with premature ejaculation, Validation of a New Distress Measure for FSD,

- P) Boehringer-Ingelheim- double blind and open label studies of a prosexual agent for hypoactive female sexual desire disorder
- Q) Biosante- studies of testosterone gel administration for post menopausal women with HSDD
- R) J&J a single-blind, multi-center, in home use study to evaluate sexual enhancement effects of a product in females.
- S) UBC-Content validity study of an electronic FSEP-R and FSDS-DAO and usability of study PRO measures in premenopausal women with FSAD, HSDD or Mixed FSAD/HSDD
- T) National registry trial for women with HSDD
- U) EndoCeutics—two studies of DHEA for vaginal atrophy and dryness in post menopausal women
- V) Palatin—study of SQ Bremelanotide for HSDD and FSAD
- W) Trimel- a double-blind, placebo controlled study for women with acquired female orgasmic disorder.
- X) S1 Biopharma- a phase 1-B non-blinded study of safety, tolerability and efficacy of Lorexys in premenopausal women with HSDD
- Y) HRA – qualitative and cognitive interview study for men experiencing PE

XIII) Publications

A) Books

- 1) Pariser SR, Levine SB, McDowell M (eds.), Clinical Sexuality, Marcel Dekker, New York, 1985
- 2) Sex Is Not Simple, Ohio Psychological Publishing Company, 1988
 - (a) Translated into German as Angstfreie Sexualität: Glück und Erfüllung in der Liebe, Wilhelm Heyne Verlag, Muchen, 1992
 - (b) Reissued in paperback as: Solving Common Sexual Problems: Toward a Problem Free Sexual Life, Jason Aronson, Livingston, NJ, 1997
- 3) Sexual Life: A Clinician's Guide. Plenum Publishing Corporation. New York, 1992
 - (a) See review in Archives of Sexual Behavior 28(4): 361-363,1999
- 4) Sexuality in Midlife. Plenum Publishing Corporation. New York, 1998
 - (a) See review in Am Journal of Psychiatry 156((9):1468, 1999
 - (b) See review in Contemporary Psychology APA Review of Books 44(4):293-295, 1999
 - (c) See review J Sex Education and Therapy January, 2000
 - (d) See review J Sex and Marital Therapy, Winter, 2000
- 5) Editor. Clinical Sexuality. Psychiatric Clinics of North America, March, 1995.
- 6) Editor, (Candace Risen and Stanley Althof, associate editors) Handbook of Clinical Sexuality for Mental Health Professionals. Routledge, New York, 2003
 1. see review American Journal of Psychiatry April, 2005

2. 2006 SSTAR Book Award: Exceptional Merit
3. see review in Archives of Sexual Behavior 35(6):757-758
4. see two reviews in Journal of Sex and Marital Therapy 33(3):272-276
- 7) Demystifying Love: Plain Talk For The Mental Health Professional.
Routledge, New York, 2006
 - (a) See review in Psychiatric Times, August 2008 by Leonore Tiefer
 - (b) See review in Journal of Sex and Marital Therapy 34(5)-459-460.
- 8) Senior editor, (Candace B. Risen and Stanley E. Althof, Associate editors),
Handbook of Clinical Sexuality for Mental Health Professionals. 2nd edition
Routledge, New York, 2010. See review by Pega Ren, JSex&Marital Therapy
- 9) Barriers to Loving: A Clinician's Perspective. Routledge, New York, 2014.
- 10) Senior editor Candace B. Risen and Stanley E. Althof, Associate editors),
Handbook of Clinical Sexuality for Mental Health Professionals. 3rd edition
Routledge, New York, 2016

- B) Research and Invited Papers When his name is not listed in a citation, Dr. Levine is either the solo or the senior author
- 1) Sampliner R. Parotid enlargement in Pima Indians. Annals of Internal Medicine 1970; 73:571-73
 - 2) Confrontation and residency activism: A technique for assisting residency change: World Journal of Psychosynthesis 1974; 6: 23-26
 - 3) Activism and confrontation: A technique to spur reform. Resident and Intern Consultant 173; 2
 - 4) Medicine and Sexuality. Case Western Reserve Medical Alumni Bulletin 1974:37:9-11.
 - 5) Some thoughts on the pathogenesis of premature ejaculation. J. Sex & Marital Therapy 1975; 1:326-334
 - 6) Marital Sexual Dysfunction: Introductory Concepts. Annals of Internal Medicine 1976;84:448-453
 - 7) Marital Sexual Dysfunction: Ejaculation Disturbances . Annals of Internal Medicine 1976; 84:575-579
 - 8) Yost MA: Frequency of female sexual dysfunction in a gynecology clinic: An epidemiological approach. Archives of Sexual Behavior 1976;5:229-238
 - 9) Engel IM, Resnick PJ, Levine SB: Use of programmed patients and videotape in teaching medical students to take a sexual history. Journal of Medical Education 1976;51:425-427
 - 10) Marital Sexual Dysfunction: Erectile dysfunction. Annals of Internal Medicine 1976;85:342-350
 - 11) Articles in Medical Aspects of Human Sexuality
 - (a) Treating the single impotent male. 1976; 10:123, 137
 - (b) Do men enjoy being caressed during foreplay as much as women do? 1977; 11:9
 - (c) Do men like women to be sexually assertive? 1977;11:44

- (d) Absence of sexual desire in women: Do some women never experience sexual desire? Is this possibility genetically determined? 1977; 11:31
- (e) Barriers to the attainment of ejaculatory control. 1979; 13:32-56.
- (f) Commentary on sexual revenge. 1979; 13:19-21
- (g) Prosthesis for psychogenic impotence? 1979; 13:7
- (h) Habits that infuriate mates. 1980; 14:8-19
- (i) Greenberger-Englander, Levine SB. Is an enema an erotic equivalent? 1981; 15:116
- (j) Ford AB, Levine SB. Sexual Behavior and the Chronically Ill Patients. 1982; 16:138-150
- (k) Preoccupation with wife's sexual behavior in previous marriage 1982; 16:172
- (l) Co-existing organic and psychological impotence. 1985; 19:187-8
- (m) Althof SE, Turner LA, Kursh ED, Bodner D, Resnick MI, Risen CB. Benefits and Problems with Intracavernosal injections for the treatment of impotence. 1989; 23(4):38-40
- 12) Male Sexual Problems. Resident and Staff Physician 1981; 2:90-5
- 13) Female Sexual Problems. Resident and Staff Physician 1981; 3:79-92
- 14) How can I determine whether a recent depression in a 40 year old married man is due to organic loss of erectile function or whether the depression is the source of the dysfunction? Sexual Medicine Today 1977; 1:13
- 15) Corradi RB, Resnick PJ, Levine SB, Gold F. For chronic psychologic impotence: sex therapy or psychotherapy? I & II Roche Reports; 1977
- 16) Marital Sexual Dysfunction: Female dysfunctions 1977; 86:588-597
- 17) Current problems in the diagnosis and treatment of psychogenic impotence. Journal of Sex & Marital Therapy 1977; 3:177-186
- 18) Resnick PJ, Engel IM. Sexuality curriculum for gynecology residents. Journal of Medical Education 1978; 53:510-15
- 19) Agle DP. Effectiveness of sex therapy for chronic secondary psychological impotence Journal of Sex & Marital Therapy 1978; 4:235-258
- 20) DePalma RG, Levine SB, Feldman S. Preservation of erectile function after aortoiliac reconstruction. Archives of Surgery 1978; 113:958-962
- 21) Conceptual suggestions for outcome research in sex therapy Journal of Sex & Marital Therapy 1981; 6:102-108
- 22) Lothstein LM. Transsexualism or the gender dysphoria syndrome. Journal of Sex & Marital Therapy 1982; 7:85-113
- 23) Lothstein LM, Levine SB. Expressive psychotherapy with gender dysphoria patients Archives General Psychiatry 1981; 38:924-929
- 24) Stern RG Sexual function in cystic fibrosis. Chest 1982; 81:422-8
- 25) Shumaker R. Increasingly Ruth: Towards understanding sex reassignment surgery Archives of Sexual Behavior 1983; 12:247-61
- 26) Psychiatric diagnosis of patients requesting sex reassignment surgery.

- Journal of Sex & Marital Therapy 1980; 6:164-173
- 27) Problem solving in sexual medicine I. British Journal of Sexual Medicine 1982;9:21-28
- 28) A modern perspective on nymphomania. Journal of Sex & Marital Therapy 1982;8:316-324
- 29) Nymphomania. Female Patient 1982;7:47-54
- 30) Commentary on Beverly Mead's article: When your patient fears impotence. Patient Care 1982;16:135-9
- 31) Relation of sexual problems to sexual enlightenment. Physician and Patient 1983 2:62
- 32) Clinical overview of impotence. Physician and Patient 1983; 8:52-55.
- 33) An analytical approach to problem-solving in sexual medicine: a clinical introduction to the psychological sexual dysfunctions. II. British Journal of Sexual Medicine
- 34) Coffman CB, Levine SB, Althof SE, Stern RG Sexual Adaptation among single young adults with cystic fibrosis. Chest 1984;86:412-418
- 35) Althof SE, Coffman CB, Levine SB. The effects of coronary bypass in female sexual, psychological, and vocational adaptation. Journal of Sex & Marital Therapy 1984;10:176-184
- 36) Letter to the editor: Follow-up on Increasingly Ruth. Archives of Sexual Behavior 1984;13:287-9
- 37) Essay on the nature of sexual desire Journal of Sex & Marital Therapy 1984; 10:83-96
- 38) Introduction to the sexual consequences of hemophilia. Scandanavian Journal of Haemology 1984; 33:(supplement 40).75-
- 39) Agle DP, Heine P. Hemophila and Acquired Immune Deficiency Syndrome: Intimacy and Sexual Behavior. National Hemophilia Foundation; July, 1985
 - (a) Translated into German
 - (b) Translated into Spanish
- 40) Turner LA, Althof SE, Levine SB, Bodner DR, Kursh ED, Resnick MI. External vacuum devices in the treatment of erectile dysfunction: a one-year study of sexual and psychosocial impact. Journal of Sex & Marital Therapy
- 41) Schein M, Zyzanski SJ, Levine SB, Medalie JH, Dickman RL, Alemagno SA. The frequency of sexual problems among family practice patients. Family Practice Research Journal 1988; 7:122-134
- 42) More on the nature of sexual desire. Journal of Sex & Marital Therapy 1987;13:35-44
- 43) Waltz G, Risen CB, Levine SB. Antiandrogen treatment of male sex offenders. Health Matrix 1987; V.51-55.
- 44) Lets talk about sex. National Hemophilia Foundation January, 1988
- 45) Sexuality, Intimacy, and Hemophilia: questions and answers . National

- Hemophilia Foundation January, 1988
- 46) Prevalence of sexual problems. *Journal Clinical Practice in Sexuality* 1988;4:14-16.
- 47) Kursh E, Bodner D, Resnick MI, Althof SE, Turner L, Risen CB, Levine SB. Injection Therapy for Impotence. *Urologic Clinics of North America* 1988; 15(4):625-630
- 48) Bradley SJ, Blanchard R, Coates S, Green R, Levine S, Meyer-Bahlburg H, Pauly I, Zucker KJ. Interim report of the DSM-IV Subcommittee for Gender Identity Disorders. *Archives of Sexual Behavior* 1991;;20(4):333-43.
- 49) Sexual passion in mid-life. *Journal of Clinical Practice in Sexuality* 1991 6(8):13-19
- 50) Althof SE, Turner LA, Levine SB, Risen CB, Bodner DR, Resnick MI. Intracavernosal injections in the treatment of impotence: A prospective study of sexual, psychological, and marital functioning. *Journal of Sex & Marital Therapy* 1987; 13:155-167
- 51) Althof SE, Turner LA, Risen CB, Bodner DR, Kursh ED, Resnick MI. Side effects of self-administration of intracavernosal injection of papaverine and phentolamine for treatment of impotence. *Journal of Urology* 1989;141:54-7
- 52) Turner LA, Froman SL, Althof SE, Levine SB, Tobias TR, Kursh ED, Bodner DR. Intracavernous injection in the management of diabetic impotence. *Journal of Sexual Education and Therapy* 16(2):126-36, 1989
- 53) Is it time for sexual mental health centers? *Journal of Sex & Marital Therapy* 1989;
- 54) Althof SE, Turner LA, Levine SB, Risen CB, Bodner D, Kursh ED, Resnick MI. Sexual, psychological, and marital impact of self injection of papaverine and phentolamine: a long-term prospective study. *Journal of Sex & Marital Therapy*
- 55) Althof SE, Turner LA, Levine SB, Risen CB, Bodner D, Kursh ED, Resnick MI. Why do so many men drop out of intracavernosal treatment? *Journal of Sex & Marital Therapy*. 1989;15:121-9
- 56) Turner LA, Althof SE, Levine SB, Risen CB, Bodner D, Kursh ED, Resnick MI. Self injection of papaverine and phentolamine in the treatment of psychogenic impotence. *Journal of Sex & Marital Therapy*. 1989; 15(3):163-78
- 57) Turner LA, Althof SE, Levine SB, Risen CB, Bodner D, Kursh ED, Resnick MI. Treating erectile dysfunction with external vacuum devices: impact upon sexual, psychological, and marital functioning. *Journal of Urology* 1990;141(1):79-82
- 58) Risen CB, Althof SE. An essay on the diagnosis and nature of paraphilia *Journal of Sex & Marital Therapy* 1990; 16(2):89-102.
- 59) Althof SE, Turner LA, Levine SB, Risen CB, Bodner DB, Kursh ED,

- Resnick MI. Through the eyes of women: the sexual and psychological responses of women to their partners' treatment with self-injection or vacuum constriction therapy. *International Journal of Impotence Research* (supplement 2)1990;346-7.
- 60) Althof SE, Turner LA, Levine SB, Risen CB, Bodner DB, Kursh ED, Resnick MI. A comparison of the effectiveness of two treatments for erectile dysfunction: self injection vs. external vacuum devices. . *International Journal of Impotence Research* (supplement 2)1990;289-90
 - 61) Kursh E, Turner L, Bodner D, Althof S, Levine S. A prospective study on the use of the vacuum pump for the treatment of impotence. *International Journal of Impotence Research* (supplement 2)1990;340-1.
 - 62) Althof SE, Turner LA, Levine SB, Risen CB, Bodner DB, Kursh ED, Resnick MI. Long term use of intracavernous therapy in the treatment of erectile dysfunction in *Journal of Sex & Marital Therapy* 1991; 17(2):101-112
 - 63) Althof SE, Turner LA, Levine SB, Risen CB, Bodner DB, Kursh ED, Resnick MI. Long term use of vacuum pump devices in the treatment of erectile dysfunction in *Journal of Sex & Marital Therapy* 1991;17(2):81-93
 - 64) Turner LA, Althof SE, Levine SB, Bodner DB, Kursh ED, Resnick MI. A 12-month comparison of the effectiveness of two treatments for erectile dysfunction: self injection vs. external vacuum devices. *Urology* 1992;39(2):139-44
 - 65) Althof SE, The pathogenesis of psychogenic impotence. *J. Sex Education and Therapy*. 1991; 17(4):251-66
 - 66) Mehta P, Bedell WH, Cumming W, Bussing R, Warner R, Levine SB. Letter to the editor. Reflections on hemophilia camp. *Clinical Pediatrics* 1991; 30(4):259-260
 - 67) Successful Sexuality. Belonging/Hemophilia. (Caremark Therapeutic Services), Autumn, 1991
 - 68) Psychological intimacy. *Journal of Sex & Marital Therapy* 1991; 17(4):259-68
 - 69) Male sexual problems and the general physician, *Georgia State Medical Journal* 1992; 81(5): 211-6
 - 70) Althof SE, Turner LA, Levine SB, Bodner DB, Kursh E, Resnick MI. Through the eyes of women: The sexual and psychological responses of women to their partner's treatment with self-injection or vacuum constriction devices. *Journal of Urology* 1992; 147(4):1024-7
 - 71) Curry SL, Levine SB, Jones PK, Kurit DM. Medical and Psychosocial predictors of sexual outcome among women with systemic lupus erythematosus. *Arthritis Care and Research* 1993; 6:23-30
 - 72) Althof SE, Levine SB. Clinical approach to sexuality of patients with spinal cord injury. *Urological Clinics of North America* 1993; 20(3):527-34

- 73) Gender-disturbed males. *Journal of Sex & Marital Therapy* 19(2):131-141, 1993
- 74) Curry SL, Levine SB, Jones PK, Kurit DM. The impact of systemic lupus erythematosus on women's sexual functioning. *Journal of Rheumatology* 1994; 21(12):2254-60
- 75) Althof SE, Levine SB, Corty E, Risen CB, Stern EB, Kurit D. Clomipramine as a treatment for rapid ejaculation: a double-blind crossover trial of 15 couples. *Journal of Clinical Psychiatry* 1995;56(9):402-7
- 76) Risen CB, Althof SE. Professionals who sexually offend: evaluation procedures and preliminary findings. *Journal of Sex & Marital Therapy* 1994; 20(4):288-302
- 77) On Love, *Journal of Sex & Marital Therapy* 1995; 21(3):183-191
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 - 40) *Principles and Practices of Sex Therapy*, 6th edition, (2020) KSK Hall, IM Binik (editors), Guilford Press, New York in *Journal of Sex and Marital Therapy* i47(4): May 2021. Doi 10.1080/0092623X2021.1920736

**IN THE UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF ARKANSAS
CENTRAL DIVISION**

DYLAN BRANDT, et al.,

PLAINTIFFS,

v.

No. 4:21-CV-00450-JM

LESLIE RUTLEDGE, et al.,

DEFENDANTS.

DECLARATION OF DR. MARK REGNERUS

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

I. CREDENTIALS & SUMMARY OF OPINIONS

1. I am Professor of Sociology at the University of Texas at Austin. I received my Ph.D. from the University of North Carolina at Chapel Hill in 2000. I became an Assistant Professor of Sociology at UT-Austin in 2002, an Associate Professor in 2007, and a full Professor in 2018.

2. I have published numerous articles and four books on sexual relationship behavior and decision-making since 2003.¹ The books, peer-reviewed journal articles, and essays I have written include material on sexual orientation and, more recently, the science of transgender medicine. I am an experienced peer reviewer, having reviewed dozens of manuscripts in the past decade on these and related topics—including for top journals in both sociology and sex/sexuality studies. I have extensive survey administration experience as well, having fielded three na-

¹ Regnerus, M. D. (2007). *Forbidden fruit: Sex & religion in the lives of American teenagers*. Oxford University Press.; Regnerus, M. & Uecker, J. (2011). *Premarital sex in America: How young Americans meet, mate, and think about marrying*. Oxford University Press.; Regnerus, M. (2017). *Cheap sex: The transformation of men, marriage, and monogamy* Oxford University Press.; Regnerus, M. (2020). *The future of Christian marriage*. Oxford University Press.

EXHIBIT

2

tionally-representative surveys since 2011, and consulted on survey construction for several others. A more complete review of my professional experience, publications, and research is provided in my curriculum vitae, a copy of which is attached hereto as Exhibit A.

3. My experience in the area of transgender research primarily concerns basic methodological matters, involving design, measurement, statistical inference, interpretation of data, and reflections on the research and publication norms that have developed in this new domain in conjunction with media interest and professional and organizational pressures.

4. I have been retained as an expert witness by the State of Arkansas in connection with this litigation. I have actual knowledge of the matters stated in this report. I base the following opinions on my own knowledge, research, experience, and publications, and the work of other academics and writers. The materials I have used to research and write this report are the standard sources used by other experts in my field. I am receiving \$250 per hour for my time spent preparing this report. My compensation is not dependent upon the outcome of this litigation or the substance of my opinions.

5. The focus of this report is on science: scientific evidence, researcher conduct, the culture of scientific organizations, and the role of values in inquiry. In particular, I focus on the unscientific process by which “affirmative” treatment of transgender-identifying adolescents has come to be the default position advocated by various professionals and organizations. This is what the sociology of science concerns—an evaluation of how science operates. In this case, I probe how the nascent field of transgender research has, in the United States, come to make premature claims about “standards of care” and profess a level of “consensus” about affirmative care that is uncharacteristically rapid for such a new scientific subfield. Something is amiss.

6. A summary of the key points I discuss in this statement includes:

- a. The science of the origins and course of gender identity remain in flux.
- b. The demographics of transgender-identifying adolescents is shifting in ways that are not yet understood.
- c. Adolescent gender transition treatments are not supported by randomized clinical trials—an absence that is difficult to account for.
- d. There is a great deal of evidence that discussion of gender dysphoria has been captured by the assumptions of activists promoting what is sometimes called “gender ideology.”
- e. The evidence for suicide risk among gender dysphoric minors is ambiguous at best, and the evidence for claims that treatments for adolescent gender transition lead to sustained improvement in mental health is remarkably weak.
- f. The practice of “affirmative” treatment for young people with gender dysphoria is characterized by dubious assumptions and questionable value judgments that result in a harmful, consumer-driven medical culture.

7. I have reviewed the declaration of Deanna Adkins, dated June 11, 2021 (“Adkins”). Dr. Adkins identifies affirmative care as treatment for gender dysphoria “aimed at eliminating the clinically significant distress a patient experiences by helping the patient live in alignment with their gender identity.”² The same treatment is referred to both in the medical literature and in this report using similar terms, including “gender transition,” “gender affirming care,” and “affirmative” treatment—an approach that (typically) recommends the hormonal and surgical procedures that Arkansas has prohibited doctors from performing on minors.

² Adkins, D. (2021) Declaration, U.S. District Court, Eastern District of Arkansas, Case No.: 4:21CV450-JM, p. 4.

8. I make no claims here about the most prudent course of treatment for a particular patient. Instead, as a sociologist, my claims highlight the unscientific processes by which “gender affirming” treatment has come to appear not simply as the dominant approach but increasingly the only permitted approach. This has happened amid a surge in cases of gender dysphoria and transgender identity that emerged suddenly, was unanticipated, and remains demonstrably undertheorized.³ In other words, scholars have been insufficiently curious about these recent developments and appear instead to be more interested in connecting research strategies and conclusions to fit affirmative care prescriptions. This is the “elephant in the room” that ought to give pause to practitioners and their professional societies. Instead, many have pressed ahead without sufficient interest in understanding why the current realities have come to be.

9. Since pubertal blockers are already permitted and prescribed for the treatment of precocious puberty in one’s natal sex, the plaintiffs’ witnesses frame Arkansas’s law as discrimination regarding who can access such treatments. But the issues at stake are even more fundamental than a question of fairness. Those fundamental issues include: First, is affirmative care demonstrably and consistently helpful to minors, in terms of enhanced, long-term psychological and physical health? Second, ought minors be permitted to make such consequential, life-altering decisions?

10. Lurking in the background are other inexplicable patterns besides a rapid surge in gender dysphoria. Twenty years ago, far more natal males than females exhibited gender dys-

³ Bernadette Wren, who was until her retirement a senior clinician at the UK Tavistock gender clinic, described the situation this way: “There are morally complex, there are clinically complex, there are politically complex issues that we are grappling with and there aren’t any easy answers. One of the things about the gender field is you can’t plausibly develop a foundational theory of gender identity in which to ground the work.” See Gossling, G. (2020). Bernadette Wren: On change. *In mind*. <https://100years.tavistockandportman.nhs.uk/bernadette-wren-on-change>

phoria. Ten years ago, comparable numbers of natal males and females sought help for it. Today, the sex ratio has reversed: for every one natal male seeking help, approximately three natal females do. Why? And why aren't researchers more interested in understanding this than they are in shuttling patients (regardless of their natal sex) toward "affirmative" care?

11. The plaintiffs' witnesses repeatedly reference current treatment regimens, "consensus," "standards of care," etc. But at a basic level, the question is whether any putative consensus has been formed without undue pressure. The evidence suggests that it has not. There is now little professional space for clinicians and psychologists to endorse anything except the "affirmative" approach, which has rapidly colonized adolescent endocrinology in less than a decade.

12. There is no global or even Western "consensus" on transgender treatments for adolescents. There is, rather, a coalition of organizations in the United States, Canada, the Netherlands, and Australia that use multiple platforms—scientific, medical, legal, and media—to suggest there is a consensus and employ language intended to reinforce the claim of a professional consensus backing "affirmative" care. In reality—that is, when you include numerous pediatricians, psychotherapists, some researchers and endocrinologists, together with national health care systems in several European countries—there is no wide, shared consensus about the prudence and intelligence of giving puberty blockers and cross-sex hormones to adolescents. Only professional organizations whose assertions are partial to transgender activists would suggest there is a consensus. Indeed, how could a scholarly consensus emerge so quickly in a domain where research barely existed two decades ago and where most of what has been written is less

than seven years old? Even some researchers acknowledge this: “...in actual practice, no consensus exists whether to use these early medical interventions.”⁴

II. UNDERSTANDING THE DEMOGRAPHICS OF TRANSGENDER-IDENTIFYING ADOLESCENTS

13. Transgender self-identifications have surged in the United States, and throughout much of the West, in the past 10 years. What had once comprised around 0.3 percent of the total population as recently as 2011 doubled to 0.6 percent by 2016 (with adolescent transgender self-identification comprising 0.7 percent). Since then, the pace of increase has accelerated further, especially among youth. Population-based survey data from 10 state and nine urban school districts found that an average of 1.8 percent of high school students identify as transgender.⁵ A study in *Pediatrics*, leaning on a 2016 statewide survey in Minnesota, revealed a figure of 2.7 percent.⁶

14. Countries like the UK—with a national health system—are better poised to keep centralized statistics about adolescent gender clinic patients. In 2009-10, a total of 32 natal females and 40 natal males were referred to the country’s Gender Identity Development Service (or GIDS).⁷ Five years later, those figures rose to 399 natal females and 250 natal males. At the

⁴ Vrouenraets, L. J., Fredriks, A. M., Hannema, S. E., Cohen-Kettenis, P. T., & de Vries, M. C. (2015). Early medical treatment of children and adolescents with gender dysphoria: An empirical ethical study. *The journal of adolescent health : Official publication of the Society for Adolescent Medicine*, 57(4), 367–373, p. 367. <https://doi.org/10.1016/j.jadohealth.2015.04.004>

⁵ The states are as follows: Colorado, Delaware, Hawaii, Maine, Maryland, Massachusetts, Michigan, Rhode Island, Vermont, and Wisconsin; the nine large urban school districts are: Boston, Broward County, Cleveland, Detroit, District of Columbia, Los Angeles, New York City, San Diego, and San Francisco; see Johns, M. M., Lowry, R., Andrzejewski, J., Barrios, L. C., Demissie, Z., McManus, T., Rasberry, C. N., Robin, L., & Underwood, J. M. (2019). 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 Morbidity and mortality weekly report*, 68(3), 67–71. <https://doi.org/10.15585/mmwr.mm6803a3>

⁶ Rider, G. N., McMorris, B. J., Gower, A. L., Coleman, E., & Eisenberg, M. E. (2018). Health and care utilization of transgender and gender nonconforming youth: A population-based study. *Pediatrics*, 141(3) e20171683. <https://doi.org/10.1542/peds.2017-1683>

⁷ Tavistock & Portman NHS Foundation Trust. (2019, 28 June). Referrals to the Gender Identity Development Service (GIDS) level-off in 2018-19. <https://tavistockandportman.nhs.uk/about-us/news/stories/referrals-gender-identity-development-service-gids-level-2018-19/>

most recent year of data reporting (2018-19), the numbers climbed to 1,740 natal females and 624 natal males. Beginning in 2011-12, the share of natal females outnumbered those of natal males, but by 2018-19, the sex ratio of referrals had exploded to 2.8 females for every male. This includes 171 children under age 10, 52 of whom are ages 3-6. A similar sex ratio is reported in North American gender clinics.⁸

15. A June 6, 2021 answer to a Freedom of Information Act request revealed that 8,741 patients are awaiting their first visit to the UK's Charing Cross Gender Identity Clinic, a sizable number for what once affected less than 1 in 10,000 children, according to DSM-5 prevalence rates.⁹

16. Between 2015 and 2019, there was also a 27% increase among American high school boys in the share that identified as nonheterosexuals (from 4.5 to 5.7 percent). The same estimate among girls was even larger: a 46% increase (from 12.2 to 17.8 percent).¹⁰ But the pace of growth in adolescent transgender self-identifications eclipses the climb in rates of nonheterosexual orientations.

17. In 2020, a Pew research survey revealed that among Americans born between 1997 and 2002 (or Gen Z), 1.8 percent now identify as transgender, an estimate that is 50 percent

⁸ Sorbara, J. C., Chiniara, L. N., Thompson, S., & Palmert, M. R. (2020). Mental health and timing of gender-affirming care. *Pediatrics*, 146(4) e20193600. <https://doi.org/10.1542/peds.2019-3600>

⁹ Tavistock & Portman NHS Foundation Trust (2021, June 3). Reply to Freedom of Information request for Charing Cross and GIC waiting and intake figures made by Harry Burns. https://www.whatdotheyknow.com/request/request_for_charing_cross_gic_wa?nocache=incoming-1805111#incoming-1805111

¹⁰ Rapoport, E., Athanasian, C. E., & Adesman, A. (2021). Prevalence of nonheterosexual identity and same-sex sexual contact among high school students in the US From 2015 to 2019. *JAMA pediatrics*. doi:10.1001/jamapediatrics.2021.1109

higher than that of Millennials (1.2 percent), and nine times higher than found among Gen X respondents (0.2 percent).¹¹ Other surveys have found as high as 10 percent of high schoolers identifying as transgender or gender non-conforming.¹²

18. Intersex cases, often used to call attention to transgender cases, are distinctive and occur in roughly one in every 5,000 births, an estimate consonant across three continents.¹³ They are considered a type of disorder of sex development (DSD), and are not, as has sometimes been suggested, evidence of a “spectrum” of biological sex.

19. In the “Factual Background” section of the Memorandum in Support of Plaintiffs’ Motion, gender identity is described as both “innate” and “immutable,” as well as “durable and cannot be altered through medical intervention,” citing Dr. Adkins’s declaration as its sole support. Although Adkins appears to have characterized gender identity using the term “innate” before,¹⁴ the report she has submitted in this case makes no use of the term (nor of “immutable”), instead describing a person’s gender identity merely as “fixed.” It is fair to say the terminology, together with the science of the origins and course of gender identity, remains in flux. Indeed, this fact is acknowledged. Guidelines published by the World Professional Association for

¹¹ Jones, J. M. (2021, February 24) LGBT identification rises to 5.6% in latest U.S. estimate. *Gallup*. <https://news.gallup.com/poll/329708/lgbt-identification-rises-latest-estimate.aspx>

¹² Kidd, K. M., Sequeira, G. M., Douglas, C., Paglisotti, T., Inwards-Breland, D. J., Miller, E., & Coulter, R. W. (2021). Prevalence of gender-diverse youth in an urban school district. *Pediatrics*, 147(6) e2020049823. <https://doi.org/10.1542/peds.2020-049823>

¹³ Kim, K. S., & Kim, J. (2012). Disorders of sex development. *Korean journal of urology*, 53(1), 1-8. doi: 10.4111/kju.2012.53.1.1; Thyen, U., Lanz, K., Holterhus, P. M., & Hiort, O. (2006). Epidemiology and initial management of ambiguous genitalia at birth in Germany. *Hormone research in paediatrics*, 66(4), 195-203. <https://doi.org/10.1159/000094782>; Sax, L. (2002). How common is intersex? A response to Anne Fausto-Sterling. *Journal of sex research*, 39(3), 174-178. <https://doi.org/10.1080/00224490209552139>

¹⁴ Adkins, D., (2016). Declaration, U.S. District Court, Middle District of North Carolina, Case 1:16-cv-00236-TDS-JEP https://www.aclu.org/sites/default/files/field_document/AdkinsDecl.pdf.

Transgender Health (WPATH), for example, recognize that “this field of medicine [i.e., providing cross-sex hormones to people who identify as transgender] is evolving,”¹⁵ and that “[t]erminology in the area of health care for transsexual, transgender, and gender-nonconforming people is rapidly evolving; new terms are being introduced, and the definitions of existing terms are changing.”¹⁶ The Endocrine Society’s guidelines likewise acknowledge that “[t]erminology and its use vary and continue to evolve.”¹⁷

20. Categorical claims about the immutability of sexual orientation have recently fared well in legal decisions in the West. But to invoke that description in the absence of a genuine consensus on the etiology of gender dysphoria—especially amid the sudden surge in cases—suggests political calculation is at work.

21. Accounting for the surge in adolescent transgender cases has been very challenging, for two reasons. First, it was an unexpected development. Ten years ago, there was simply no clinical literature on females ages 11 to 21 suffering from gender dysphoria.¹⁸ Early onset gender dysphoria, however, has been documented for years, primarily in natal boys.

22. The surge in adolescent transgender cases cannot be simplistically attributed to “pent-up demand”—that is, by suggesting that gender dysphoria and transgender self-identification exhibited longstanding manifestations that simply went undiagnosed or were entirely stigmatized. If that were true, we should be witnessing a parallel and documentable rise in gender dysphoria among, say, middle-aged adults. But no such rise has been observed.

¹⁵ World Professional Association for Transgender Health. (2012). *Standards of care for the health of transsexual, transgender, and gender-conforming people* [7th version]. <https://www.wpath.org/publications/soc>

¹⁶ World Professional Association for Transgender Health. (2012), p. 95.

¹⁷ Hembree, W. C., Cohen-Kettenis, P. T., Gooren, L., Hannema, S. E., Meyer, W. J., Hassan Murad, M., 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 & metabolism*, 102, 11, 3869–3903, p. 3874. <https://doi.org/10.1210/jc.2017-01658>

¹⁸ Shrier, A. (2020). *Irreversible damage: The transgender craze seducing our daughters*. Regnery Publishing.

23. Second, the surge makes for a very sensitive research environment, all the more so given the rapid clinical shift in some contexts from a more “watchful waiting” approach to adolescent gender dysphoria to an “affirmative care” approach, wherein a much swifter move to puberty blockers and cross-sex hormones is suggested. This development appears to constitute much of the political struggle being witnessed over adolescent gender dysphoria, and it makes research efforts in this domain subject to far greater policing during the peer-review process as well as in post-publication media and activist scrutiny.

24. One recent study about the surge in adolescent demand for gender dysphoria treatment in the UK and four Nordic countries noted that “[t]he reasons for the increase are not known,” but fingered four forces as playing a potential role: (1) the increased awareness of gender identity issues, (2) the supply of services for the same, (3) de-stigmatization, and (4) social and media influences.¹⁹

25. In an attempt to understand this surge, Brown University public health scientist Lisa Littman explored possible “cluster outbreaks” of what she identified as “rapid onset gender dysphoria” (ROGD) among adolescents, meaning that the dysphoria happens suddenly either during or after puberty among teenagers who displayed no indications of such tendency in their childhood.²⁰ (Others identify this as “adolescent-onset” GD.²¹) The study, which inquired of parents of teens, noted that ROGD tended to occur within groups of friends: more than one-third

¹⁹ Kaltiala, R., Bergman, H., Carmichael, P., de Graaf, N. M., Egebjerg Rischel, K., Frisé, L., Schorkopf, M., Suomalainen, 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. doi: 10.1080/08039488.2019.1667429

²⁰ Littman, L. (2018). Rapid-onset gender dysphoria in adolescents and young adults: A study of parental reports. *Plos one*, 13(8), e0202330. <https://doi.org/10.1371/journal.pone.0202330>

²¹ de Vries, A. L. (2020). Challenges in timing puberty suppression for gender-nonconforming adolescents. *Pediatrics*, 146(4). doi: <https://doi.org/10.1542/peds.2020-010611>; Seveler, M., & Meyer-Bahlburg, H. F. (2019). Late-onset transgender identity development of adolescents in psychotherapy for mood and anxiety problems: Approach to assessment and treatment. *Archives of sexual behavior*, 48(7), 1993-2001. <https://doi.org/10.1007/s10508-018-1362-9>

of the friendship groups in the study witnessed half or more of the group identifying as transgender in a similar time frame. This, Littman noted, is about 70 times higher than the expected (0.7%) prevalence rate. Only 13 percent of parents noted no evidence at all of a “social influence.”

26. Parents of the adolescents in the study tended to describe “a process of immersion in social media, such as ‘binge-watching’ YouTube transition videos and excessive use of Tumblr, immediately preceding their child becoming gender dysphoric.”²² Littman also observed that 22 percent of adolescents in her study “had been exposed to online advice about what to say to doctors to get hormones.” Moreover, “the vast majority of parents were reasonably sure or positive that their child misrepresented their history to their doctor or therapist.”²³

27. Studies like Littman’s are exploratory, however, and not designed to discern causation. Professor Littman did not draw hard conclusions from her survey, which was nonrepresentative and relied on an opt-in sampling strategy that is very common in the study of transgender patients. Rather, she documented the associations between ROGD and certain social and psychiatric conditions.

28. An outcry on social media emerged after the Littman study was published. The journal’s editors pledged to “seek further expert assessment on the study’s methodology and analyses.” That is, they re-reviewed the study, a very unusual move in the sciences. This post-publication review resulted in no substantive changes to the study’s results, suggesting the motivation was rooted in political rather than scientific concerns. This example highlights the challenging atmosphere both for understanding and documenting what is going on.

²² Littman (2018), p. 3.

²³ Littman (2018), p. 36.

29. University of Utah psychology professor Lisa Diamond, upon noting the high levels of diverse gender self-identities in recent surveys, remarked last year, “Clearly, we need a more thorough understanding of youth who consider themselves gender fluid, genderqueer, or nonbinary, and of how they resemble and differ from transgender youth.”²⁴

30. Neither adolescent-onset gender dysphoria nor the rise in nonbinary self-identities fit the narrative that gender identity is “immutable” or “durable.” Rather, it suggests profound fluidity. What is durable or immutable about a “nonbinary” gender self-identity? Dr. Adkins, on the other hand, maintains that a person’s gender identity “is fixed, is not subject to voluntary control, cannot be voluntarily changed, and is not undermined or altered by the existence of other sex-related characteristics that do not align with it,” an assertion that seems out of step with the American Academy of Pediatrics (AAP) policy statement on the care and support for transgender and gender diverse children and adolescents, which holds that the self-recognition of gender identity “develops over time” and yet “[f]or some people, gender identity can be fluid, shifting in different contexts.”²⁵ Meanwhile, Columbia University sociologist Tey Meadow reports in her article on the production of legal gender classifications: “Many courts look to medical definitions of sex.... yet there is no consensus about when gender change actually happens.”²⁶

²⁴ Diamond, L. M. (2020). Gender fluidity and nonbinary gender identities among children and adolescents. *Child development perspectives*, 14(2), 110-115. <https://doi.org/10.1111/cdep.12366>

²⁵ Rafferty, J. & Committee on Psychosocial Aspects of Child and Family Health.(2018). Ensuring comprehensive care and support for transgender and gender-diverse children and adolescents, 142 *Pediatrics* 4 e20182162; doi: <https://doi.org/10.1542/peds.2018-2162>.

²⁶ Meadow, T. (2010). “A rose is a rose”: On producing legal gender classifications, *Gender & society* 24(6), 814–837, p. 824. <https://doi.org/10.1177/0891243210385918>

III. STUDY CONCLUSIONS OF TRANSGENDER TREATMENT EFFECTS ARE DEMONSTRABLY INADEQUATE.

31. Despite ample scientific resources—adequate funding, the interest of professional organizations, and competent researchers—the science of gender identity (and transgender outcomes) is often characterized by modest evidence followed by overreaching conclusions. Any talk of “consensus” or of enduring “standards” are baseless assertions.

32. One notable development is the explosion in the number of academic journals focused on topics of sexuality and gender identity. There has been, on average, at least one new peer-reviewed journal in the domain of sexuality and gender launched every year for the past 30 years. The supply of journals is certainly in part a function of demand. But it is also invariably the case that where the competition for publication in peer-reviewed journals is tight (and therefore, there is a scarcity of supply), the pathway to publication is more challenging. Hence, the quality of what is published tends to be higher. The opposite happens when there is a large supply of journals: the barrier to publication is lower, and so typically is the quality.

33. It remains the fact that little is understood about the long-term physical effects of puberty blockers and cross-sex hormones, especially when they are administered during those years that are critical for biological and brain development.²⁷ This is in part a function of (1) how few minors experienced these treatments in the past—a small pool to study, and (2) the fact that the surge in such treatments remains less than a decade old. In other words, too few and too new.

²⁷ Wren, B. (2014). Thinking postmodern and practising in the enlightenment: Managing uncertainty in the treatment of children and adolescents. *Feminism & psychology*, 24(2), 271–291, p. 287. <https://doi.org/10.1177/0959353514526223>; Heneghan, C., & Jefferson, T. (2019, February 25). *BMJ EBM spotlight*. Gender-affirming hormone in children and adolescents. <https://blogs.bmj.com/bmjebmspotlight/2019/02/25/gender-affirming-hormone-in-children-and-adolescents-evidence-review/>

34. Adolescence is also a crucial period of social development. Artificially holding a child in a pre-pubescent state for several years while his or her peers navigate the social milestones and minefields of adolescence is likely to have at least some “subtle negative psychosocial and self-confidence effects.”²⁸ Indeed, the American Academy of Pediatrics recognizes that “[d]elaying puberty beyond one’s peers can also be stressful and can lead to lower self-esteem and increased risk taking.”²⁹ And the Endocrine Society’s guidelines recognize “the sense of social isolation from having the timing of puberty be so out of sync with peers.”³⁰

35. But what the research does not tell us is the isolated effect of puberty blockers (and similarly, that of subsequent cross-sex hormones), since dysphoria rarely manifests apart from other (possibly confounding) psychiatric conditions and the experience of traumas.³¹

36. Seven endocrinologists and psychologists recently discussed the clinical characteristics of 79 children presenting to a new gender clinic in Australia, noting a high number of conflicted family situations and documented trauma.³² Only five percent of their sample was believed to exhibit “healthy” levels of functioning.

37. Despite this, many of the new clinic’s patients and their families openly pressed the clinicians for “affirmative” treatment, believing that method was the only solution and “that their distress would be completely alleviated if they pursued the pathway of medical treatment.”

This frustrated the authors: “Lost were our efforts to highlight the many different pathways in

²⁸ Levine, S. (2020) Declaration, U.S. Circuit Court, Dane County, Wisconsin, Case No.: 20-CV- 454, p.41.

²⁹ Rafferty, J. & Committee on Psychosocial Aspects of Child and Family Health.(2018), p. 5.

³⁰ Hembree et al. (2017), p. 3885.

³¹ E.g. In Littman (2018), 62 percent of parents reported their child had been previously diagnosed with a psychiatric disorder, while 48 percent reported a traumatic or stressful event occurring prior to the onset of their child’s gender dysphoria, p. 13.

³² Kozłowska, K., McClure, G., Chudleigh, C., Maguire, A. M., Gessler, D., Scher, S., & Ambler, G. R. (2021). Australian children and adolescents with gender dysphoria: Clinical presentations and challenges experienced by a multidisciplinary team and gender service. *Human Systems*, 1(1), 70-95. <https://doi.org/10.1177/26344041211010777>

which gender variation could be expressed, to explain potential adverse effects of medical treatment, to explore issues pertaining to future fertility and child rearing, and to highlight the importance of ongoing psychotherapy.” The authors attributed this predictable pattern to information that patients received from (1) their peers, (2) previously encountered health workers, and (3) the Internet. Many children, they noted, arrived with “strongly entrenched beliefs and with no interest in further exploring their medical, psychological, social, or familial situation.” The study’s authors also asserted that many of the patients “did not have the cognitive, psychological, or emotional capacity to understand the decisions they were making.”³³

38. These forces complicate treatment of gender dysphoria. A market increasingly characterized by patient demand for puberty blockers and, later, cross-sex hormones does not make for an atmosphere conducive to addressing pertinent co-occurring diagnoses. But, as psychotherapist Robert Withers observes, “failure to address relevant psychological issues can result in trans people making unnecessary, permanent changes to their bodies, without adequate scientific justification for doing so.”³⁴ Withers additionally notes that “[m]any of today’s young people have also made ‘gender affirming’ medical treatment their goal. Unfortunately, the evidence base supporting the efficacy of such treatment is extremely poor.”³⁵

39. Large, longitudinal data collection efforts on the psychological health effects of transgender medicine remain rare but do exist. The Swedish Total Population Register, a massive longitudinal survey effort that collected information from over 9.7 million Swedes, is an example. A study based on this data appeared in 2020 in the *American Journal of Psychiatry*.³⁶ Its

³³ Kozłowska et al. (2021). All quotes are from p. 15.

³⁴ Withers, R. (2020) Transgender medicalization and the attempt to evade psychological distress. *Journal of analytical psychology*, 65: 865–889, p. 865. <https://doi.org/10.1111/1468-5922.12641>

³⁵ Withers (2020), p. 869.

³⁶ Bränström, R., & Pachankis, J. E. (2020). Reduction in mental health treatment utilization among transgender individuals after gender-affirming surgeries: a total population study. *American journal of psychiatry*, 177(8), 727–734. <https://doi.org/10.1176/appi.ajp.2019.19010080>

authors tracked dysphoric respondents over time and assessed their subsequent use of mental health treatment (for a mood or anxiety disorder), as well as other related measures (such as hospitalization after a suicide attempt). There was no evidence that initiating hormone treatment paid benefits in reduced subsequent use of mental health treatment, but the authors concluded that “gender-affirming” surgery is associated with reduced demand for subsequent mental health treatment in a sample of persons diagnosed with “gender incongruence.”

40. However, a cursory reading of the study itself tells a far less optimistic story than the authors’ own confident interpretations of the post-surgical data. From the available published data, I was able to calculate the “Number Needed to Treat,” or NNT, which is a measure of clinical impact. It helps relate the actual size of the effect of the treatment back to the realities of clinical practice to aid physicians in decisions about whether a particular treatment is “worth it.”³⁷ A high NNT accompanied by significant risk (in the treatment) is considered high-risk, low payoff. On the other hand, a high NNT accompanied by modest risk (such as prescribing a daily statin pill to reduce risk of a subsequent heart attack) is considered low risk, low payoff. In this study, the NNT appears to be a staggering 49, meaning the beneficial effect of transgender surgery (or more commonly, a series of surgeries) is so small that a clinic may have to perform 49 gender-affirming surgeries before they could expect to witness one additional post-surgical patient’s reduction in subsequent mental health assistance. If no other treatment was available, or if the treatment was non-invasive and the hazards were insignificant, clinics might consider surgery a low-risk but low-payoff approach. But even the most common surgeries here (e.g., bi-

³⁷ Citrome, L. (2014). Quantifying clinical relevance. *Innovations in clinical neuroscience*, 11(5-6), 26–30.

lateral mastectomy) are considered major surgeries—and particular ones are exceptionally challenging, with elevated likelihood of suffering a complication.³⁸ Conducting surgery on 49 patients in order to secure one patient who modestly benefits in slightly less psychological services? It ought to give physicians pause, but in a demand-oriented industry, it does not.

41. The journal received numerous letters pointing out that the study’s analysis was flawed and its conclusions unsupported by the data. Almost one year later, the *American Journal of Psychiatry* published seven letters of critique, an editorial note on the subsequent statistical review those critiques prompted, and the resulting correction that nullified the study’s claim of a post-surgical mental health benefit. The correction curbed what conclusions the authors had originally made—that “this study provides timely support for policies that ensure coverage of gender-affirming treatments.”³⁹ This example is indicative of a wider trend of “looking” for statistical significance, however weak, to support claims that are consonant with the political wishes of transgender medical practitioners.

42. In just the past two years, three countries’ national gender medicine councils have commissioned focused studies on the efficacy of the “affirmative” approach to treating minors. These in-depth reviews by Finland, Sweden, and the UK’s National Institute for Health and Care

³⁸ A recent study revealed that while just over 10 percent of a group of 1,212 adult “transmasculine” patients elected to undergo genital reconstruction surgery, those 129 patients reported 281 complications—more than two per patient, on average—requiring 142 “revisions.” The three most common complications? Urethral fistulas or strictures, and worsened mental health. The only documentable benefit? A surge in their “genital self-image.” See Robinson, I. S., Blasdel, G., Cohen, O., Zhao, L. C., & Bluebond-Langner, R. (2021). Surgical outcomes following gender affirming penile reconstruction: Patient-reported outcomes from a multi-center, international survey of 129 transmasculine patients. *The journal of sexual medicine*, 18(4), 800-811. <https://doi.org/10.1016/j.jsxm.2021.01.183>

³⁹ Bränström, R. & Pachankis, J. E. (2020) Correction to Bränström and Pachankis. *American journal of psychiatry* 177(8): 734. <https://doi.org/10.1176/appi.ajp.2020.1778correction>

Excellence (NICE) in Britain have all concluded that claims of benefit for medical gender interventions in children are based on “low quality evidence.”⁴⁰

43. Sweden’s review of the evidence base and ethics considerations found “knowledge gaps and uncertain knowledge” to be a “central theme.”⁴¹ A summary of their review of the literature reported the following: “No studies explaining the increase of children and adolescents seeking [treatment] for gender dysphoria were identified. The literature on management and long-term effects in children and adolescents is sparse, particularly regarding gender affirming surgery. All identified studies are observational, and few are controlled or followed-up over time.”⁴² They conclude by observing that “scientific activity in the field seems high,” meaning extensive, but that a “large part of the literature that was considered relevant” was only published after 2017.

44. The UK’s Royal College of General Practitioners issued a report in mid-2019 asserting that “[t]he significant lack of evidence for treatments and interventions which may be offered to people with dysphoria is a major issue facing this area of healthcare.”⁴³ After the report highlights characteristics of the “affirmative” approach, it notes “a significant lack of robust, comprehensive evidence around the outcomes, side effects and unintended consequences of such

⁴⁰ Society for Evidence Based Gender Medicine. (2021, May 5). 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

⁴¹ Swedish National Council on Medical Ethics. (2019, April 26). Letter to the Ministry of Health and Social Affairs re: treatment of gender dysphoria among children and adolescents (unofficial translation), p.2. <https://smer.se/wp-content/uploads/2019/04/Skrivelse-konsdysfori-eng-%C3%B6vers%C3%A4ttning.pdf>

⁴² Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU). (2019). Gender dysphoria in children and adolescents: An overview of the literature. *SBU*. Report No. 307: SBU 2019/427. <https://www.sbu.se/en/publications/sbu-bereder/gender-dysphoria-in-children-and-adolescents-an-inventory-of-the-literature/report-307>

⁴³ Royal College of General Practitioners. (2019). The role of the GP in caring for gender-questioning and transgender patients, RCGP position statement. <https://www.rcgp.org.uk/-/media/Files/Policy/A-Z-policy/2019/RCGP-position-statement-providing-care-for-gender-transgender-patients-june-2019.ashx?la=en>

treatments for people with gender dysphoria, particularly children and young people, which prevents (general practitioners) from helping patients and their families in making an informed decision.”

45. The UK NICE pair of reports each concluded that invasive treatment of youth doesn’t result in a confident determination of demonstrable success. Those studies, one report notes, “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.” The studies “all lack appropriate controls.” Moreover, the claims of “clinical effectiveness, safety, and cost-effectiveness” of such treatments clearly are not substantiated.⁴⁴

46. These assessments offer reasons to be far more cautious about treating underage persons in such a way that permanently alters bodies as a response to problems of the mind.

47. Data from the UK’s Tavistock clinic study were requested by the High Court during the hearing for *Bell v. Tavistock*, a case involving plaintiff Keira Bell, a young British woman who took puberty blockers at age 16, proceeded to cross-sex hormones, and had “top surgery” at age 20—all of which she now regrets. The Tavistock Clinic, however, did not provide the data, which was published only the day after the High Court ruled against the clinic.⁴⁵ Repeatedly the court judgment stated it was “surprising” that the Tavistock had not kept better data

⁴⁴ National Institute for Health and Care Excellence (NICE). (2021). Evidence review: Gonadotrophin releasing hormone analogues for children and adolescents with gender dysphoria, p.13. <https://www.evidence.nhs.uk/document?id=2334888&returnUrl=search%3fq%3dtransgender%26s%3dDate>; National Institute for Health and Care Excellence (NICE). (2021). Evidence review: Gender-affirming hormones for children and adolescents with gender dysphoria. <https://www.evidence.nhs.uk/document?id=2334889&returnUrl=search%3Fq%3Dgender%2Bdysphoria>

⁴⁵ Barnes, H. & Cohen, D. (2020, December 11). Tavistock puberty blocker study published after nine years. *BBC News*, <https://www.bbc.com/news/uk-55282113>

and could not produce it in a timely manner when asked: “...though this research study was commenced some 9 years ago, at the time of the hearing before us the results of this research had yet to be published.”⁴⁶

48. The Tavistock study results found no demonstrable psychological benefit, nor was there any evidence of reduced body dissatisfaction for those receiving the blockers. (This varies from Dutch study findings reporting improvement in the same.⁴⁷) Thus, if the purpose of the treatment was to improve mental feelings of wellness or reduce negative body image, the clinic’s own study shows that puberty blockers failed in this regard. Not only was there no benefit, thoughts of self-harm actually increased for some natal female participants after a year on the blockers.⁴⁸

49. In sum, the science of transgender medicine—including but not limited to adolescents—does not speak with a univocal voice about the long-term psychological and physical benefits of hormonal and surgical treatment of dysphoria. Much published research in this domain is very recent, relies on nonrepresentative, opt-in samples, “loaded” survey questions, and/or exhibits overreaching conclusions. To discern any obvious “consensus” or “standards” from existing research would make little scientific sense.

⁴⁶ Bell & A v. Tavistock and Portman NHS Foundation Trust. (2020). U.K. High Ct. 2020 EWHC3274 (Admin). CO/60/2020, para. 24. <https://www.judiciary.uk/wp-content/uploads/2020/12/Bell-v-Tavistock-Judgment.pdf>

⁴⁷ de Vries, A. L., McGuire, J. K., Steensma, T. D., Wagenaar, E. C., Doreleijers, T. A., & Cohen-Kettenis, P. T. (2014). Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics*, 134(4), 696-704. doi: <https://doi.org/10.1542/peds.2013-2958>

⁴⁸ Carmichael, P., Butler, G., Masic, U., Cole, T. J., De Stavola, B. L., Davidson, S., Skageberg, E. M., Khadr, S., & Viner, R. M. (2021). 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. *Plos one*, 16(2), e0243894. <https://doi.org/10.1371/journal.pone.0243894>; Biggs, M. (2019). Britain’s puberty blocking experiment. In: H. Brunsell-Evans & M. Moore, (Eds.), *Inventing transgender children and young people*, (pp. 40-55). Cambridge Scholars Publishing.

IV. THE ABSENCE OF RANDOMIZED CLINICAL TRIALS RESEARCH

50. I have reviewed the declaration of Armand H. Matheny Antommara, dated June 11, 2021. Dr. Antommara claims that in Arkansas, “adolescents with gender dysphoria are not being subject to...experimentation.”⁴⁹ The FDA, however, has not approved hormonal therapies for treatment of gender dysphoria. Hence, it is undeniable that the protocol of treatments for transgender-identifying youth, including its hormonal regimens, remains at least technically experimental by definition.

51. It’s not as if hormonal treatments have never been put to a clinical trial. The hormones estradiol and testosterone certainly have. The same is true of GnRH agonists (i.e., puberty blockers), which have been evaluated for adult infertility, prostate cancer, ovarian protection during chemotherapy, and even for tests of male contraceptives.⁵⁰ But these drugs have not been tested in randomized clinical trials as treatments for adolescent gender transition procedures. Puberty blockers have been approved only for treatment of precocious puberty.

52. Dr. Antommara is right when he states that, “With respect to study design, randomized trials generally provide “high” quality evidence and observational studies, in comparison, “low.”⁵¹ But the entire gender medicine industry merits criticism for complicity in failing to conduct such a rigorous clinical trial. Invasive, and even life-threatening, clinical trials are regularly conducted in the quest for lifesaving treatments among children with serious diseases or conditions.

⁴⁹ Antommara, A. H. M. (2021). Declaration, U.S. District Court, Eastern District of Arkansas, Case No.: 4:21CV450-JM, p. 11.

⁵⁰ Garner, C. (1994). Uses of GnRH agonists. *Journal of obstetric, gynecologic, & neonatal nursing*, 23(7), 563-570. <https://doi.org/10.1111/j.1552-6909.1994.tb01922.x>

⁵¹ Antommara (2021), p. 7.

53. Dr. Antommara maintains that to propose and carry out “randomized placebo-controlled trials (trials that compare pharmacological treatment to no pharmacological treatment) in gender dysphoria are currently unethical.” He appeals to the principle of clinical “ equipoise,” namely, the assumption (underlying the ethics of randomized control groups) that there is no clear “better” intervention present.⁵² That is, he maintains that there is no clinical equipoise in the case of treating gender dysphoria; a control group in such a randomized trial would, he believes, receive an inferior, less-effective treatment as compared with the “affirmative” approach.

54. But this claim is in no small part a function of the putative “consensus” mentioned above and discussed more fully below. That is, since “affirmative” treatments are often the subject of patient demand, and are now endorsed by certain American professional organizations, there is indeed an assumption that clinical equipoise is not present. It is a situation, however, that is based not on longitudinal medical and social science research but on media-fostered patient demand and premature professional organizational claims and pressure. In other words, any lack of equipoise is more a psychological or cultural than a scientific development.

55. Further, even if (as Dr. Antommara claims) equipoise were lacking for randomized *placebo-controlled* trials (i.e., trials that compared groups that did and did not receive hormones), that would be no obstacle to randomized trials *without* placebo groups to “compare different types, dosages and methods of administration of active treatments.”⁵³ But no such trials have been conducted.

⁵² Antommara (2021), p. 8; Cook, C., & Sheets, C. (2011). Clinical equipoise and personal equipoise: two necessary ingredients for reducing bias in manual therapy trials. *Journal of Manual & Manipulative Therapy*, 19(1), 55-57. doi: 10.1179/106698111X12899036752014

⁵³Haupt, C., Henke, M., Kutschmar, A., Hauser, B., Baldinger, S., Saenz, S. R., & Schreiber, G. (2020). Antiandrogen or estradiol treatment or both during hormone therapy in transitioning transgender women. *Cochrane database of systematic reviews*, p. 10. <https://doi.org/10.1002/14651858.CD013138.pub2>

V. THE IDEOLOGICAL CAPTURE OF GENDER DYSPHORIA

56. There is a great deal of evidence that discussion of gender dysphoria has recently become unmoored from empirical assessments and instead has been captured by the activist assumptions of those advocating for what is sometimes called “gender ideology.” Ideological capture operates not unlike “regulatory capture,” a more familiar phrase. The end is the same—the corruption of authority by the successful co-opting of political or professional organizations to serve the interests of a particular interest group. Ideological capture is characterized by incorrigible commitments to certain conclusions regardless of the data and can lead whole organizations to disregard outcomes that are not consistent with the ideologically-motivated sense of rightness.⁵⁴ Ideological capture is inimical to the dissent and open debate that is critical to healthy medical and social science. As I explain below, the ideological capture of gender dysphoria is evidenced by efforts to re-educate people in the use of identity language, by the rapid formation of a putative consensus in American professional societies, by the entrepreneurial explosion of gender clinics across the nation, by pressure-based suppression of open debate, by inconsistent claims concerning adolescents’ ability to give informed consent, and even by the Department of Justice’s recent inconsistent actions.

A. Re-education in the Parlance of Gender Ideology

57. To classify something in the social world is to penetrate the imagination, to alter public frameworks of knowledge and discussion, and to shift the perception of everyday life. It is why French sociologist Pierre Bourdieu understood this elite-driven effort as the power of “legitimate naming.”⁵⁵ In the domains of gender and sexuality—fraught as they are with great

⁵⁴ Chuang, J. A. (2010). Rescuing trafficking from ideological capture: Prostitution reform and anti-trafficking law and policy. *University of Pennsylvania law review*, 158(6), 1655–1728.

⁵⁵ Bourdieu, P. (1985). The social space and the genesis of groups. *Theory and society*, 14(6), 723-744.

moral valence—there is poignant and bitter struggle over words and terms, and the politics of using them or avoiding them. This suggests we are not witnessing a simple quest for better understanding of an emergent population. We are also seeing social and cultural change fostered through scholarship wed to political activism.

58. The complaint and reports submitted by the plaintiffs in this case reflect this ideological effort. For example, Adkins’ claim that “[e]veryone has a gender identity”⁵⁶ is freighted with dubious ideological assumptions, as the following considerations show. The Endocrine Society guidelines describe “[e]xamples of conditions with similar features” to gender dysphoria, including “body identity integrity disorder (a condition in which individuals have a sense that their anatomical configuration as an able-bodied person is somehow wrong or inappropriate).”⁵⁷ Dr. Anne Lawrence, who identifies as transgender, has also noted the parallels between gender dysphoria and body integrity identity disorder (BIID).⁵⁸ A person with BIID is able-bodied but identifies as an amputee and reports feeling trapped in a fully functional body. Such persons “often assert [that] their motives for wanting to change their bodies reflect issues of identity.”⁵⁹

59. Now, it is one thing to recognize that some people with BIID make such identity claims. But it is something else altogether to say that, because *some people with BIID* make that claim, therefore *everyone* has to be defined in terms of whether they identify as able-bodied, as an amputee, or as something in between. To make this further claim is to advocate a highly disputable ideology that says an able-bodied person’s identifying as an amputee is not a disorder at all, but simply one of multiple “functional identities” that an able-bodied person may happen to

⁵⁶ Adkins (2021), p. 3.

⁵⁷ Hembree et al. (2017), p. 3878.

⁵⁸ Lawrence, A. A. (2006). Clinical and theoretical parallels between desire for limb amputation and gender identity disorder. *Archives of sexual behavior*, 35, 263-78.

⁵⁹ Lawrence (2006), p. 263.

have. But it is another thing (and altogether inappropriate) to use the terms in which persons experiencing mental distress or a pathology understand themselves as the new prism through which all persons must be defined. Claiming that “everyone has a gender identity” is an effort to do precisely that: to define everyone who does *not* suffer gender incongruence in terms of the self-experience of those who do.

60. One of the reasons why advocates include (in their articles, briefs, reports, etc.) sections defining terms is because new words are a source of social change itself. They are not simply illuminating but indoctrinating. Certainly, the challenges of measurement and data collection can benefit from clarification of terms. But they can become vehicles of cultural change themselves by endorsing particular ways of speaking about matters of gender identity that are highly contested. Even official surveys, the root source of so much social science raw data, are not only not exempt from politicization and the fostering of “legitimate naming,” but are now a medium of the same.⁶⁰

61. Plaintiffs’ complaint is also saturated with references to “well-established standards of care,” “best practices,” and lists a litany of terms and statements like these in a section entitled “Standards of Care...” where one might expect to see prescriptions rather than definitions. Such rhetoric fosters a sense that the author(s) are attempting to re-educate the reader rather than convince them of the merits of a position through sound argument and evidence. What was meant to map and understand the experience of gender dysphoria—particularly but not only in adolescents—has turned instead to name (new terms and protocols) and shame (the cautious or contrarian voice).

⁶⁰ The GenIUSS Group. (2014). Best practices for asking questions to identify transgender and other gender minority respondents on population-based surveys. J.L. Herman (Ed.). The Williams Institute.

62. I concur with psychiatrist Dr. Stephen Levine, who has explained that “clinical work in the gender identity arena, which used to be based on symptoms and social, vocational, and educational dysfunction, is now based on sociopolitical concepts. Cultural forces have provided a new narrative about the vital importance of having strict consonance between one’s sexed body and gender identity.”⁶¹ This new narrative is not grounded in evidence-based science but in political activism.

B. The Rapid Formation of a Putative Consensus

63. In her report, Dr. Adkins writes, “All of the major medical professional groups in the United States . . . agree that [gender transitioning] is safe, effective, and medically necessary treatment for the health and wellbeing of children and adolescents suffering from gender dysphoria.”⁶² But, despite the fact that American professional associations have endorsed the “affirmative” approach to treating dysphoric adolescents, there is no wide, international consensus about its superiority. That a consensus on hormonal and surgical interventions at earlier ages should have coalesced so rapidly among American professional associations—and with so much projected confidence—in the absence of obvious, consistent indicators of treatment efficacy, and amid a surge in cases of gender dysphoria, is curious and concerning. It suggests, rather, a concerted effort to suppress alternative treatment approaches in favor of a demand-driven endorsement of hormonal and surgical treatments.

64. Closely connected to the idea of ideological capture is that of a “Castro consensus,” wherein a consensus “is viewed as a proxy for truth.”⁶³ Certainly, “when a consensus is

⁶¹ Levine, S. B. (2019). Informed consent for transgendered patients. *Journal of sex & marital therapy*, 45(3), 218-229, p. 219.

⁶² Adkins, D. (2021), p. 6.

⁶³ Allen, J., Lay, C., & Montanez, G. (2020) A Castro consensus: Understanding the role of dependence in consensus formation, 1-9, p. 1. https://www.researchgate.net/publication/344703449_A_Castro_Consensus_Understanding_the_Role_of_Dependence_in_Consensus_Formation

fashioned via the independent and free deliberations of many, it is a strong indicator of truth.”

But “not all consensuses are independent and freely formed.” Some are pieced together by “external pressure,” while “dependence among individuals can force consensus around an issue, regardless of the underlying truth of the affirmed position.” Indeed, simple bias can lead to a purported (and premature) consensus, given that decision-makers (and researchers) “are both human and political.”⁶⁴ This is an accurate description of what has occurred in the domain of medicine concerned with the treatment of gender dysphoria.

65. For instance, WPATH, formed in 1979, has evolved from its beginnings as a group of professionals seeking to understand and assist those with gender dysphoria to acting as a professional association that purports to offer “consensus” clinical guidelines while simultaneously acknowledging that “WPATH is committed to advocacy for . . . changes in public policies and legal reforms.”⁶⁵ WPATH’s treatment recommendations shape the recommendations of other professional organizations; the APA’s guidelines, for example, complement WPATH’s recommendations and label any approach other than “affirming” to gender dysphoric youth as unethical.⁶⁶

66. In the short span of a decade, psychiatrists, psychologists, pediatricians, and their patients have been pressed both to think about and to treat child and adolescent dysphoria in one

⁶⁴ Socol, Y., Shaki, Y. Y., & Yanovski, M. (2019). Interest, bias, and consensus in science and regulation, *Dose-response*, 17, 1-5. <https://doi.org/10.1177/1559325819853669>

⁶⁵ World Professional Association for Transgender Health (2012), p. 2; Levine, S. B. (2018). Ethical concerns about emerging treatment paradigms for gender dysphoria. *Journal of sex & marital therapy*, 44(1), 29-44; Vrouenraets et al. (2015).

⁶⁶ American Psychological Association. (2015). Guidelines for psychological practice with transgender and gender nonconforming people. *American psychologist*, 70(9), 832-864.

“correct” manner—via the “affirmative” approach. In turn, psychotherapeutic alternatives are now more difficult to come by, even disparaged as “conversion” therapies, as discussed below.⁶⁷

C. The Entrepreneurial Explosion of Gender Clinics

67. When this contrived consensus meets a free market health care delivery system, it is no surprise that the result is an explosion in gender clinics. Less than 15 years ago, the United States featured a solitary pediatric gender clinic (Boston Children’s Hospital’s Gender Management Service, founded in 2007). But today there are over 300 clinics that provide some form of “gender affirmative” care to minors, ranging from full service operations (i.e., hormone and surgical services) to private practice doctors that will perform surgeries on minors.

68. Planned Parenthood clinics, as noted in the organization’s recent annual report, are “the second largest provider of hormone therapy to those who identify as transgender/have gender dysphoria.”⁶⁸ Planned Parenthood’s director of health media was recently reported as confirming that the organization offers hormone therapy to transgender patients in 16 states. Mara Keisling, executive director of the National Center for Transgender Equality, remarked about Planned Parenthood that “It’s possible they’re the largest provider of trans health in the country.”⁶⁹

⁶⁷ For example, see Turban, J. L., Beckwith, N., Reisner, S. L., & Keuroghlian, A. S. (2020). Association between recalled exposure to gender identity conversion efforts and psychological distress and suicide attempts among transgender adults. *JAMA psychiatry*, 77(1), 68–76. doi:10.1001/jamapsychiatry.2019.2285.

⁶⁸ Planned Parenthood Federation of America. (2021). 2019-2020 annual report, p. 11. https://www.plannedparenthood.org/uploads/filer_public/67/30/67305ea1-8da2-4cee-9191-19228c1d6f70/210219-annual-report-2019-2020-web-final.pdf

⁶⁹ Allen, S. (2017, January 10). The attack on Planned Parenthood hurts transgender people, too. *Daily beast*. <https://www.thedailybeast.com/the-attack-on-planned-parenthood-hurts-transgender-people-too>

69. Planned Parenthood operates its gender services on an “informed consent” basis, with no need for a diagnosis or mental health exam.⁷⁰ In other words, access to treatment is offered if the patients indicate they understand and accept the possible side effects. “I had no gate-keeping at all,” one patient reported. “I had a prescription in my hand the same day I went in.” The “affirmative” approach leads to patient-driven, on-demand services, with potentially disastrous consequences.⁷¹

70. It is clear that clinics make their own decisions about treatment, and will prove even more aggressive than professional organizations’ own recommendations. For example, New York’s Mount Sinai Center for Transgender Medicine and Surgery (CTMS) operates with a “patient-centered model,” and reported that 45 percent of 139 patients seeking vaginoplasty were deemed ready for surgery, well above the 15 percent who met WPATH’s criteria for surgery eligibility.⁷²

71. In a mid-2020 contribution to the *Journal of Medical Ethics*, an Australian attorney and six co-authors make the ethical case for supporting the practice of “ongoing puberty suppression,” that is, to “permanently prevent the development of secondary sex characteristics, as a way of affirming (one’s) gender identity.”⁷³ In other words, there should be no assumptions about what comes next in the affirmative treatment regime. There is reason to question the clinical stability of an approach that is so rapidly giving young people suffering significant psychiat-

⁷⁰ Urquhart, E. (2016, January 29). Planned Parenthood is helping transgender patients access hormone therapy. *Slate*. <https://slate.com/human-interest/2016/01/how-planned-parenthood-helps-transgender-patients-get-hormone-therapy.html>

⁷¹ Allen (2017).

⁷² Lichtenstein, M., Stein, L., Connolly, E., Goldstein, Z. G., Martinson, T., Tiersten, L., Shin, S. J., Pang, J. H., & Safer, J. D. (2020). The Mount Sinai patient-centered preoperative criteria meant to optimize outcomes are less of a barrier to care than WPATH SOC 7 criteria before transgender-specific surgery. *Transgender Health*, 5(3), 166-172.

⁷³ Notini, L., Earp, B. D., Gillam, L., McDougall, R. J., Savulescu, J., Telfer, M., & Pang, K. C. (2020). Forever young? The ethics of ongoing puberty suppression for non-binary adults. *Journal of medical ethics*, 46(11), 743-752. <https://jme.bmj.com/content/46/11/743.abstract>

ric distress the agency to accept experimental medical interventions with irreversible effects, especially in an ideologically-charged atmosphere where medical professionals hold the treatments out to be the child's only hope of leading a peaceful, happy life.

72. Reports like these highlight how—in a few short years—advocates have injected American sexual politics into the medical evaluation and treatment of gender dysphoria. In a study to be published in the *Archives of Sexual Behavior*, a co-author and I observed in a survey of over 5,000 adults that the central framework through which Americans perceive the treatment of adolescent transgender patients is that of bodily autonomy and choice. That is, American adults' attitudes about abortion are the strongest predictor of what they think about “affirmative” treatment for minors, even after controlling for religion, political affiliation, voting behavior, and a variety of other factors.⁷⁴ This makes sense. And we are hardly the first to note it. Years ago journalists observed that the same principles at work in understanding abortion attitudes—about access to and control over one's body—are applied to decision-making about transgender treatments, even invasive ones. By extension, then, it is unsurprising to see how the authority over treatment decisions, including among minors, appear to have shifted from physician to patient.⁷⁵

D. Pressure-based Suppression of Open Debate

73. Physicians and researchers have been sanctioned for questioning “affirmative” gender treatment. Some have resigned, some have been demoted, and others fired. A few examples may prove illuminating. Allan Josephson, chief of the University of Louisville's Division

⁷⁴ Regnerus, M. & Vermurlen, B. (Conditional accept, 2021). Approval of hormonal and/or surgical interventions for adolescents experiencing gender dysphoria. *Archives of sexual behavior*.

⁷⁵ Urquhart, E. (2016, March 11). Gatekeepers vs. informed consent: Who decides when a trans person can medically transition? *Slate*. <https://slate.com/human-interest/2016/03/transgender-patients-and-informed-consent-who-decides-when-transition-treatment-is-appropriate.html>

of Child and Adolescent Psychiatry and Psychology for nearly 15 years, was demoted after public remarks he offered criticized aspects of affirmative treatment, saying the “notion that gender identity should trump chromosomes, hormones, internal reproductive organs, external genitalia, and secondary sex characteristics when classifying individuals is counter to medical science.”⁷⁶

74. The *Archives of Sexual Behavior*’s editor Kenneth Zucker likewise endured professional and personal scrutiny for his work on the transgender experience. Zucker was head of a Toronto addiction and mental health clinic’s “Gender Identity Service” until he was fired in 2015 after an external review by two adolescent psychiatrists found his method insufficiently “affirmative” for transgender-identifying youth. His crime? Too much caution, patience in treatment, and displaying concern for parents and family dynamics. (Zucker won a legal settlement and an apology,⁷⁷ and he remains the editor-in-chief of *Archives*, the top sexology journal in the field.) Intimidation of this nature discourages wider interest in this field, narrowing the pool of researchers to those who don’t rock the boat or question the purported consensus. This is not how a healthy field of science works.

75. Angela Sämfiord, a child and adolescent psychiatrist at Sahlgrenska University Hospital in Gothenburg, Sweden, launched the Lundstrom Gender Clinic in 2016. Two years later, she resigned because of her own fears about the lack of evidence for hormonal and surgical treatments. Her decision-making process reveals what others have also noted: “There’s a lot of tension between some approaches of gender clinics and the trans community. Patients found it hard to accept that they needed to undergo a full mental health assessment before being referred

⁷⁶ Watkins, M. (2019, March 29). Professor sues U of L, claims he was demoted over comments seen as anti-LGBTQ. *Courier journal*. <https://www.courier-journal.com/story/news/2019/03/29/anti-lgbt-comments-university-of-louisville-professor-sues-over-demotion/3300002002/>

⁷⁷ Rizza, A. (2018, October 7). CAMH to pay more than half a million settlement to head of gender identity clinic after releasing fallacious report. *National post*. <https://nationalpost.com/news/camh-reaches-settlement-with-former-head-of-gender-identity-clinic>

for medical treatment. Parents would say that nobody ever discussed that other issues...might be implicated in the child's dysphoria."⁷⁸ Her patients displayed "many psychiatric symptoms," she notes. Gender dysphoria was just "one part of a complex problem." "Concentrating only on the gender dysphoria meant we might miss other things," she held. "When I realized the complexity [of these cases]...and that health care professionals are still expected to okay gender-affirming treatment despite the lack of evidence that we currently have, it preyed on my conscience." Sämford's story contributed to Sweden's recent decision to curb hormonal treatments for adolescents.

76. The controversy over a CBS *60 Minutes* segment about detransitioners, which aired on May 23, 2021, provides another sobering illustration of the ideological capture of much of this field of treatment. It is healthy to have an open public discussion regarding patients who have undergone a gender transition but who wish to detransition back to their natal sex. Yet not only did activists seek to alter the *60 Minutes* episode (or prevent it from airing altogether)—researchers did too, including Dr. Johanna Olson-Kennedy, who posted on social media that "so many of us worked hard to dissuade them from doing this segment." Lesley Stahl, the segment's correspondent and lead interviewer, reported that she could not remember another story "where comments and criticisms began surfacing from advocates before the piece aired."⁷⁹ Other major media outlets are feeling comparable pressure to vet transgender news stories prior to release.⁸⁰

⁷⁸ McCall, B. & Nainggolan, L. (2021, April 23). Transition therapy for transgender teens drives divide. *WebMD*. <https://www.webmd.com/children/news/20210427/transition-therapy-for-transgender-teens-drives-divide>

⁷⁹ Zubrow, K. (2021, May 23). Inside the 60 Minutes report on transgender healthcare issues. *CBS News*. <https://www.cbsnews.com/news/60-minutes-transgender-health-care-issues-2021-05-23/>

⁸⁰ Manning, S. (2021, June 26). BBC Pride activists demand right to vet transgender news stories on Radio 4's Today programme after host Justin Webb clashed with Pink News CEO over Stonewall's stance on single-sex spaces. *Daily Mail*. <https://www.dailymail.co.uk/news/article-9728735/BBC-Pride-activists-demand-right-vet-transgender-news-stories-Radio-4s-Today-programme.html>

77. The evidence demonstrates that desistance rates—that is, the share of adolescents who ceased identifying as transgender and accepted their natal sex—are around 90 percent for patients being treated with a “watchful waiting” approach.⁸¹ But for dysphoric adolescents put on the “gender affirmation” schedule, the reverse has become true. Rather than pressing a pause button for time to think, 98 percent of the adolescents put on puberty blockers at the UK’s Tavistock clinic proceeded to cross-sex hormones,⁸² thereby triggering irreversible effects.⁸³ In other words, the “watchful waiting” method consistently predicts desistance. Taking the “affirmative” approach almost guarantees transition.

78. But transgender activists and their allies in the professions have sought to minimize the experiences of people who regret their transition and silence the voices of those who have detransitioned because of the challenges these present to the transgender identity narrative. Serious studies into this increasing phenomenon have been successfully squelched due to pressure from activists,⁸⁴ but the fact is that transition regret is real.⁸⁵ Recently, a wave of rapid adolescent transitions numbering in the tens of thousands has been accompanied by a surge of young people who have come to see that their transition was not the answer to their problems after all. There are so many detransitioners that suppression of their stories is becoming impossible. One

⁸¹ Singh, Bradley, and Zucker (2021) recently released a longitudinal study where the desistance rate was 88%. See: Singh, D., Bradley, S. J., & Zucker, K. J. (2021). A follow-up study of boys with gender identity disorder. *Frontiers in psychiatry*, 12, 1-18. <https://doi.org/10.3389/fpsyt.2021.632784>

⁸² Carmichael et al. (2021)

⁸³ de Vries, A. L., Steensma, T. D., Doreleijers, T. A., & Cohen-Kettenis, P. T. (2011). Puberty suppression in adolescents with gender identity disorder: A prospective follow-up study. *The journal of sexual medicine*, 8(8), 2276-2283. <https://doi.org/10.1111/j.1743-6109.2010.01943.x>

⁸⁴ Hardy, R. (2017, October 13). How a psychotherapist who has backed transgender rights for years was plunged into a Kafkaesque nightmare after asking if young people changing sex might later regret it. *Daily mail*. <https://www.dailymail.co.uk/news/article-4979498/James-Caspian-attacked-transgender-children-comments.html>

⁸⁵ Djordjevic, M. L., Bizic, M. R., Duisin, D., Bouman, M. B., & Buncamper, M. (2016). Reversal surgery in regretful male-to-female transsexuals after sex reassignment surgery. *The journal of sexual medicine*, 13(6), 1000-1007. <https://doi.org/10.1016/j.jsxm.2016.02.173>; Entwistle, K. (2021). Debate: Reality check—Detransitioners' testimonies require us to rethink gender dysphoria. *Child and adolescent mental health*, 26(1), 15-16. [doi/epdf/10.1111/camh.12380](https://doi.org/10.1111/camh.12380)

recent study surveyed 237 detransitioners, both male and female, and noted that over half of the respondents had three mental health co-morbidities.⁸⁶ The majority of the sample, a full 70 percent, said a reason for detransitioning was due to realizing their “gender dysphoria was related to other issues.”

79. Additionally, 62 percent marked health concerns as a reason for detransitioning, 50 percent said they did not find transition beneficial for their dysphoria, and 45 percent found other ways of dealing with their dysphoria. None of these reasons comport with the trans-affirmative narrative claiming that detransition is primarily due to social pressure or discrimination.⁸⁷ “Lack of support from social surroundings (13%), financial concerns (12%) and discrimination (10%)” were the least compelling reasons for detransitioning.⁸⁸

80. Further, not even all who experience regret or difficulties attributable to their transition will actually seek to physically detransition. There are many reports of individuals having regret but seeking to make the best of the irreversible changes and situation they find themselves in.⁸⁹ Consider the pioneer patient of the Dutch protocol, “B,” who was followed for 22 years until the age of 35. It was reported that “he indicated no regrets about his treatment.”⁹⁰ However, B “scored high on the measure for depression. Owing to ‘shame about his genital appearance and his feelings of inadequacy in sexual matters,’ he could not sustain a romantic relationship.”⁹¹

⁸⁶ Vandenbussche, E. (2021). Detransition-related needs and support: A cross-sectional online survey. *Journal of homosexuality*, 1-19. <https://doi.org/10.1080/00918369.2021.1919479>

⁸⁷ Turban, J. L., Loo, S. S., Almazan, A. N., & Keuroghlian, A. S. (2021). Factors leading to “detransition” among transgender and gender diverse people in the United States: A mixed-methods analysis. *LGBT health*, 8(4), 273-280. <https://doi.org/10.1089/lgbt.2020.0437>

⁸⁸ Vandenbussche (2021), p. 5.

⁸⁹ E.g.: Jax, R. (2017). *Don't get on the plane: Why a sex change will ruin your life*. CreateSpace Independent Publishing Platform.; Heyer, W. (2018). *Trans life survivors*. Bowker Identifier Services.; Teller Report. (2020, May 12). Aleksa Lundberg: “I am a gay feminine man with a female body.” <https://www.tellerreport.com/news/2020-05-12-aleksa-lundberg--%22i-am-a-gay-feminine-man-with-a-female-body%22.SyWGzCjDcU.html>

⁹⁰ Cohen-Kettenis, P. T., Schagen, S. E. E., Steensma, T. D., de Vries, A. L.C., & Delemarre-van de Waal, H. A. (2011) Puberty suppression in a gender-dysphoric adolescent: A 22-year follow-up. *Archives of sexual behavior*, 40(4), 843–847, p.843.

⁹¹ Biggs (2019) p. 49; Cohen-Kettenis et al. (2011), p. 845.

One cannot help but wonder whether B could have enjoyed greater lifetime wellbeing if he had not been placed on the medicalized transgender trajectory at the tender age of 13.

81. The scholar/activist authors of a 2020 *JAMA Psychiatry* study paint an entire class of cautious therapeutic approaches as intrinsically harmful, using survey language asking transgender patients if a therapist had ever attempted to “try to stop you being trans.”⁹² This sends a clear message to psychiatrists and psychotherapists alike about their role in the doctor-patient relationship here—as a supplier of whatever the patient wishes to do. In a marketplace where professionals, just like any business, are subject to public reviews of their work, the label of “transphobic” is unwelcome and may have serious adverse professional consequences.

82. Yet the idea that it is a “conversion” to become convinced that perhaps you were not born in the wrong body and that you may be able to live with the body you have strains simple logic. In any case, there is no defined psychotherapeutic method for treating gender dysphoria that can be widely characterized and consistently identified as “conversion therapy” in order to be banned. Nor has there been a clinical trial evaluating specific psychotherapeutic methods of counseling gender dysphoria that could potentially demonstrate whether one or more such methods are indeed helpful or harmful.

⁹² Turban et al. (2020). This study was thoroughly critiqued in: 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. The authors concluded: “Turban et al.’s (2020) singular endorsement of ‘affirmative’ therapies, which their data failed to substantiate, contributes to the alarming trend to frame any non-‘affirming’ approaches as harmful. We are deeply concerned that this false dichotomy, reinforced by Turban et al.’s unproven claims of the harms of GICE, will have a chilling effect on the ethical psychotherapists’ willingness to take on complex GD patients, which will make it much harder for GD individuals to access quality mental health care. We maintain that availability of a broad range of non-coercive, ethical psychotherapies for individuals with GD is essential to meaningful informed consent, which requires consideration of the full range of treatment options, from highly invasive to non-invasive. Further, given the potential of agenda-free psychotherapy to ameliorate GD non-invasively among young people with GD, withholding this type of intervention, while promoting “affirmation” approaches that pave the way to medical transition, is ethically questionable. We believe that exploratory psychotherapy that is neither “affirmation” nor “conversion” should be the first-line treatment for all young people with GD, potentially reducing the need for invasive and irreversible medical procedures.” P. 13

83. For these reasons, I concur with Dr. Stephen Levine, who has highlighted the quandary facing professionals attempting to provide “informed” counsel to patients about the biological, social, and psychological risks posed by any treatment approach.⁹³ Such risks are real and ought to be discussed—this is what ethical informed consent does. But obtaining informed consent could be perceived as an attempt to “convert” the person from pursuing gender affirmation treatments (e.g., hormones, surgery).

84. The ideological capture of much of this field of treatment makes for a difficult environment for psychological treatment. One British psychotherapist observes this challenge, noting that “[s]ome therapists, trans people, and their allies seem to regard any psychological description of GD as inherently pathologizing and equate it with gay conversion therapy.”⁹⁴

85. Many other examples of undue pressure could be given, both within and outside the professions. Amazon.com’s decision to withdraw from selling books that so much as suggest the idea that gender dysphoria is (or had been associated with) a mental disorder is one. Public fora for legitimate debate are actively being curbed.⁹⁵ Even reviews of books are being retracted and withdrawn.⁹⁶ Certain conclusions are now penalized both professionally and in the wider social and economic marketplace. To suppose that such external social and political pressures do not affect basic social or medical research on transgender-related matters would be naïve.

⁹³ Levine (2019).

⁹⁴ Withers (2020), p. 865.

⁹⁵ Trachtenberg, J. A. (2018, March 11). Amazon won’t sell books framing LGBTQ+ identities as mental illnesses. *Wall street journal*. <https://www.wsj.com/articles/amazon-wont-sell-books-framing-lgbtq-identities-as-mental-illnesses-11615511380>

⁹⁶ Novella, S. & Gorski, D. (2021, June). Retraction notice for Hall, H. (2021, June 15.) Book review: *Irreversible damage: The transgender craze seducing our daughters*, by Abigail Shrier. *Science-based medicine*. <https://science-basedmedicine.org/irreversible-damage-the-transgender-craze-seducing-our-daughters/>

E. Inconsistent Claims about Adolescents' Ability to Consent

86. A central and persistent concern about hormonal (and subsequent surgical) courses of treatment for gender dysphoria in adolescents is their ability to genuinely consent to treatments that will almost invariably lead to de facto sterilization. As gender therapist Diane Ehrensaft admits, “continuity of care in gender affirmation” from puberty blockers to cross-sex hormones results in “discontinuity in potential capacity to ever create progeny with their own genetic material.”⁹⁷ The bar to informed consent for such medical treatments—especially experimental ones—has long been elevated for minors.

87. But in a recent issue of *International Journal of Transgender Health*, Dutch child and adolescent psychiatrist Annelou de Vries and six co-authors registered their disappointment with the *Bell v Tavistock* decision (discussed below), asserting that “minors as young as 12 years of age frequently possess this ability”—that is, the competency to understand the consequences of a decision to begin puberty blockers.⁹⁸ In asserting this, de Vries and her colleagues claim to concur with “all the major medical associations.”

88. Even these medical associations, however, give grounds to doubt that adolescents are competent to consent. The APA recognizes that “adolescents can become intensely focused on their immediate desires, resulting in outward displays of frustration and resentment when faced with any delay in receiving the medical treatment from which they feel they would benefit and to which they feel entitled. This intense focus on immediate needs may create challenges in

⁹⁷ Ehrensaft, D. (2021, April 7). Fertility issues for transgender and nonbinary youth. Training presentation sponsored by the UC San Francisco Child and Adolescent Gender Center. Discussion and video links available at: <https://4thwavenow.com/2021/04/13/tmi-genderqueer-11-year-olds-cant-handle-too-much-info-about-sterilizing-treatments-but-do-get-on-with-those-treatments/>

⁹⁸ de Vries, A. L., Richards, C., Tishelman, A. C., Motmans, J., Hannema, S. E., Green, J., & Rosenthal, S. M. (2021). *Bell v Tavistock and Portman NHS Foundation Trust* [2020] EWHC 3274: Weighing current knowledge and uncertainties in decisions about gender-related treatment for transgender adolescents, *International journal of transgender health*, p. 5. doi: 10.1080/26895269.2021.1904330

assuring that adolescents are cognitively and emotionally able to make life-altering decisions to change their name or gender marker, begin hormone therapy (which may affect fertility), or pursue surgery.”⁹⁹ For its part, the Endocrine Society guidelines recognize that “no objective tools to make such an assessment [i.e., of an adolescent’s competence in decision making] are currently available” and notes that some “believe that . . . abilities (such as good risk assessment) do not develop until well after 18 years.”¹⁰⁰

89. The American Medical Association (AMA) presents a curious case. In an April 26, 2021 letter to the National Governors Association (NGA), the AMA wrote to urge the NGA to “oppose state legislation that would prohibit the provision of medically necessary gender transition-related care to minor patients.”¹⁰¹ But this statement is flatly inconsistent with the position the AMA has taken concerning adolescents’ abilities in other contexts. In its 2005 amicus brief to the U.S. Supreme Court in *Roper v. Simmons*, a case that concerned capital punishment for crimes committed by minors, the AMA asserted that “[a]dolescents’ behavioral immaturity mirrors the anatomical immaturity of their brains. To a degree never before understood, scientists can now demonstrate that adolescents are immature not only to the observer’s naked eye, but in the very fibers of their brains.”¹⁰²

90. The AMA brief makes an additional pair of comparative claims about the adolescent brain: “First, adolescents rely for certain tasks, more than adults, on the amygdala, the area of the brain associated with primitive impulses of aggression, anger, and fear. Adults, on the

⁹⁹ American Psychological Association (2015), p. 842.

¹⁰⁰ Hembree et al. (2017), p. 3884.

¹⁰¹ Madara, J. L. (2021, April 26). Official AMA letter to legislators. <https://www.ama-assn.org/press-center/press-releases/ama-states-stop-interfering-health-care-transgender-children>

¹⁰² American Medical Association et al. (2005). Brief of Amici Curiae in *Roper v. Simmons*, (U.S. Sup. Ct.), 543 U.S. 551 (No. 03-633), 2004 WL 1633549, p. 10. The AMA was joined in their claims by the American Psychiatric Association, American Society for Adolescent Psychiatry, American Academy of Child & Adolescent Psychiatry, American Academy of Psychiatry and the Law, National Association of Social Workers, Missouri chapter of the National Association of Social Workers, and the National Mental Health Association.

other hand, tend to process similar information through the frontal cortex, a cerebral area associated with impulse control and good judgment. Second, the regions of the brain associated with impulse control, risk assessment, and moral reasoning develop last, after late adolescence.”¹⁰³ This is widely recognized today in the conventional wisdom that it is not until around age 25 that (prefrontal) brain development is stabilized in human beings.

91. One of the attorneys who penned the brief in *Roper* on behalf of the AMA and other organizations, later reinforced—by referring to the brief itself—that the “ability of adolescents to make cost-benefit calculations, as compared to adults, is deficient. Additionally, their susceptibility to peer pressure is greater because of this impaired judgment. Moreover, adolescents are more volatile than adults, experiencing more extreme emotions that are not as regulated as they are in adults.”¹⁰⁴

92. When it comes to criminal activity, the AMA asserts that minors cannot be trusted to navigate peer pressure, weigh costs and benefits, make clear-minded judgments, and move ahead with life-altering decisions. But when it comes to transgender medicine and its life-altering consequences, the AMA asserts that minors are competent to make such decisions.

93. Is a child at the cusp of puberty competent to weigh the risks and consequences that transgender medicine entails? That was the question at stake in *Bell v Tavistock*. In 2020, Keira Bell petitioned the court to review the treatment given to minors and young people, saying she had been rushed to transition, was not given other therapeutic options, and lacked the capacity to understand the long-term implications of her decisions at the time. “I was an unhappy girl who needed help,” Bell stated. “Instead, I was treated like an experiment.”¹⁰⁵ In its December

¹⁰³ American Medical Association et al., p. 11.

¹⁰⁴ Haider, A. (2006) *Roper v. Simmons*: The role of the science brief. *Ohio state journal of criminal law* 3: 369-377, p. 372.

¹⁰⁵ Bell, K. (2021, April 7). Keira Bell: My story. *Persuasion*. <https://www.persuasion.community/p/keira-bell-my-story>

2020 decision, the UK’s highest court ruled that children could not give genuine consent to hormonal treatments offered at the National Health Service’s gender clinic.

94. In its verdict, the UK High Court also highlighted a “lack of clarity over the purpose of the treatment: in particular, whether it provides a “pause to think” in a “hormone neutral” state or is a treatment to limit the effects of puberty, and thus the need for greater surgical and chemical intervention later.”¹⁰⁶

95. What has become clear is that the use of puberty blockers in the present is linked to the potential outcomes of future drugs and surgeries, thus revealing a presumption of medical “path dependence” in these treatment protocols. That is why the court determined that puberty blockers and cross-sex hormones are essentially two parts of “one clinical pathway.”¹⁰⁷ Consequently, for minors to be competent to consent to blockers, they would have to adequately understand and consent to the effects of future cross-sex hormones as well.

96. In a subsequent case (*AB v Tavistock and Portman NHS Trust*), parents were given the power to consent on behalf of their kids under age 16 without judicial review. But parental consent for an adolescent’s sterilization is likely co-occurring here, given the new near-universal rates of transition from puberty blockers to cross-sex hormones.¹⁰⁸ Parental consent to sterilization used to be against the law in many locales, creating ethical dilemmas that commonly required judicial review.¹⁰⁹

¹⁰⁶ Bell & A v. Tavistock & Portman NHS Foundation Trust. (2020), para. 134.

¹⁰⁷ Bell & A v. Tavistock & Portman NHS Foundation Trust. (2020), para. 136.

¹⁰⁸ What is critical here about the pairing of puberty blockers then cross-sex hormones is that if patients commence puberty blockers early enough, they will not go through puberty (of their natal sex); hence, their gametes do not have enough time to mature (for the purpose of being subsequently harvested for possible future artificial reproduction). See Hudson, J., Nahata, L., Dietz, E., & Quinn, G. P. (2018). Fertility counseling for transgender AYAs. *Clinical practice in pediatric psychology*, 6(1), 84-92. doi: 10.1037/cpp0000180

¹⁰⁹ For example, it remains illegal in Oregon to sterilize a person under age 15, regardless of parental permission. See also Boynton, M. (1994). Sterilization of minors. *Minn med.* 77(1):23-4. <https://pubmed.ncbi.nlm.nih.gov/8127303/>

97. Two additional countries (Sweden and Finland) have also scaled back their protocols concerning adolescent transgender treatments after witnessing surging cases and the sex ratio inversion—far more natal girls than boys seeking medical treatment for gender dysphoria. Finnish guidelines now hold that that identity exploration is a natural phase of adolescence and therefore medical interventions ought to be restricted until their “identity and personality development appear to be stable.” Brain development, they observe, continues until early adulthood—about age 25—which affects young people’s ability to assess the consequences of their decisions on their own future selves for rest of their lives.¹¹⁰

98. “Cross-sex identification in childhood, even in extreme cases, generally disappears during puberty,” the Finnish document maintains. Moreover, the new guidelines prioritize non-invasive psychotherapeutic interventions as the first course of action, due to “variations in gender identity in minors.”¹¹¹ Finally, Finnish guidelines similarly recommend further study, citing “a need for more information on the disadvantages of procedures and on people who regret them.”¹¹²

99. Sweden’s rollback—in the wake of a 1,500 percent increase in youth gender clinic referrals over a ten-year period—is even more pronounced. Hormonal treatments will no longer to be offered to persons under age 18, although clinical trials research on 16-18-year-olds will be allowed. This followed a late 2019 Swedish health system publication and a similar evidence review published in October 2020 that revealed little evidence to suggest that puberty-

¹¹⁰ Council for Choices in Healthcare (COHERE). (2020). Medical treatment methods for dysphoria associated with variations in gender identity in minors – recommendation-summary. Healthcare Services Selection Council (Palko). Government, Finland. https://palveluvalikoima.fi/documents/1237350/22895008/Summary_minors_en.pdf/aaf9a6e7-b970-9de9-165c-abadfae46f2e/Summary_minors_en.pdf

¹¹¹ Council for Choices in Healthcare (COHERE) (2020).

¹¹² Council for Choices in Healthcare (COHERE) (2020).

blocking and hormonal treatments improve the mental health and psychosocial functioning of minors. The literature provides very little knowledge about their safety in the long term.¹¹³

100. When the UK’s judgment in *Bell v Tavistock* was announced, plaintiff Keira Bell responded, “I am delighted at the judgment of the court today. It was a judgment that will protect vulnerable young people. I wish that it had been made for me before I embarked on the devastating experiment of puberty blockers. My life would be very different today. This time last year I joined this case with no hesitation, knowing what I knew about what had and has been going on at the gender identity clinic. My hope was that outside of the noise of the culture wars the court would shine a light on this harmful experiment on vulnerable children and young people. These drugs seriously harmed me in more ways than one and they have harmed many more particularly young girls and women.”¹¹⁴

F. The Department of Justice’s Dramatic Flip-Flop on *Bostock*

101. Not to be overlooked in a discussion of matters bearing on the politically-charged nature of issues affecting persons who identify as transgender is the Department of Justice (DOJ) Civil Rights Division’s dramatic flip-flop on implementation of the U.S. Supreme Court’s decision in *Bostock v. Clayton County, Georgia*. That decision held that firing an individual because they are transgender violates Title VII of the Civil Rights Act.

102. On January 17, 2021, the DOJ’s Civil Rights Division issued a memorandum addressing *Bostock*’s implications for various provisions of law, for religious liberty, and for the DOJ’s own employment practices.¹¹⁵ But a mere five days later—after the inauguration of a new

¹¹³ Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) (2019).

¹¹⁴ Bell, K. (2020) Keira Bell case: Statements from BBC interview. Transcript available here: <https://our-duty.group/2020/12/02/keira-bell-case-statements/>

¹¹⁵ Daukas, J. B. (2021, January 17). Department of Justice memorandum to the Civil Rights Division on the application of *Bostock v. Clayton County*. Although the DOJ removed the January 17 memorandum from the Internet, it is archived online here: <https://web.archive.org/web/20210120125231/https://www.justice.gov/crt/page/file/1356531/download>

presidential administration—the Civil Rights Division withdrew the memorandum.¹¹⁶ The whip-lash-inducing speed with which the Civil Rights Division reversed itself after the new administration took over simply highlights the politically-charged nature of the matter.

103. I have reviewed the Civil Rights Division’s statement of interest filed in this lawsuit, which accentuates the point to an even greater degree. The Civil Rights Division’s January 17 memorandum articulated several reasons why the *Bostock* decision did not bear on the Equal Protection Clause. But on June 17, the Civil Rights Division filed a statement of interest in this lawsuit that repeatedly appeals to *Bostock* in support of the plaintiffs’ Equal Protection claim in this lawsuit. The DOJ Civil Rights Division’s direct contradiction of the precise legal position that it took only a few months ago renders undeniable the politically-charged nature of matters bearing on individuals who identify as transgender.

VI. RISK OF SUICIDE AS AN UNCLEAR MOTIVATION FOR “AFFIRMATIVE” TREATMENT

104. Parents’ fears about children’s suicide are understandable and ought never to be dismissed. However, such fears should not affect scholarly evaluations of the genuine risk of suicide or equate suicidality with suicide itself. The association of the two varies notably in sub-populations.¹¹⁷ What is merited, in place of references to “affirmative” treatments as “lifesaving,” is an examination of the nature of suicide risk among the self-identified transgender population. Too often, however, suicidal “ideation” is equated with “attempted” suicide, and even seems to be treated as a proxy for suicide.

¹¹⁶ Friel, G. B. (2021, January 22). Department of Justice memorandum to the Civil Rights Division withdrawing the memorandum on the application of *Bostock v. Clayton County*. <https://www.justice.gov/crt/page/file/1373621/download>

¹¹⁷ Han, B., Compton, W. M., Gfroerer, J., & McKeon, R. (2015). Prevalence and correlates of past 12-month suicide attempt among adults with past-year suicidal ideation in the United States. *The journal of clinical psychiatry*, 76(3), 295–302. <https://doi.org/10.4088/JCP.14m09287>

105. Suicides and attempted suicides among the self-identified transgender population are indeed higher than those in the population at large. It is, however, difficult to determine this subpopulation's scope of suicide risk with accuracy. Moreover, suicide rates have increased notably in the general population over the past decade.¹¹⁸

106. One of the most recent evaluations of suicidal ideation using the CDC's 2019 Youth Risk Behavior Survey noted that 19 percent of Americans ages 14-18 report having seriously thought about suicide (i.e., had suicidal ideation) in 2019.¹¹⁹ Nine percent reportedly attempted suicide. The CDC did not track such rates among youth identifying as transgender, but did note elevated rates among individuals identifying as lesbian, gay, or bisexual. Previous research has noted that between 25 to 30 percent of adolescents identifying as transgender report having attempted suicide during their lifetimes.¹²⁰

107. Nevertheless, localized estimates of suicidal ideation and attempts among transgender-identifying adolescents vary notably. A 2017 chart review from a Cincinnati gender clinic noted that among patients (ages 12-22) diagnosed with gender dysphoria, 30 percent reported at least one suicide attempt.¹²¹ (Overall, 58 percent of the Cincinnati clinic patients exhibited at least one additional psychiatric diagnosis.) Two similar studies support these findings, with attempted suicide rates among transgender or dysphoric adolescents of between 26 and 31

¹¹⁸ Whalen, J. (2018, May 15). Youth suicidal behavior is on the rise, especially among girls. *Wall street journal*. <https://www.wsj.com/articles/youth-suicidal-behavior-is-on-the-rise-especially-among-girls-1526443782>

¹¹⁹ Ivey-Stephenson, A. Z., Demissie, Z., Crosby, A. E., Stone, D. M., Gaylor, E., Wilkins, N., Lowry, R., & Brown, M. (2020). Suicidal ideation and behaviors among high school students - Youth Risk Behavior Survey, United States, 2019. *MMWR Suppl.*, 69(Suppl. 1), 47-55. doi: 10.15585/mmwr.su6901a6. See also: Gender Identity Development Service. (2021). Evidence base: Psychosocial difficulties. <https://gids.nhs.uk/evidence-base>

¹²⁰ Olson, J., Schrager, S. M., Belzer, M., Simons, L. K., & Clark, L. F. (2015). Baseline physiologic and psychosocial characteristics of transgender youth seeking care for gender dysphoria. *Journal of adolescent health*, 57(4), 374-380; Grossman, A.H., Park, J.Y., & Russell, S.T. (2016). Transgender youth and suicidal behaviors: Applying the interpersonal psychological theory of suicide. *Journal of gay & lesbian mental health*, 20(4), 329-349.

¹²¹ Peterson, C. M., Matthews, A., Copps-Smith, E. and Conard, L. A. (2017). Suicidality, self-harm, and body dissatisfaction in transgender adolescents and emerging adults with gender dysphoria. *Suicide and life-threatening behavior*, 47, 475-482. <https://doi.org/10.1111/sltb.12289>

percent.¹²² Others note lower rates, including 14 percent in a Toronto clinic and 10 percent in an Australian clinic.¹²³

108. The UK’s Gender Identity Development Service (GIDS) observes that suicide remains “extremely rare” among dysphoric youth, even while noting their rates of self-harm are consonant with those among adolescents in the general population. An extensive, longitudinal “chart study” of all 8,263 adult, adolescent, and child referrals to an Amsterdam gender clinic between 1972 and 2017 documented that 41 natal men (0.8 percent) and 8 natal women (0.3 percent) died by suicide.¹²⁴ Among the former, suicide deaths had decreased over time, while it did not change in natal women. Only four suicide deaths were observed among patients referred to the clinic before the age of 18 (0.2 percent), which was a lower risk than among adult patients (0.7 percent).

109. The Tavistock report also revealed that after a year on puberty blockers, a significant increase was noted in responses to the statement “I deliberately try to hurt or kill myself.” This finding, however, was not replicated across the duration of the study.¹²⁵

110. In 2020, the Swedish National Board of Health and Welfare reported that minors with gender dysphoria have a high incidence of “co-occurring psychiatric diagnoses, self-harm behaviors, and suicide attempts compared to the general population” and that suicide mortality

¹²² Eisenberg, M. E., Gower, A. L., McMorris, B. J., Rider, G. N., Shea, G., & Coleman, E. (2017). Risk and protective factors in the lives of transgender/gender nonconforming adolescents. *Journal of adolescent health*, 61(4), 521-526. <https://doi.org/10.1016/j.jadohealth.2017.04.014>; Grossman, A. H. & D'Augelli, A. R. (2007). Transgender youth and life-threatening behaviors. *Suicide and life-threatening behavior*, 37(5), 527-537. <https://guilfordjournals.com/doi/abs/10.1521/suli.2007.37.5.527>

¹²³ Sorbara, J. C., Chiniara, L. N., Thompson, S., & Palmert, M. R. (2020). Mental health and timing of gender-affirming care. *Pediatrics*, 146(4). <https://doi.org/10.1542/peds.2019-3600>; Kozłowska et al. (2021).

¹²⁴ The median age at first visit, however, was 25. See Wiepjes, C. M., den Heijer, M., Bremmer, M. A., Nota, N. M., de Blok, C. J. M., Coumou, B. J. G., & Steensma, T. D. (2020). Trends in suicide death risk in transgender people: Results from the Amsterdam cohort of Gender Dysphoria study (1972–2017). *Acta psychiatrica Scandinavica*, 141(6), 486-491. <https://doi.org/10.1111/acps.13164>

¹²⁵ Biggs (2019).

rates are higher among people with gender dysphoria than in the general population. They also observe, however, complications in figuring out what is to blame: “At the same time, people with gender dysphoria who commit suicide have a very high rate of co-occurring serious psychiatric diagnoses, which in themselves sharply increase risks of suicide. Therefore, it is not possible to ascertain to what extent gender dysphoria alone contributes to suicide, since these psychiatric diagnoses often precede suicide.”¹²⁶

111. Hence, the evidence for actual suicide risk among gender dysphoric minors is simply unclear, and not just because completed suicides are far more apt to be documented in terms of demographic characteristics rather than sexual and gender-related ones. Rather, as one psychiatrist aptly notes, “Suicide is rare and noisy,” that is, understanding particular causes is challenging. The white male suicide rate, for example, is the highest in the United States by a significant margin. But to suggest that race or sex plays a compelling motivation in suicidal decision-making does not make sense. Complicating matters here is the known, elevated frequency of “significant psychopathology” among dysphoric adolescents.¹²⁷ This makes direct, unmediated claims about the causes of suicidal ideation very difficult.

112. Some propose suicidality as a central motivation for endorsing the “affirmative” approach to treating dysphoric adolescents.¹²⁸ But “suicidality” is a subjective measure that may

¹²⁶ Swedish National Board of Health and Welfare. (2020). The evolution of the diagnosis of gender dysphoria: Prevalence, co-occurring psychiatric diagnoses and mortality from suicide. *Socialstyrelsen*, p. 11.

¹²⁷ Kaltiala-Heino, R., Sumia, M., Työläjärvä, 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(1), 1-9. <https://doi.org/10.1186/s13034-015-0042-y>

¹²⁸ Turban, J. L., King, D., Carswell, J. M., & Keuroghlian, A. S. (2020). Pubertal suppression for transgender youth and risk of suicidal ideation. *Pediatrics*, 145, e20191725. <https://doi.org/10.1542/peds.2019-1725>. This touted study, however, proves insufficient for the claims it makes. Oxford University sociologist Michael Biggs argues that the study leans on “a low-quality survey which is known to have elicited unreliable answers on puberty blockers.” Biggs concludes that Turban’s study “provided no evidence to support the recommendation ‘for this treatment to be made available for transgender adolescents who want it.’” See Biggs, M. (2020). Puberty blockers and suicidality in adolescents suffering from gender dysphoria. *Archives of Sexual Behavior*, 49, 2227-2229. <https://link.springer.com/content/pdf/10.1007/s10508-020-01743-6.pdf>

include suicidal ideation, planning, or actual documented attempts. Further, suicidal ideation and suicidal behavior are not as tightly associated as some surmise. For example, young adults are at least three times as likely to report past-year thoughts of suicide than are adults age 50 and older.¹²⁹ But the actual suicide rate among older Americans remains well above that among young adults, and far above children below age 15.¹³⁰ New data, collected during the COVID-19 era, complicates matters further, given that young adults ages 18-24 reported suicidal thoughts in the past month at rates 12 times higher than that of respondents age 65 and over, and six times that reported by those between 45 and 64 years old (25.5, 3.8, and 2.0 percent, respectively).¹³¹ Based on thoughts of suicide, then, it could be said that there is a crisis of suicidality among the young. But the crisis of actual suicide affects older Americans to a greater degree.

113. Simply documenting elevated “suicidality” among self-identified transgender youth does not recommend a particular treatment approach.¹³² As one psychoanalyst put it, “We treat suicide first of all by keeping people safe, and by helping them become more resilient.”¹³³ Understanding the relationship between gender dysphoria and suicidality is complex; that is, there is an association, but the dysphoria may or may not be a central cause. Research has noted recently that particular aspects of body dissatisfaction may constitute independent risk factors for

¹²⁹ Lipari, R. N., Hughes, A., & Williams, M. (2016, June 16). State estimates of past year serious thoughts of suicide among young adults: 2013 and 2014. *The CBHSQ report*, 1-7. Substance Abuse and Mental Health Services Administration (US). PMID: 27854411.

¹³⁰ Hedegaard, H., Curtin, S. C., Warner, M. (2021). Suicide mortality in the United States, 1999–2019. *NCHS data brief*, no. 398. Hyattsville, MD: National Center for Health Statistics. doi: <https://dx.doi.org/10.15620/cdc:101761>.

¹³¹ Czeisler, M. É., Lane, R. I., Petrosky, E., Wiley, J. F., Christensen, A., Njai, R., Weaver, M. D., Robbins, R., Facer-Childs, E. R., Barger, L. K., Czeisler, C. A., Howard, M. E. & Rajaratnam, S. M. W. (2020). Mental health, substance use, and suicidal ideation during the COVID-19 pandemic — United States, June 24–30. *MMWR Morbidity & mortality weekly report*, 69(32), 1049–1057. doi: <http://dx.doi.org/10.15585/mmwr.mm6932a1>

¹³² Day, D. S., Saunders, J. J., & Matorin, A. (2019). Gender dysphoria and suicidal ideation: Clinical observations from a psychiatric emergency service. *Cureus*, 11(11), e6132. <https://doi.org/10.7759/cureus.6132>

¹³³ Shriner (2020), pp. 137-138.

suicidality among patients with gender dysphoria.¹³⁴ In other words, dissatisfaction with appearance—all the more in the age of Instagram and the selfie—may be a factor in the elevated risk of attempted suicide. In the absence of data analyses that can control for the effects of other confounding and contributing factors, it becomes very difficult to establish that gender dysphoria is a solitary or primary driver of suicidality, all the more since the majority of gender dysphoric minors never attempt suicide.

114. An earlier study of 55 transgender youth reported that “nearly half of the sample reported having seriously thought about taking their lives and one quarter reported suicide attempts.”¹³⁵ Among them, however, “a significantly greater proportion of those who had attempted suicide expressed weight-related body dissatisfaction than those who had not,” a finding observed in other studies as well.¹³⁶ They also tended to ruminate about how others evaluated their bodies.

115. The specter of suicide has nevertheless become a central narrative among supporters of the affirmative treatment approach. Advocates for the “affirmative” approach compare puberty suppression to cancer treatments, claiming that these interventions are as “life-saving” for gender-dysphoric youth as oncology treatments are for those afflicted with cancer.¹³⁷ However, the science behind claims that such treatments lead to sustained improvement in mental health—improvement that cannot possibly occur in its absence—is remarkably weak. Moreover, gender

¹³⁴ Peterson et al. (2017).

¹³⁵ Grossman & D’Augelli (2007), p. 527.

¹³⁶ Day et al. (2019), p. 2; Grossman & D’Augelli (2007).

¹³⁷ In the Tavistock study, children were barred from beginning GnRha treatment if their baseline bone density was too low or agreed to stop treatment if it fell below a certain threshold. In the original Dutch protocol, several participants had to discontinue treatment due to medical complications from the hormone therapy. Did these children die from lack of medicine? Was the progression of their natural puberty and release of sex congruent hormones akin to the progression of metastatic cancer? Of course not. One hopes that these children were rightly encouraged in resilience, rather than surmise that they were doomed to commit suicide because they could not tolerate living in their body apart from transgender medical interventions.

dysphoric youth commonly display significant psychiatric co-morbidities that contribute to their elevated rates of suicidal ideation and attempts.¹³⁸

VII. THE ROLE OF VALUES IN THE PRODUCTION OF SCIENCE

116. Many scientists have long asserted the reality and importance of the fact/value distinction. That is, there are facts—real things—and then there are values, our opinions or attitudes. The study of transgender medicine undermines any strong confidence in this distinction because what a person values shapes what they discern as facts.

117. Misunderstanding the place of values in science is not just an intellectual problem. It can have practical consequences, especially where science has implications for public health and policy. A trio of philosophers aptly note: “If values play a role in science, then the public and public officials cannot take scientific results as given and scientific authorities as beyond challenge. Responsible public policy will require responsible use of science; responsible use of science will require explicit critical awareness of its value assumptions.”¹³⁹

118. Although this report has focused on the scientific evidence, researcher behavior, and the culture of scientific organizations, it is nevertheless easy to observe how values saturate the “affirmative” approach. This is not a criticism per se. Values necessarily infuse the sciences, including the medical sciences as well. The Endocrine Society openly notes how particular values affect their counsel: “These recommendations place a high value on avoiding an unsatisfactory physical outcome when secondary sex characteristics have become manifest and irreversible, a higher value on psychological well-being, and a lower value on avoiding potential harm

¹³⁸ Swedish National Board of Health and Welfare (2020).

¹³⁹ Kincaid, H., Dupré, J., & Wylie, A., (Eds.). (2007). *Value-free science? Ideals and illusions*. Oxford University Press, pp. 4-5.

from early pubertal suppression.”¹⁴⁰ That is, the Endocrine Society is more concerned with helping young people achieve a certain subjective satisfaction with their physical appearance than it is avoiding possible harms of experimental medications or addressing the long-term health and well-being of its young patients.

119. The Endocrine Society is not alone here. Adolescent psychiatrist Annelou de Vries and her colleagues, cited earlier, make a play for the same privileging of physical appearance in their criticism of the UK court’s *Tavistock* decision: “Our deep concern is that the High Court overlooked . . . the lifelong benefits of having a physical appearance which is congruent with one’s gender identity (e.g., no or less breast development and less feminine body shape in an affirmed male and no low voice, Adam’s apple, or masculine facial features in an affirmed female).”¹⁴¹

120. Indeed, value-laden questions may outnumber purely clinical ones in this domain. Is the physician’s role one of granting the requests of patients in order to fulfill what the latter believe or want to be true, or is the physician’s role to treat the gender dysphoria with as little longstanding harm to the wellbeing of the body and mind as possible? Are we to master our feelings and emotions or be subject to them?

121. The very experience of social, hormonal, and surgical “transition” is a value leap—the introduction of a new meaning of “life cycle.” The “body and its meanings” are now considered “contingent.”¹⁴² The concept of “gender identity” requires body dissociation *de facto*, subjugating material reality to the subjective feelings of youth susceptible to suggestion.

¹⁴⁰ Hembree et al. (2017), p. 3881.

¹⁴¹ de Vries et al. (2021), p. 4.

¹⁴² Pyne, J. (2014). Gender independent kids: A paradigm shift in approaches to gender non-conforming children. *The Canadian journal of human sexuality*, 23(1), 1-8, p. 5. <https://doi.org/10.3138/cjhs.23.1.CO1>

122. Dr. Adkins describes common pre-pubertal social transitioning behaviors, including “...allowing children to wear clothing, to cut or grow their hair, to use names and pronouns, and to access restrooms and other sex-separated facilities and activities in line with their gender identity instead of the sex assigned to them at birth.”¹⁴³ But she gets this wrong. These behaviors are not in line with some immutable thing called a “gender identity.” Rather, they are in line with current, valued (and culture-specific) expressions of sex-typed behavior. If “gender identity,” a concept not invented until mere decades ago, was associated with each of these practices, from where (and why) did such norms arise? Instead of questioning the exclusive validity of two-dimensional, historically contingent gender stereotypes, many have instead capitulated to (social) media-intensified values about dress, attire, look, and practice. Rather than impugn one’s own body, perhaps norms associated with this or that “gender identity” ought to be more flexible.

123. Bernadette Wren, who was a senior clinician at the Tavistock clinic until her retirement, wrote in 2014 how trendy postmodern ideas about gender had impacted clinicians’ work with children and adolescents, namely, by adopting the idea of “all gender as fictional and artificial.” After discussing the possible conundrums that arise when directing minors toward irreversible physical changes in light of these conceptions, Wren concluded: “...the meaning of trans is constantly shaped and re-shaped, [and] rests on no foundation of truth. The therapist is not burdened with needing to be right or certain, but to offer a reflexive and thoughtful space to help clients explore the architecture and borders of their gendered world view.”¹⁴⁴

¹⁴³ Adkins (2021), p. 7.

¹⁴⁴ Wren, B. (2014). Thinking postmodern and practising in the enlightenment: Managing uncertainty in the treatment of children and adolescents. *Feminism & Psychology*, 24(2), 271-291, p. 271 and p. 287, respectively.

124. Wren recognizes the value-laden nature of gender medicine for minors: “We are concerned about overstepping what the current evidence can tell us about the safety of our interventions. And we are fully alive to the complexities of informed consent, especially with respect to irreversible bodily change and fertility – and to the possibility of young people having later misgivings around medical intervention. We see that these are not matters of narrow ‘clinical’ judgement, but relate to broader social acceptance of the challenges brought by new medical technologies, new ideologies of self-determination and new models of parental responsiveness and love.”¹⁴⁵

VIII. CONCLUSION

125. The field of adolescent transgender medicine is saturated by conflict over competing values. High quality longitudinal research is rare. Randomized clinical trials research has not occurred. American professional societies promote “affirmative” treatment strategies not because they are effective in long-term studies of psychological and physical health outcomes—they’ve not been shown to be—but in large part due to a demand-driven medical culture in which emphasis is placed on liking what one sees in a mirror, or, increasingly, how others respond to a selfie. Meanwhile, the basics of the explosion in gender dysphoria, especially among natal girls, remain understudied—perhaps now on purpose—and minors’ ability to consent is wielded in ideologically motivated (and varying) ways. This is not how healthy medical research operates.

126. An obviously premature consensus has been contrived among some professionals in this field of medicine. Activists and other interested parties have played a significant role in shaping medical policy, and researchers have taken steps to quash debate and to push medical

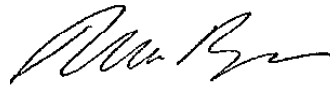
¹⁴⁵ Wren, B. (2020). Debate: You can't take politics out of the debate on gender-diverse children. *Child and adolescent mental health*, 25(1), 40-42, p. 41. <https://doi.org/10.1111/camh.12350>

practice in directions that outpace and even contradict the available evidence. As I have documented, such practices are often openly observable. That is, researchers who are assumed by the public to be unbiased and disinterested in the results have acted in ways contrary to this assumption, even going so far as to suppress public discussion and debate. The pace and extent of ideological capture is staggering.

127. Given the state of disarray in the science here, states have compelling reasons to protect their young people by requiring that they reach adulthood before submitting to the experimental, life-altering gender transition treatments discussed above.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on July 7, 2021.

A handwritten signature in black ink, appearing to read 'Mark Regnerus', is written above a horizontal line.

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2000–2001: Postdoctoral Research Associate, Carolina Population Center.

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A**

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- Sikkink, David and Mark Regnerus. 1996. “For God and the Fatherland: Protestant Symbolic Worlds and the Rise of German National Socialism.” Pp. 133-147 in Christian Smith (ed.), *Disruptive Religion: The Force of Faith in Social Movement Activism*. New York: Routledge.

Non-Peer-Reviewed Journal Articles and Book Chapters

- Regnerus, Mark D. 2020. "Measurement and Analytic Vulnerabilities in the Study of Structural Stigma." (Commentary). *Social Science & Medicine* 244: 112567.
- Regnerus, Mark D. 2019. "Sexual Media as Competition in the Heterosexual Relationship Market" (Commentary). *Archives of Sexual Behavior* 48: 2279-2281.
- Regnerus, Mark. 2019. "Comment on Barbara Risman's review of Cheap Sex: The Transformation of Men, Marriage, and Monogamy." *Contemporary Sociology* 48: 130-131.
- Regnerus, Mark D. 2018. "Reproducing Homes: Intergenerational Transmission of Marriage and Relationship Legacy." In *The Home: Multidisciplinary Reflections* (Antonio Argandoña, editor). Cheltenham, UK: Edward Elgar. 24 pp.
- Regnerus, Mark D. 2015. "The Family as First Building Block." In *The Thriving Society: On the Social Conditions of Human Flourishing* (James R. Stoner, Jr. and Harold James, editors), pp 49-66. Princeton, NJ: The Witherspoon Institute.
- Regnerus, Mark. 2012. "Contemporary Mating Market Dynamics, Sex-Ratio Imbalances, and Their Consequences." *Society* 49: 500-505.
- Regnerus, Mark. 2012. "Parental Same-Sex Relationships, Family Instability, and Subsequent Life Outcomes for Adult Children: Answering Critics of the New Family Structures Study with Additional Analyses." *Social Science Research* 41: 1367-1377.
- Regnerus, Mark D. 2010. "Sexual Behavior in Young Adulthood." The Changing Spirituality of Emerging Adults Project. 16 pp.
- Regnerus, Mark D. 2009. "Imitation Sex and the New Middle Class Morality" (chapter 6 of *Forbidden Fruit*), reprinted in *Speaking of Sexuality: Interdisciplinary Readings, 3rd Edition* (Nelwyn B. Moore, J. Kenneth Davidson, and Terri D. Fisher, editors). New York, NY: Oxford University Press.
- Regnerus, Mark D. and Jeremy E. Uecker. 2007. "How Corrosive Is College to Religious Faith and Practice?" Social Science Research Council. 6 pp.
- Reprinted as Regnerus, Mark D., and Jeremy E. Uecker. 2008. "College Students Value Religion." *Opposing Viewpoints in Context: America's Youth*. Jamuna Carroll, editor. Farmington Hills, MI: Greenhaven Press. link.galegroup.com/apps/doc/EJ3010300238/OVIC?u=txshracd2598&xid=ea8e31f3. 7 pp.
- Regnerus, Mark D., Christian Smith, and Melissa Fritsch. "Religion in the Lives of American Adolescents: A Review of the Literature." A Research Report of the National Study of Youth and Religion, No. 3. Chapel Hill, NC: University of North Carolina, 2003.
- Regnerus, Mark D. "Living up to Expectations." Report, Center for Research on Religion and Urban Civil

Society, University of Pennsylvania, 2003.

Regnerus, Mark D. "Making the Grade: The Influence of Religion upon the Academic Performance of Youth in Disadvantaged Communities." Report, Center for Research on Religion and Urban Civil Society, University of Pennsylvania, 2001.

Regnerus, Mark. "Challenges to Liberal Protestant Identity and Diversity Work: a Qualitative Study." *Sociological Analysis* 1998, 1: 139-149.

Book Reviews

Review of: *Nationalizing Sex: Fertility, Fear, and Power*, Richard Togman (New York: Oxford University Press, 2019). In *Review of Politics* 82: 500-502 (2020).

Review of: *Charitable Choices: Religion, Race, and Poverty in the Post-Welfare Era*, John P. Bartkowski and Helen A. Regis (New York: NYU Press). In *Social Forces* 82: 861-863 (2003).

Review of: *They Still Pick Me Up when I Fall: The Role of Youth Development and Community Life*, Diana Mendley Rauner (New York: Columbia University Press). In *Social Forces* 79: 1545-1547 (2001).

Select Essays and Op-Eds (all sole-authored)

"Weak Data, Small Samples, and Politicized Conclusions on LGBT Discrimination." *Public Discourse*, January 12, 2020.

"New Data Show 'Gender-Affirming' Surgery Doesn't Really Improve Mental Health. So Why are the Study's Authors Saying It Does?" *Public Discourse*, November 13, 2019.

"Does 'Conversion Therapy' Hurt People who Identify as Transgender? The New JAMA Psychiatry Study Cannot Tell Us." *Public Discourse*, September 18, 2019.

"Queering Science." *First Things*, December 2018.

"The Death of Eros." *First Things*, October 2017.

"Can Same-Sex Marriage Really Reduce Teen Suicide?" *Public Discourse*, February 24, 2017. 4 pp.

"Hijacking Science: How the 'No Differences' Consensus about Same-Sex Households and Children Works." *Public Discourse*, October 14, 2016. 5 pp.

"Making Differences Disappear: The Evolution of Science on Same-Sex Households." *Public Discourse*, May 12, 2015. 4 pp.

"Minecraft over Marriage." *First Things*, March 31, 2015. 5 pp.

"The Good-Enough Marriage." *First Things*, December 4, 2014. 4 pp.

"The Pornographic Double-Bind." *First Things*, November 11, 2014. 3 pp.

"Diversity as Slogan and Reality." *First Things*, October 9, 2014. 3 pp.

"Resurrecting the Dead in America." *First Things*, September 11, 2014. 4 pp.

“The Government’s in Your Bedroom, but This Time It’s Okay.” *National Review*, July 16, 2014. 3 pp.

“‘Right Side of History,’ or Primed to Say Yes?” *National Review*, August 20, 2013. 5 pp.

“Assessing the Australian Study.” *National Review*, June 6, 2013. 3 pp.

“Sex is Cheap: Why Young Men Have the Upper Hand in Bed, Even When They’re Failing in Life.” *Slate*, February 25, 2011. (9th-most read *Slate* article of 2011.) 4 pp.

“Freedom to Marry Young.” *Washington Post*, April 26, 2009. 2 pp.

RESEARCH GRANTS

Principal Investigator, “The Relationships in America Survey Project.” \$328,426 grant from the Austin Institute, January 2014-September 2014. (Approved, 100% under PI’s supervision)

Principal Investigator, “The New Family Structures Study.” \$640,000 grant from the Witherspoon Institute, May 2011-August 2013. (Approved, 100% under PI’s supervision)

Principal Investigator, “The New Family Structures Study (supplementary assistance).” \$90,000 grant from the Bradley Foundation, Nov 2011-Nov 2012. (Approved, 100% under PI’s supervision)

Principal Investigator, “The New Family Structures Study.” \$55,000 planning grant from the Witherspoon Institute, Oct 2010-June 2011. (Approved, 100% under PI’s supervision)

Principal Investigator, “The New Pentecostals and Political and Social Activism.” \$9,565 grant from the National Science Foundation (Dissertation Improvement Grant, for Nicolette Manglos), 2010-2011. (Approved but returned)

Co-Investigator, “Developing Health Behaviors in Middle Adolescence” (Lynn Rew, PI, The University of Texas at Austin School of Nursing). \$1,276,919 grant from the National Institute of Nursing Research, 2006-2011. (Approved, <5% under Regnerus’ supervision). R01-NR009856.

Principal Investigator, “Testing Differences: The Transfer and Transformation of HIV Testing from the West to Sub-Saharan Africa.” \$7,500 grant from the National Science Foundation (Dissertation Improvement Grant, for Nicole Angotti), 2008-2009. (Approved)

Co-Investigator, “Religious Organizations, Local Norms, and HIV in Africa” (Susan Watkins, PI, University of Pennsylvania). \$864,000 grant from the National Institute of Child Health and Human Development, June 2005-May 2008. (Regnerus is PI of \$279,000 sub-contract to The University of Texas at Austin). R01-HD050142-01.

Seed grant for “Sex and Emotional Health in Emerging Adulthood.” \$4,000 grant from the Population Research Center and \$2,000 grant from the College of Liberal Arts, The University of Texas at Austin, 2007.

SELECT INVITED PRESENTATIONS

“The Future of Christian Marriage.”

- University of Mary, Bismarck, ND, April 2021
- Faulkner University, Montgomery, AL, March 2021

“The Transformation of Men, Marriage, and Monogamy.” Universidad Francisco de Vitoria, Madrid, November 2018.

Author meets critics panel on *Cheap Sex: The Transformation of Men, Marriage, and Monogamy*. Society for the Scientific Study of Religion, Las Vegas, NV, October 2018.

“The Transformation of Men, Marriage, and Monogamy.” Archdiocese of Denver, September 2018.

Author meets critics panel on *Virgin Nation: Sexual Purity and American Adolescence* (by Sara Moslener, Oxford University Press, 2016). American Academy of Religion, San Antonio, TX, November 2016.

“Intergenerational Transmission of Marriage and Relationship Legacy.” Home Renaissance Foundation, London, United Kingdom, November 2015.

“The Future of Marriage and Family in America.” University of St. Thomas, Houston, TX, March 2015.

“The New Family Structures Study and the Challenges of Social Science.” Brigham Young University, Provo, UT, October 2014.

“Sex in America: Sociological Trends in American Sexuality.” Ethics and Religious Liberty Commission, Nashville, TN, April 2014.

“Premarital Sex in America.” Department of Sociology, University of North Carolina at Chapel Hill, Chapel Hill, NC, January 2012.

Book discussion session on *Premarital Sex in America*. Society for the Study of Emerging Adulthood, Providence, RI, October 2011.

“The Future of Sex and Marriage in American Evangelicalism.” National Association of Evangelicals Advisory Board, Washington, D.C., October 2011.

Heyer Lecture. Austin Presbyterian Theological Seminary, Austin, TX, September 2011.

Thematic session on “The Cultural War and Red/Blue Divide: Re-examining the Debate Demographically and Behaviorally.” American Sociological Association, Las Vegas, NV, August 2011.

“Sexual Economics: The Forces Shaping How Young Americans Meet, Mate, and Marry.” Heritage Foundation, Washington, D.C., May 2011.

“Marital Realities, Current Mindsets, and Possible Futures.” Institute of Marriage and Family Canada, Ottawa, Canada, May 2011.

Panel on “Teen Pregnancy: What Is California Doing Right?” Zócalo Public Square, Los Angeles, CA, December 2010.

“Marriage and Parenthood in the Imagination of Young Adults.” Baby Makes Three: Social Scientific Research on Successfully Combining Marriage and Parenthood (seminar), Princeton, NJ, June 2010.

“Saving Marriage Before It Starts.” Q Conference, Lyric Opera, Chicago, IL, April 2010.

“The Price of Sex in Contemporary Heterosexual Relationships.” TEDxUT, The University of Texas at Austin, Austin, TX, April 2010.

“Love and Marriage in the Minds of Emerging Adults.” Child Trends and Heritage Foundation, Washington, D.C., October 2009.

“Forbidden Fruit? Sex and Religious Faith in the Lives of Young Americans.” Baylor University, Waco, TX, September 2007.

“Great Expectations: Culture, Emotion, and Disenchantment in the Sexual Worlds of Young Americans.” Bay Area Colloquium on Population, Berkeley, CA, September 2007.

CONFERENCE PRESENTATIONS

“The Math Behind Declining Christian Marriage,” Society for the Scientific Study of Religion, Las Vegas, NV, October 2018.

“Consent and the Presumption of the Exchange Theory of Relationship Behavior.” Paper presented at the annual meeting of the American Political Science Association, Boston, MA, September 2018.

“Is There a Recession in Marriage among Western Christians?” Paper presented at the annual meeting of the Society for the Scientific Study of Religion, Atlanta, GA, October 2016.

“Gender and Heterosexual Sex.” Panel discussion at the annual meeting of the American Sociological Association, New York, NY, August 2013.

“The New Family Structures Study: Introduction and Initial Results.” Paper presented at the annual meeting of the Population Association of America, San Francisco, CA, May 2012.

“Religious Distinctions in Nonmarital Romantic Relationship Formation” (with Ellyn Arevalo). Paper presented at the annual meeting of the Society for the Scientific Study of Religion, Milwaukee, WI, October 2011.

“Premarital Sexual Initiation and Fertility among Pentecostal Adolescents in Brazil.” Paper presented at the annual meeting of the Population Association of America, Washington, D.C., April 2011.

“Red Sex, Blue Sex: Distinguishing Political Culture and Religious Culture in the Sexual Decisions of Young Americans.” Paper presented at the annual meeting of the Society for the Scientific Study of Religion, Denver, CO, October 2009.

“Bare Market: Campus Sex Ratios and Romantic Relationships” (with Jeremy Uecker). Paper presented at the annual meeting of the Population Association of America, Detroit, MI, May 2009.

“Religion and Sexual Initiation in Brazil” (with Ana Paula Verona). Paper presented at the annual meeting of the Population Association of America, Detroit, MI, April 2009.

ADVISING

Ph.D. Committees in the Department of Sociology (Year Degree Awarded, * Co-Chair/Co-Supervisor, ** Chair/Supervisor)

2016 Jennifer McMorris
 2015 Stanley Kasun
 2015 Nina Palmo
 2012 Nicolette Manglos **
 2012 Catherine McNamee
 2011 Charles Stokes
 2010 Nicole Angotti **
 2010 Georgina Martínez Canizales
 2010 Viviana Salinas
 2010 Jeremy Uecker **
 2010 Ana Paula Verona
 2008 Margaret Vaaler
 2008 Sara Yeatman
 2007 Amy Burdette *
 2007 Bryan Shepherd
 2007 Jenny Trinitapoli **
 2007 Elisa Zhai

M.A. Committees in the Department of Sociology (Year Degree Awarded, * Co-Chair/Co-Supervisor, ** Chair/Supervisor)

2013 Ellyn Arevalo *
 2012 Kristen Redford **
 2011 David McClendon **
 2010 Aida Ramos Wada
 2008 Nicolette Manglos **
 2007 Andrea Henderson
 2006 Jeremy Uecker **

Undergraduate Thesis Supervision for Honors, Plan II, BDP (Year Degree Awarded, * Reader, ** Supervisor)

2019 Clarisa Trevino **
 2014 Tiffany Fong *
 2011 Mary Lingwall **
 2008 Hong Nguyen **

Ph.D. Committees at other universities (Year Degree Awarded)

2018 Yana Mikhaylova, Higher School of Economics, Moscow

DEPARTMENTAL AND UNIVERSITY SERVICE

Member, Executive Committee, Department of Sociology, 2012-2014

Member, Graduate Admissions Committee, Department of Sociology, 2012-2014

Member, Promotion and Tenure Committee, Department of Sociology, 2012-2014

Member, Undergraduate Research Award Selection Committee, College of Liberal Arts, 2010-2012

Guest presenter, Peer Educator Sexual Health courses, University Health Services, 2008-2012

Presenter, Orange Jackets' Week of Women, Tejas Club, Spring 2011

Moderator, Thesis Symposium, Plan II Honors Program, 2011

Member, Graduate Steering Committee, Department of Sociology, 2010-2011

Member, Promotion and Tenure Committee, Department of Sociology, 2010-2011

Member, Executive Committee, Department of Sociology, 2009-2011

Presenter, TEDxUT, The University of Texas at Austin, Spring 2010

Member, Governing Board, Population Research Center, 2009-2010

Member, Graduate Admissions Committee, Department of Sociology, 2009-2010

Presenter, Sexual Health Panel, Tejas Club, Fall 2009

Member, Graduate Steering Committee, Department of Sociology, 2007-2009

Participant and presenter, Faculty Fellows Program, The University of Texas at Austin, 2007-2009

Chair, Religion Faculty Search Committee, Department of Sociology, Fall 2008

Member, Population Junior Faculty Search Committee, Department of Sociology, Fall 2007

Member, Speaker Colloquium Committee, Department of Sociology, Fall 2007

PROFESSIONAL SERVICE AND ORGANIZATIONAL MEMBERSHIP

Co-organizer and session chair, *The Moynihan Report at 50: Reflections, Realities, and Prospects*.
Princeton University, Princeton, NJ, October 30-31, 2015

Distinguished Article Award Committee member, American Sociological Association (Religion Section),
2010-2011

- Committee chair, 2011

Editorial Board member, *Interdisciplinary Journal of Research on Religion*, 2005–2011

Editorial Board member, *Journal for the Scientific Study of Religion*, 2004–2011

Distinguished Article Award Committee member, Society for the Scientific Study of Religion, 2009-2010

- Committee chair, 2010

Nominating Committee member, Society for the Scientific Study of Religion, 2007-2009

Jack Shand Research Award Committee member, Society for the Scientific Study of Religion, 2005-2007

Council member, American Sociological Association (Religion Section), 2004-2007

Member of:

American Academy of Religion, 2017-2019

Population Association of America, 2004-2018

Society for the Scientific Study of Religion, 1996-present

Ad-hoc reviewer for:

American Journal of Sociology, American Sociological Review, Archives of Sexual Behavior, Biodemography and Social Biology, Gender & Society, Interdisciplinary Journal of Research on Religion, International Journal of Environmental Research and Public Health, Journal for the Scientific Study of Religion, Journal of Adolescent Health, Journal of Behavioral Addictions, Journal of Family Issues, Journal of Health and Social Behavior, Journal of Homosexuality, Journal of Marriage and Family, Journal of Psychology and Christianity, Pediatrics, Perspectives on Psychological Science, Review of Religious Research, Social Forces, Social Problems, Social Psychology Quarterly, Social Science & Medicine, Social Science Quarterly, Social Science Research, Sociological Forum, Sociological Inquiry, The Sociological Quarterly, National Institutes of Health (2007), National Science Foundation (2010, one review), Templeton Foundation (2012, 2019)

**IN THE UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF ARKANSAS
CENTRAL DIVISION**

DYLAN BRANDT, et al.,

PLAINTIFFS,

v.

No. 4:21-CV-00450-JM

LESLIE RUTLEDGE, et al.,

DEFENDANTS.

DECLARATION 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.

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. 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.

8. IN MY OPINION, A LACK OF SCIENTIFIC SUPPORT and THE ETHICAL PRINCIPLE OF INFORMED CONSENT CURRENTLY PROHIBIT HORMONAL

“AFFIRMATION-TRANSITION” TREATMENTS FOR GENDER DYSPHORIA IN CHILDREN: 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).

9. 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.

10. PREVIOUS LEGAL CASES AS AN EXPERT WITNESS: Over my career, I have provided expert medical record review and testified at deposition in less than a dozen cases. 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, Jane Doe vs Board of Education of the Highland School District, Ashton Whitaker vs. Kenosha Unified School District, Terri Bruce vs State of South Dakota, Kadel vs. Falwell, 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).

11. 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.

12. BASES FOR OPINIONS: My opinions documented in this report are based on my 1) knowledge, training, and clinical experience in caring for thousands of patients over many years; (2) detailed methodological reviews of hundreds of relevant peer-reviewed science publications; (3) consults, discussions, and team analyses with colleagues and other experts in the field, including attendance and participation in various professional conferences, and 4) analysis of evidence in this case including the plaintiff's filed complaint and plaintiff's expert reports. My investigation in this case is ongoing and I will supplement, amend or update this report as additional information becomes available for review including discovery, experts, and observations of witnesses. The materials I have relied upon in preparing this report are the same types of materials that experts in my field of study regularly rely upon when forming opinions on these subjects.

Evidence Reviewed: My investigation is continuing and additional evidence will be reviewed as it becomes available.

12A. Peer Reviewed Published Research Articles and related materials, etc. (See citations below and also attached Exhibit B).

12B. Relevant case documents I have reviewed—dozens of relevant scientific research articles and review, the legal complaint in this case, and all expert witness declarations. I look forward to reviewing other evidence as it becomes available.

12C. Evidence documenting the recent, very public, disclosures of the multiple and serious methodological errors, failures, and defects of “transitioning treatment” research. This includes:

THE BRANSTROM LONG-TERM TREATMENT OUTCOME STUDY: The historic Branstrom study is 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 evidence* of benefits for gender reassignment hormone and surgical treatments. The Branstrom study is truly a devastating and historic blow to the WPATH and gender transgender 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_devotes_from_WPATH_prioritizing_psychotherapy_no_surgery_for_minors.

SWEDEN'S FLAGSHIP KAROLINSKA HOSPITAL 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 health 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-report (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. *BMJ* 2020;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-55282113> journal.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 UK HIGH COURT FINDS TRANSITIONING TREATMENTS “EXPERIMENTAL”. In an internationally reported case, the High Court of London ruled these “gender transitioning” treatments were “experimental,” ordering protections for children. The case is currently on appeal but whatever the system concludes the evidence produced during the hearing proved these “treatments” are highly controversial with a high risk of irreversible harm (including sterilization of the patient) and of unproven benefit. See Puberty blockers: Under-16s 'unlikely to be able to give informed consent', BBC, 1 December 2020 “Children under 16 with gender dysphoria are unlikely to be able to give informed consent to undergo treatment with puberty-blocking drugs, three High Court judges have ruled.... “Given the long-term consequences of the clinical interventions at issue in this case, and given that the treatment is as yet innovative and experimental, we recognise that clinicians may well regard these as cases where the authorization of the court should be sought prior to commencing the clinical treatment... The judges pointed to the lack of evidence about the long-term effects of puberty. See, <https://www.bbc.com/news/uk-england-cambridgeshire-55144148>.

THE SEGM REVIEW SUMMARIZES THE HEALTH RISKS of TRANSITIONING: Consistent with changes in Sweden, Finland, England, and Arkansas, the Society for Evidence

Based Gender Medicine 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 ARKANSAS—SHOWS THAT MOST YOUNG GENDER DYSPHORIA CHILDREN GROW OUT OF THE PROBLEM WITH NO MEDICAL INTERVENTION. See Devita Singh¹, Susan J. Bradley² 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>.

ARKANSAS FOLLOWS FINLAND, SWEDEN, and THE UK in PROTECTING CHILDREN FROM EXPERIMENTAL “TRANSITIONING”: I have reviewed the legislation in question in this case. This carefully crafted legislation is compatible with current science and protects Arkansas children as Finland, Sweden, and the UK are moving to protect children from these experimental, dangerous “transitioning treatments.”

It is truly extraordinary that the plaintiffs’ experts, Drs. Adkins and Antommara seem to have “forgotten” to discuss the extraordinary international controversies and changes in their field.

13. OPINIONS regarding the plaintiff’s expert witness declarations by Drs. Adkins and Antommara:

A. The plaintiffs’ expert declarations failed to accurately report, review, or properly disclose to the court the serious methodological limitations, flaws, errors, and defects in the gender transition industry’s research base, including the well-known and well-documented international controversies regarding the relevant science of these experimental interventions:

I have reviewed the expert declarations in this case from the plaintiff’s experts Drs. Adkins and Antommara. In my opinion, these appear to be political-ideological-advocate-activist ipse

dixit opinions in support of the gender affirmation medical enterprise's ("transgender") movement and not competent, appropriate, scientific, methodological opinions. Both of the plaintiff's experts improperly support the use of experimental, highly intrusive, and potentially harmful medical procedures despite the lack of credible, reliable, and valid scientific support for such treatments. In my opinion, their reports failed to include a cogent, detailed, methodological discussion of *the serious, ongoing, scientific, medical, and societal controversies* regarding the etiology, treatment, and long-term outcomes of "gender affirmation" (often mis-labeled as "transitioning") theories, methods, practices, procedures, and treatments. This omission in both of these reports is quite remarkable as the scientific errors, omissions, failures, and defective methodologies of the field of transgender medicine have produced heated controversy and garnered worldwide attention in 2020 and 2021. (See reviews of Finland, Sweden, and the UK discussed above.) In the analysis that follows, I cite published analyses of gender transition industry research, noting significant and internationally recognized errors and defects such as low quality study designs, selective "cherry-picking" of data, and the improper misreporting of key study findings. More specifically regarding the expert reports by Drs Adkins and Antommaria:

DR. AN TOMM MARIA: Dr. Antommaria's Report: In addition to the failure of ignoring the collapse of support for much of the transitioning industry in the UK, Sweden, and Finland, Dr. Antommaria provides a specious distinction between experimentation and clinical care. The underlying premise of Arkansas's SAFE Act is not a concern with innovation, but the lack of quality evidence regarding the claimed, but still unproven, safety and efficacy of the gender transition industry's experimental approach to the care of individuals who experience gender dysphoria. A fundamental obligation in providing clinical care is the use of products and procedures that are known to be safe and effective. 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.

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>)

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 Society's 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.

In his declaration, Dr. Antammaria cites several short-term studies to address questions regarding safety and efficacy of pubertal blockade as part of the “Dutch Protocol” for treating dysphoric adolescents. In 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) to support longitudinal evidence of benefit from pubertal blockade,

improvements in mood improved and the risk of behavioral disorders with pubertal blockade were found over baseline. However, since there was no control group, 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. The study by Schagen et al examined the efficacy of triptorelin in suppressing pituitary gonadotropin secretion and sex hormone levels over the first 12 months of treatment. It also reported effects on liver transaminases and creatinine over this time interval. *The data were insufficient* to form reliable conclusions about long term safety in clinically relevant outcomes as extensively detailed in my article with colleagues Hruz, P. W., Mayer, L. S. & McHugh, P. R. Growing Pains: Problems with Puberty Suppression in Treating Gender Dysphoria. The New Atlantis 52, 3-36 (2017).

DR ADKINS: In the declaration submitted by Dr. Adkins, several false or highly misleading ipse dixit assertions were made regarding the nature and effects of gender affirming medical interventions. While covered in detail below, some of the most egregious of these erroneous assertions are mentioned here.

Dr. Adkins states that “there is nothing inherently harmful about undergoing hormone treatment to sustain one’s health and it is a common practice in many non-transgender patients for reasons unrelated to treatment of gender dysphoria.” This statement fails to acknowledge 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., Yazarbas G. (2010) Sex Differences in Drug Effects. In: Stolerma I.P. (eds) *Encyclopedia of Psychopharmacology*. Springer, Berlin, Heidelberg.). Differences are not limited to pharmacokinetic 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>).

Likewise, Dr. Adkins either mistakenly or deceptively *misreported the data* when she stated that “[a]dolescents 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.” Her purported evidence for this statement is a book chapter by Turban, De Vries and Zucker. However, 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*.” Following Dr. Adkins’ inaccurate claim that “the vast majority of transgender adolescents persist in their transgender identity” in the chapter discussed, 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.

Dr. Adkins also asserted in her declaration that: “Many transgender people have been on hormone therapy for decades and we are not seeing evidence of negative health outcomes as a result.” Dr. Adkins *deceptively provides zero validated scientific evidence to support this shocking, inaccurate, and dangerous claim*. Astonishingly, no reference is made to the existing literature reporting significant adverse effects. Her omissions include, for example, the significant increase in thromboembolic stroke in biological males exposed to estrogen as part of “gender affirming” medical interventions (see, supra, Getahun et al. 2018) (detailed in my report). In contrast to Dr. Adkins’ opinions, the 2020 Bränström long-term outcome study found *no* benefits to her medical interventions, but provided evidence of severe harm with increased suicides and anxiety disorders (Bränström R, Pachankis JE. Reduction in Mental Health Treatment Utilization Among Transgender Individuals After Gender-Affirming Surgeries: A Total Population Study. *Am J Psychiatry*. 2020 Aug 1;177(8):727-734. doi: 10.1176/appi.ajp.2019.19010080. Epub 2019 Oct 4. Erratum in: *Am J Psychiatry*. 2020 Aug 1;177(8):734. PMID: 31581798). But Dr. Adkins appears to have “forgotten” to disclose or discuss this historic long-term treatment outcome study.

Dr. Adkins’ reference to the 2020 paper by Turban (see paragraph 41 of her declaration) fails to present the findings of this study in proper context thus again misreporting research findings. This includes her failure to acknowledge that there was no significant

difference in prior year suicidality between those who did and did not receive puberty blockers (*consistent with the historic Branstrom and other research and consistent with the reviews of England, Finland, and Sweden*). In fact, Dr. Adkins apparently “forgot” to report that the raw suicidality numbers were actually higher among those who received the treatment. She also failed to report that Turban’s study was based upon data from a 2015 “Transgender online survey”—an extremely unreliable sample with serious inherent biases. In fact, Turban’s online survey methodology has been multiply criticized, ridiculed, and debunked as the survey responses were actually provided by a trans advocacy political group and zero patients were assessed, interviewed, or identified—that is, a handful of political advocates could have faked the entire study. Furthermore, Turban’s study was only a cross-sectional analysis thus conclusions between exposure and outcomes were necessarily limited to associations and no causation claims could be made. See critiques of Turban’s methods including Letters to the Editor criticizing Dr. Turban’s 2020 study in Pediatrics for multiple methodological errors. [https://pediatrics.aappublications.org/content/145/2/e20191725/tab-e-letters#re-pubertal-suppression-for-transgender-youth-and-risk-of-suicidal-as-well-as-the-scathing-review-of-Turban’s-disastrous-research-in-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 \(2020\). https://doi.org/10.1007/s10508-020-01844-2](https://pediatrics.aappublications.org/content/145/2/e20191725/tab-e-letters#re-pubertal-suppression-for-transgender-youth-and-risk-of-suicidal-as-well-as-the-scathing-review-of-Turban’s-disastrous-research-in-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-(2020).-https://doi.org/10.1007/s10508-020-01844-2)

Dr. Adkins’ comparison between hormone use for “gender affirmation” and other health conditions such as polycystic ovarian syndrome (PCOS) is also inaccurate and misleading. Using Adkins’ example of treating PCOS, the basis for intervention is not limited to correcting undesired symptoms based on nothing more than psychological

preference. PCOS is a disorder that includes *objectively verified*, clinically evident insulin resistance, hyperandrogenism, and irregular menses. Associated *objectively verified* abnormalities include dyslipidemia, hypertension, increased cardiovascular risk, sleep apnea, endometrial cancer, nonalcoholic fatty liver disease (NAFLD), and type 2 diabetes mellitus (see Dubey P, Reddy SY, Alvarado L, Manuel SL, Dwivedi AK. Prevalence of at-risk hyperandrogenism by age and race/ethnicity among females in the United States using NHANES III. Eur J Obstet Gynecol Reprod Biol. 2021 May;260:189-197. doi: 10.1016/j.ejogrb.2021.03.033). In stark contrast, with transgender patients there are *zero objectively verified symptoms, none at all*.

B. The Plaintiffs' Expert Declarations Also Failed to Disclose or Accurately Report the Serious Methodological Limitations, Flaws, and Defects in the Gender Transition Industry's Methods for the Diagnostic-Labeling of "Gender Dysphoria": The plaintiff's expert disclosures offered misleading opinions about diagnostic systems. For example, 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.

C. The Plaintiffs’ Expert Disclosures Failed to Accurately Disclose and Discuss the 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.

D. The Plaintiffs’ Expert Disclosures Fail to Accurately Report 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. The plaintiffs’ expert disclosures failed to properly discuss and disclose 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).

E. The Plaintiffs’ Expert Disclosures Failed to Accurately Report Methodological and Other Problems in the Plaintiff’s Complaint: I have also reviewed the plaintiff’s filed complaint regarding Act 626. This document demonstrates and discusses many of the scientific errors, limitations, methodological errors, and informed consent errors discussed in detail below.

14. 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%.

15. 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%.

16. 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.

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

18. 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.

19. 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%.

20. 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.

21. 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.

22. 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 Intersex? A response to Anne Fausto-Sterling, *The Journal of Sex Research*, 39:3, 174-178, DOI: 10.1080/00224490209552139

23. 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.

24. 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.

25. 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.

26. METHODOLOGICAL DEFECTS of the GENDER TRANSITION INDUSTRY - WHY IS THE TRANSGENDER MEDICINE FIELD STILL SO CONTROVERSIAL AFTER DECADES OF RESEARCH?:

- A. The field of transgender medicine has long ignored basic, substantive, foundational science methodologies and ethics requirements (e.g. unverified patient reports are not a reliable basis for sterilizing vulnerable patients, unverified human memory reports are subject to contamination and misreporting, poorly designed-misreported treatment studies that show more damage than benefits are not a suitable basis for sterilizing vulnerable patients, etc.)
- B. 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, increased risk of serious suicide attempts, etc.

- C. 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.)
- D. 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).
- E. Because of the stunning 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.
- F. As a result of these many defects of methodology and ethics, the gender transition industry and its “treatments” are not generally accepted by the relevant scientific community.
- G. As a result of these many defects of methodology and ethics, the gender transition industry’s assessments and “treatments” have no known nor published error rate.

- H. A key investigative hypothesis is whether the gender transition industry is simply the latest harmful “junk science” fad and consumer fraud in the medical-psychiatric industry following the misadventures of lobotomies, recovered memory therapy, multiple personality disorder, rebirthing therapy, and others.
- I. National science reviews in England, Sweden, Finland, and by the Cochrane Review have all uncovered serious methodological and ethical failures in the gender transition industry—thus supporting the alternative investigative hypothesis that it is engaged in a form of hazardous consumer fraud resulting in harm to many vulnerable patients. (E.g., In Expósito-Campos P. A Typology of Gender Detransition and Its Implications for Healthcare Providers. *J Sex Marital Ther.* 2021;47(3):270-280. doi: 10.1080/0092623X.2020.1869126. Epub 2021 Jan 10. PMID: 33427094, the authors claim to have identified *60,000 case reports* of detransitioners world-wide on the Internet.)

27. 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.

28. 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).

29. SOCIAL MEDIA “INFLUENCERS” ARE REPORTEDLY TRAINING PATIENTS TO FABRICATE SYMPTOMS TO GAIN RAPID ACCESS TO “TRANSITION” INTERVENTIONS. Because mental health professionals and physicians are not capable of reliably discerning true from false patient reports, nobody knows how many gender dysphoria (GD) patients have been coached-trained to deceive providers to gain easier and more rapid access to hormones/surgery: An important methodological error of the gender transition industry is the reliance on patient self-reports alone—and the lack of objective corroborative evidence (no x-rays, no blood tests, no genetic tests, no MRI’s, etc)—to engage in experimental “treatments” causing sterility and other long-term harms. One potential hazard of this limited, unreliable self-

report methodology can be seen in the recently reported increase of “rapid onset gender dysphoria” ROGD in adolescent females. For decades, the large majority of GD patients were early onset males. In contrast, in just the past 5 years, the majority of new GD patients are female patients with no long-term GD history. Many of the “rapid onset” adolescent patients’ parents have reported a very rapid onset of GD symptoms linked to peer or school pressures or YouTube “training”—thus coming out as “trans” in groups of friends or following school “gender training” programs. At the same time, there have been reports of YouTube “Trans Influencers” whose “video blogs” are watched by millions as they provide detailed coaching to their adolescent girl followers on how to “lie to medical providers to obtain easier access to TG hormone and surgical treatments rapidly.” The reliance upon unverified self-report data—an unreliable diagnostic methodology—may well be one source of the ongoing and internationally reported failure of research on Gender Transition Industry interventions (sometimes mislabeled as “treatments”) to provide consistent, reliable and valid evidence of long term benefits that would offset the well-documented long-term harms, injuries, and damages (e.g. sterility, stunted growth, bone loss, etc.) produced by this burgeoning medical industry.

30. THE SCIENCE OF MEMORY SHOWS THAT UNVERIFIED PATIENT “MEMORY” REPORTS COULD BE QUITE INACCURATE THUS PRODUCING ADDITIONAL RISKS OF UNRELIABLE DIAGNOSIS AND HARMFUL INTERVENTIONS: Decades of scientific research studies have shown that human memory reports—often the sole source of evidence for providers to engage a Gender Dysphoria patient in hazardous, experimental “gender transition” treatments—are subject to manipulation, implantation, contamination by post-event sources, source amnesia, and other errors. As world memory expert Prof. Elizabeth Loftus has noted, “False memories, once created—either through misinformation or

though suggestive processes—can be experienced with a great deal of emotion, a great deal of confidence and a lot of detail, even though they’re false.” See Loftus, E. F. (2002) Memory Faults and Fixes. *Issues in Science & Technology*, National Academies of Science, 18, # 4, pp 41-50; see also, e.g., Loftus, E. F. (2005) Planting misinformation in the human mind: A 30-year investigation of the malleability of memory. *Learning and Memory*, 12, 361-366.

31. 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.

32. 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.

33. 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 (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.

34. HISTORICALLY, THE MEDICAL and SOCIAL SCIENCES HAVE AT TIMES BEEN IMPROPERLY TAINTED BY POLITICAL IDEOLOGIES. It is important for legal professionals—especially judges—to understand the essential differences between methodologically competent science as opposed to the consensus-seeking, voting processes of political-professional associations and related organizations.

Professional Association voting processes are not a reliable nor valid scientific methodology. Professional, political, or other association consensus-seeking voting processes and procedures are neither reliable nor valid, nor tested and proven scientific methodologies. They are votes taken by committees—too often small committees of activists and ideologues with inadequate methodological training. Such non-scientific voting processes and procedures have never been accepted as reliable and valid scientific methods by the relevant scientific community. Such voting processes and procedures have no known error rate. Historically, it should be noted that “professional associations” have a tainted history of supporting unproven, controversial notions that were later proven to be improper, unreliable, and/or unethical.

A. The American Medical Association (AMA): As an example of professional association support of controversial ideologies, the AMA supported eugenic proposals to “improve the quality of the human stock” by coercive sterilization of “defective and undesirable Americans” and selective breeding. During the 1890s the renowned surgeon Albert Ochsner was invited to speak about his vasectomy procedure to the meetings of the American Medical Association. Dr. Ochsner recommended surgical vasectomies to prevent the reproduction of “criminals, chronic inebriates, imbeciles, perverts, and paupers.” (See Ochsner, AJ, Surgical treatment of habitual criminals. JAMA, 1899:32:867-868).

The controversial support of the AMA for such racist, eugenics ideologically-tainted pseudoscientific notion was a political and not a scientific process. Similarly, the American Breeders Association founded an Eugenics Record Office with an advisory board that included a Harvard physiologist, a Princeton psychiatrist, a University of Chicago economist, and Alexis Carrel of the Rockefeller Institute for Medical Research, a recipient of the Nobel Prize in Medicine. This movement was focused on “terminating the bloodlines” of the “submerged lower ten percent of the population with ‘defective germ-plasm.’” (See Black, E. *War Against the Weak*, New York, NY, 2003).

With the support of professional associations like the AMA, a Model Eugenics Sterilization Law was proposed to authorize sterilization of the “socially inadequate,” that is, those supported in institutions or maintained at public expense. The model law encompassed the “feeble-minded, insane, criminalistic, epileptic, inebriate, diseased, blind, deaf, deformed, and dependent”—including “orphans, ne’er-do-wells, tramps, the homeless and paupers.” Eighteen states passed laws based on the 1922 model legislation and sixty-four thousand people were forcibly sterilized. Supporters included Margaret Sanger who in her 1932 essay “My Way to Peace” proposed that “the whole dysgenic population would have its choice of segregation or sterilization” (Sanger, M., *My Way To Peace*, *Birth Control Review*, Jan 17, 1932; Singleton, M.M. *The “Science” of Eugenics: America’s Moral Detour*, *Journal of American Physicians and Surgeons*, Vol 19, No 4, Winter 2014.)

A key lesson from this tragic era is that the non-scientific, consensus-seeking voting processes of “associations” can produce danger to the public and patients. Although directed by persons who know or should know how to conduct proper scientific methods, association voting

methods are politically-ideologically tainted processes—and not based upon valid-reliable, methodologically-competent science. Again, such professional “associations” operate via consensus-seeking and ideology and not evidence-seeking scientific methodologies. Such professional organizations make decisions by voting and not by conducting ethical, scientifically valid, methodologically reliable, peer reviewed and published science with known error rates.

B. 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).

C. 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.

The DSM has become increasingly controversial in recent years—including being "dumped" by the National Institute of Mental Health as a key basis for research funding. See Lee, C., *The NIMH Withdraws Support for DSM-5: The latest development is a humiliating blow to the APA*. Psychology Today News Blog at <https://www.psychologytoday.com/us/blog/side-effects/201305/the-nimh-withdraws-support-dsm-5> ("Just two weeks before DSM-5 is due to appear, the National Institute of Mental Health, the world's largest funding agency for research into mental health, has indicated that it is *withdrawing support for the APA's manual*. In a humiliating blow to the American Psychiatric Association, Thomas R. Insel, M.D., Director of the

NIMH, made clear the agency ... would be “re-orienting its research away from DSM categories.”). See also <https://www.nimh.nih.gov/about/directors/thomas-insel/blog/2013/transforming-diagnosis.shtml>. “Unlike our definitions of ischemic heart disease, lymphoma, or AIDS, the DSM diagnoses are based on a consensus about clusters of clinical symptoms, not any objective laboratory measure. In the rest of medicine, this would be equivalent to creating diagnostic systems based on the nature of chest pain or the quality of fever. Indeed, symptom-based diagnosis, once common in other areas of medicine, has been largely replaced in the past half century as we have understood that symptoms alone rarely indicate the best choice of treatment. Patients with mental disorders deserve better. NIMH has launched the Research Domain Criteria (RDoC) project to transform diagnosis by incorporating genetics, imaging, cognitive science, and other levels of information to lay the foundation for a new classification system.”

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.

35. MEDICINE and SOCIAL SCIENCE HAVE AT TIMES BEEN TRAGICALLY TAINTED AND THOUSANDS OF PATIENTS DAMAGED BY RELIANCE ON METHODOLOGICALLY DEFECTIVE PATIENT SELF-REPORTS and ANECDOTAL EVIDENCE: Case histories, case reports, and verbal patient reports and medical records of individual patients are all helpful sources of information and at times essential to the proper treatment of individual

patients. Such information has often proven helpful in generating testable hypotheses for scientific research. Such self-report and anecdotal information, however, can contain errors, distorted memories, misinterpretations, delusions, confusions, manipulations, and other kinds of errors. In sum, case histories, case reports, and the statements and medical records of individual patients are anecdotal case histories or patient reports (stories of often unknown reliability). Such evidence is not sufficient for reliable, valid, tested, proven, peer reviewed scientific methodologies. Case histories, case reports, and the statements and medical records of individual patients have never been accepted by the relevant scientific community as reliable, valid, peer-reviewed published scientific research. Such case histories, case reports, and the statements and medical records of individual patients have no known error rates with some case reports being highly accurate documentation of objective evidence and others being filled with highly subjective, uncorroborated, unverified verbal reports of patient emotional states.

An informative historical example of disastrous medical misdirection from anecdotal patient reports is the Repressed Memory Therapy (RMT) movement of the late 1980s and 1990s. This explosive epidemic of “recovered memories” and “multiple personality disorder” (MPD) patients led to the rapid creation of lucrative specialty clinics and hospital units throughout the nation as tens of thousands of new RMT and MPD patients accused parents of horrific crimes.

The intense furor resulted in the FBI spending tens of millions of dollars investigating hundreds of anecdotal crime reports from psychotherapy patients. After years of investigations costing tens of millions of dollars, Kenneth Lanning, the Director of the FBI Behavioral Unit, reported the lack of corroborative evidence for the patient allegations following “recovered memory therapy.” He suggested that “therapists needed to explain” why so many therapy patients came to adopt, fervently believe in, and report radically transformed, terrifying alterations

to their own biographies including “new memories” of torture at the hands of “satanic international cults” engaged in the rape, murder, and cannibalism of children. Social psychologist Richard Ofshe called the belief in satanic ritual abuse the “Achilles’ heel” of the recovered memory movement, since the newly “remembered” reports of murder, cannibalism, and fetuses aborted in “rituals” not only sounded extreme and incredible but were not linked to corroborating evidence (e.g. many patients claiming “memories” of being ritually cut open for “sacrificial birth” had zero scars and upon OB-GYN exam had never given birth). Despite the lack of validating evidence as documented by the FBI’s exhaustive investigation, in a national survey published in 1994, conducted by Gail Goodman and her colleagues, 13 percent of 7,000 therapists surveyed reported that they had “elicited recovered memories of ritual abuse”, and these respondents “overwhelmingly believed” the “memories” were real. Two additional major studies—one American, one British—came to the same conclusion as the FBI’s Lanning in 1994. Funded with \$750,000 from the federal government, Gail Goodman and her team examined many thousands of patient’s anecdotal stories of satanic ritual abuse and failed to find any corroborative evidence for the stereotypical, rote, detailed patient reports of multi-generational cults that sexually abused, killed, and/or ate children. (See Ofshe, R. and Watters, E. (1996) *Making Monsters: False Memories, Psychotherapy, and Sexual hysteria*. 2nd Edition. University of California Press; See also, Pendergrast, M. (2017).) *The repressed memory epidemic: How it happened and what we need to learn from it*. New York, NY: Springer.). Thus, prior to WPATH and prior to the ideological fervor of the Gender Affirmation Medical Enterprise, the Recovered Memory Therapy industry had shown how “politically correct” ideological fervor can overcome a lack of credible scientific evidence and engage in highly lucrative experimental “treatments” on tens of thousands of unsuspecting, vulnerable patients.

Subsequent research and many dozens of malpractice lawsuits and licensing revocations documented that the very similar self-reported “memories” provided by “recovered memory” patients to law enforcement and the media were actually the result of memory contamination by unethical, pseudoscientific psychotherapy methods and media-therapist fueled social contagion fears of a criminally abusive “patriarchy.” The patients’ new, horrific “memories” were shown to be the result of ideologically driven pseudoscientific “treatments” including hypnosis, “age regression,” dream interpretation, guided imagery, use of family photographs to stimulate “recovered memories,” interpretation of physical symptoms as so-called “body memories,” and coercive group therapy sessions similar to Maoist indoctrination groups. See Ofshe, R. and Walters, E. (1996) *Making Monsters: False Memories, Psychotherapy, and Sexual hysteria*. 2nd Edition. University of California Press; See also, Pendergrast, M. (2017). *The repressed memory epidemic: How it happened and what we need to learn from it*. New York, NY: Springer.).

A torrent of lawsuits and media exposes shut down many of the Repressed Memory Therapy-Multiple Personality Disorder (RMT-MPD) clinics. State licensing boards then proceeded to revoke or restrict the licenses of multiple leaders of the RMT-MPD movement. See, e.g., Beluck, P. *Memory Therapy Leads to a Lawsuit and Big Settlement [\$10.6 Million]*, *The New York Times*, Page 1, Column 1, Nov. 6, 1997; see also Barden RC: *Reforming the Mental Health System: Coordinated, Multidisciplinary Actions Ended “Recovered Memory” Treatments and Brought Informed Consent to Psychotherapy*. *Psychiatric Times*. 2014;31(6): June 6, 2014.

It is important to note that the relevant professional associations including the American Medical Association, the American Psychiatric Association, the American Psychological Association and others (social worker and therapist associations, etc.) were not protective of the public and did little or nothing to expose the dangerous, pseudoscience fads and frauds of the RMT-

MPD movement. In contrast, these political-professional associations protected the lucrative RMT-MPD industry that created tens of thousands of new patients requiring years of expensive treatments. The exposure of the dangers and damages of the RMT-MPD industry was done by a small number of civil attorneys, scientists, juries, and science-literate journalists. This informative historic example should give pause to those attempting to rush to fund and rapidly expand the lucrative, politically driven, pseudo-scientific, experimental gender transition industry.

In sum, some of the most tragic misadventures in the history of medicine involved the science illiterate reliance upon uncorroborated patient “stories”—self-reported evidence—as the sole basis for proceeding with controversial, experimental treatments on vulnerable patients (e.g. Lobotomies, Rolfing, Primal Screaming, Recovered Repressed Memories, Multiple Personality Disorder, Rebirthing Therapy, Coercive Holding Therapy, Reparenting, etc.). Understanding the important distinctions between scientifically valid-reliable, methodologically sound research versus unreliable, anecdotal evidence and unverified patient “memories” is essential to efforts to protect the integrity of the scientific process as well as the quality and safety of medical care. Sex discordant gender (“transgender”) assessments are currently made almost solely on unverified, uncorroborated “memory” reports of vulnerable patients.

36. 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.

37. 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.”)

38. 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.

39. PROPER INVESTIGATIONS OF DECEPTIVE MISCONDUCT. Ideological overreach 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.

40. PROPER INVESTIGATIONS OF DECEPTIVE MISCONDUCT. In my opinion, plaintiff’s expert Dr. Adkins appears to have engaged in misconduct by her signed opinion in this case stating, “The only effective treatment to avoid this serious harm is for the person to live in accordance with their gender identity and follow appropriate treatment protocols to affirm gender identity and alleviate distress.” Adkins Declaration, par. 25. As the detailed methodological analysis above amply documents, Dr. Adkin’s declaration in this case appears to document an example of unusual ignorance or potentially, a deceptive failure to properly report on, and inform the court of, the ongoing international controversies and debates regarding gender transition interventions (“treatments”) (e.g. see the relevant multiple, national science reviews cited below

from Great Britain, Sweden, and Finland, as well as the Cochrane Review all exposing the serious methodological defects, controversies, and methodological failings of gender transition research as documented below).

41. 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.

42. 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 re-

cent 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.

43. 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).

44. 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](https://doi.org/10.1016/s0193-953x(05)70184-2).

45. 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.

46. 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).

47. 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).

48. 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”.

49. 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>

50. 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 es-

sential 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.

51. 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.

52. 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, Tangpricha V, 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.

53. 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 Years. *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.

54. 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.

55. 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.

56. 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>.

57. 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 Rodri-guez-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>.

58. 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)).

59. 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.

60. 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>

61. 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.

62. 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 understanding 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, doi:10.1097/med.0000000000000236 (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>

63. 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>

64. 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.

65. 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 ideological 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.

66. 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.

67. 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”).

68. 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 dec-

ades—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.

69. 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.”*

70. 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. See 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.

71. SCHOOL ENVIRONMENT SOCIAL CONTAGION: Observers including journalists have reported that some schools in America—1st grade through College—during the past few years have been aggressively teaching that a “non-binary” identity is the real “norm” and far better than traditional gender roles. Such school programs present male and female roles in a very rigid, highly stereotyped manner then teach children (even 1st graders) that if they do or feel anything different than narrow binary sex roles (girls enjoying football, boys enjoying art) they are surely “non-binary” and should receive much social support, reinforcement, and encouragement for “transitioning.”

The rapid and historic transformation of the gender transition industry patient pool has been widely noted by researchers, journalists, and providers. This transformation from early onset, chronically dysphoric male patients to rapid onset adolescent female patients has occurred in just the last few years. The patient transformation from 3 to 1 males (for decades) to 7 to 1 females (just in the last few years) is not easily explained by any of the gender transition industry theories such as “genetics” or “brain structures” or the mysterious and tautological “immutable characteristics” theory.

Journalist Abigail Shrier’s book, *Irreversible Damage* addresses the social contagion theory of why patient demographics changed so very rapidly and expansively. Shrier’s book was reportedly named a “Book of the Year” by The Economist and “one the Best Books of 2021” by The Times (of London) and The Sunday Times (of London). Many famed scientists of various fields have praised Shrier’s work in highlighting A) the lack of competent scientific research

supporting “gender affirmation” interventions and B) the political contamination including censorship and “cancel culture” attacks on academics that make gender affirmation investigation (“transgender science”) such a controversial field. For example, several highly credible and deeply respected members of the relevant scientific and public policy-ethics communities have reportedly posted positive reviews of Shrier’s analysis on the Amazon bookseller site. These quotes are offered to demonstrate the breadth and depth and international scope of the raging controversies regarding the transgender treatment industry.

“In *Irreversible Damage*, Abigail Shrier provides a thought-provoking examination of a new clinical phenomenon mainly affecting adolescent females—what some have termed rapid-onset gender dysphoria—that has, at lightning speed, swept across North America and parts of Western Europe and Scandinavia. In so doing, Shrier does not shy away from the politics that pervade the field of gender dysphoria. It is a book that will be of great interest to parents, the general public, and mental health clinicians.” — Kenneth J. Zucker, Ph.D., adolescent and child psychologist, multi-publication scientist in this field, and Chair of the American Psychiatric Association DSM-5 Work Group on Sexual and Gender Identity Disorders.

Similarly, “Abigail Shrier’s book is thoroughly researched and beautifully written.” —Ray Blanchard, Ph.D., head of Clinical Sexology Services at the Centre for Addiction and Mental Health from 1995–2010.

Similarly, “For no other topic have science and conventional wisdom changed—been thrown away—more rapidly than for gender dysphoria. For a small but rapidly growing number of adolescent girls and their families, consequences have been tragic. This urgently needed book is fascinating, wrenching, and wise. Unlike so many of the currently woke, Abigail Shrier sees clearly what is in front of our faces and is brave enough to name it. *Irreversible Damage* will be

a rallying point to reversing the damage being done.” — J. Michael Bailey, Ph.D. professor of psychology at Northwestern University. These quotes are from the Amazon bookseller site at <https://www.amazon.com/Irreversible-Damage-Transgender-Seducing-Daughters/dp/1684510317>.

72. IDENTARIAN IDEOLOGY PROVIDES SOCIAL SUPPORT REWARDS FOR ADOLESCENTS TO ADOPT A GENDER DISCORDANT IDENTITY: Journalists have reported, “In many high schools, there is an ‘identity politics’ victims sweepstakes where white middle and upper middle class girls are simply left out of any coveted ‘oppressed victim’ status groups—thus the decision to become ‘transgender’ brings instant social support and acclaim from teachers and coaches for their courage in coming out.” Few question such personal transformation, even if the teen is deeply troubled, and even if the teen has no history of gender dysphoria. To even ask questions or explore alternative explanations could get the teacher, counselor, therapist, or physician in serious trouble.

73. 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.

74. GIVEN THE LACK OF RESEARCH, IT IS A 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.

75. 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., Työlajärvi, 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).

76. “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, Al-lyse 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.)

77. A DEVELOPMENTAL MODEL PROVIDES ALTERNATIVE HYPOTHESES TO THE UNEXAMINED “AFFIRMATION” 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. Dr. Levine has described the developmental model—an alternative hypothesis of gender dysphoria conceptualization and treatment that is more in keeping with the known science and involves reduced costs and lowered risk of permanent physical harm

(e.g., medically induced sterilization) to patients. He has written, “Gender dysphoria can be alternatively conceptualized in developmental terms, as an adaptation to a psychological problem that was first manifested as a failure to establish a comfortable conventional sense of self in early childhood. This paradigm starts from the premise that all human lives are influenced by past processes and events. Trans lives are not exceptions to this axiom. (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). Mental Health Professionals (MHPs) who think of gender dysphoria through this paradigm may work both to identify and address causes of the basic problem of the deeply uncomfortable self, and also to ameliorate suffering when the underlying problem cannot be solved. They work with the patient and (ideally) family to inquire what forces may have led to the trans person repudiating the gender associated with his sex. The developmental paradigm is mindful of temperamental, parental bonding, psychological, sexual, and physical trauma influences, and the fact that young children work out their psychological issues through fantasy and play.” (See Expert Report by Steven Levine, MD). A recent study documented “clustering” of new presentations in specific schools and among specific friend (peer) groups, pointing to social influences (See the Littman study at Brown University discussed above). Both of these findings strongly suggest cultural factors. From the beginning of epidemiological research into this arena, there have always been some countries, Poland and Australia, for example, where the patient sex ratios were reversed as compared to North America and Europe, again demonstrating a powerful effect of cultural influences (e.g. social contagion). See S. Levine (2018), Informed Consent for Transgendered Patients, J. of Sex & Marital Therapy, at 6, DOI: 10.1080/0092623X.2018.1518885; S. Levine (2016), Reflections on the Legal Battles Over Prisoners with Gender Dysphoria, J. American Academy Psychiatry and Law, 44, 236 at 238.

78. 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.).

79. 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.

80. ADDITIONAL OPINIONS TO BE DISCUSSED AS NEEDED: There are additional relevant data and important considerations regarding existing understanding of the role of physicians and other healthcare workers in alleviating suffering in patients who experience gender dysphoria due to sex-gender identity discordance that are not fully discussed in this report. They include:

- the inherent complexity of human psychological and physical development from birth to adulthood
- the relationship and differences between puberty and adolescence
- the molecular mechanisms of steroid hormone action in regulating cellular gene expression
- the physiology of sexual function including the hypothalamic-pituitary-gonadal axis in males and females and diseases that are associated with dysfunction of these processes
- the expansive and growing field of sex-specific personalized medicine in relation to human health
- the historical development and use of the scientific method (e.g. principles of hypothesis generation, testing of the null hypothesis, fundamentals of statistical analyses, differences between statistical and clinical significance)
- the design and conduct of human clinical trials
- the proper role of institutional review boards in the approval and supervision of clinical trials to mitigate risk
- the National Institutes of Health (NIH) processes for establishment of research priorities (e.g., research funding announcements), procedures for scientists to apply for grant funding, peer

review of research proposals, requirements for examining sex as a biological variable, safety monitoring, and requirements for sharing study results

— the process for gaining FDA approval for new medications and new medical indications for existing medications including objective assessment of relative risk versus benefit as demonstrated from properly controlled clinical trials

These topics will be discussed, as needed, to provide the court with the necessary scientific and medical information for proper litigation of this case.

81. A DETAILED, METHODOLOGICAL REVIEW OF THE BRANSTROM STUDY IS QUITE ESSENTIAL FOR UNDERSTANDING THE INTERNATIONAL TRANSITIONING TREATMENT CONTROVERSIES: Perhaps the most significant medical research study in the history of this field is the Branstrom study, which documented *no benefits* from transitioning treatments and suggested increased risks of suicide and anxiety following such treatment: In 2020, Branstrom, et al, published a research report claiming that “the longitudinal association between gender-affirming surgery and reduced likelihood of mental health treatment lends support to the decision to provide gender-affirming surgeries to transgender individuals who seek them.” This research appeared to be an historic first—empirical evidence that gender transition surgeries demonstrated long-term benefits. (See Branstrom R, Pachankis JE: Reduction in mental health treatment utilization among transgender individuals after gender-affirming surgeries: a total population study. *Am J Psychiatry* 2020; 177: 727–734.)

Almost immediately, however, the relevant scientific community—including multiple MD, PhD methodology experts—exposed the Branstrom study *as a series of methodological blunders and/or manipulative deceptions*. Multiple science experts concluded that, “These methodological shortcomings preclude any statement on the suitability of early surgery in persons seeking

treatment for gender non-congruence based on the results presented in this article.” They also noted evidence supporting the theory that these “errors” could well be purposeful and designed to support an ideological perspective when they noted, “people diagnosed with gender incongruence have a dramatically worse overall mental health outcome (after “transitioning” treatments) than the general population, which is, in fact, the answer to their stated aim and research question, but this (most essential) finding is not even referred to in the title or in the Conclusions section of the article.” (See Kalin, N.H., Reassessing Mental Health Treatment Utilization Reduction in Transgender Individuals After Gender-Affirming Surgeries: A Comment by the Editor on the Process by the Editor-in-Chief The American Journal of Psychiatry, *Am J Psychiatry* 2020; 177:764; doi: 10.1176/appi.ajp.2020.20060803; see also Anckarsäter, H., (MD, Ph.D.) and Gillberg, C., (M.D., Ph.D.) Methodological Shortcomings Undercut Statement in Support of Gender-Affirming Surgery, *Am J Psychiatry* 2020; 177:764–765; doi: 10.1176/appi.ajp.2020.19111117.

Additional methodology experts noted other serious flaws in the Branstrom study including: “For those whose last surgery was 10 or more years earlier, how many completed suicide, died of other causes, or left Sweden prior to study initiation?” *The authors failed to find out (or hid negative results)*. The methodology experts also noted, “A drop in hospitalizations for suicide attempts alone provides a very incomplete picture. When the data for such findings are accessible in the Swedish national registers, this omission is glaring. The lack of control subjects, the limited 1-year time frame, and the avoidance of examining completed suicides and psychiatric hospitalizations are substantial study shortfalls.” “*The study supports only weak conclusions about psychiatric medication usage and nothing decisive about suicidality*. In overlooking so much available data, *this study lacks the evidence to support its pro gender-affirmation surgery*

conclusion.” See Van Mol, A., Laidlaw, M. K., Grossman, M., McHugh, P., Gender-Affirmation Surgery Conclusion Lacks Evidence, *Am J Psychiatry* 177:8, August 2020 ajp.psychiatryonline.org 765.

Additional methodology experts noted, “The study confirms *the strong association between psychiatric morbidity and the experience of incongruity between gender identity and biological sex*. However, *the Branstrom study does not demonstrate that either hormonal treatment or surgery has any effect on this morbidity*. It seems that the main message of this article is that the incidence of mental health problems and suicide attempts is especially *high* in the year *after* the completion of gender-affirming surgery [It is telling that the authors somehow ignored this most essential finding -*Note this appears to be more potential evidence of deception, research fraud, and/or licensing violations.*]” See Curtis, D. (M.D., Ph.D.), Study of Transgender Patients: Conclusions Are Not Supported by Findings, *Am J Psychiatry* 2020; 177:766; doi: 10.1176/appi.ajp.2020.19111131.

Still more reviewers concluded, “The data presented in Figure 1 in the article support findings from previous studies showing that *transgender individuals have baseline mental health distress that is higher than that of the general population, but it is not possible to conclude from these data whether gender-affirming surgery relieves that distress.*” “Because of the *limitations in the study design*, it is not possible to determine the cause of the differences in mental health service utilization or whether true reductions in psychological distress actually occurred. (They failed to even measure increased suicides, etc.) “Therefore, the authors’ conclusion that the results of their study should be interpreted to support policies that provide gender-affirming surger-

ies *cannot be supported.*” See Malone, W. and Roman, S., Calling Into Question Whether Gender-Affirming Surgery Relieves Psychological Distress, *Am J Psychiatry* 2020; 177:766–767; doi: 10.1176/appi.ajp.2020.19111149.

Finally, yet another (MD, PhD) reviewer noted in detail, “The Branstrom and Pachankis study on mental health treatment and suicide attempts ... *is misleading because the study design is flawed.*” “The authors first found what was already known ... *the rate of psychiatric morbidity is much higher in persons with gender dysphoria compared with the general population (both before AND after “transitioning”).* The authors then explored if the risk for mental health treatment changes as a function of years since starting hormonal treatment. They find no effect (odds ratio = 1.0), but *they do find a trend toward increased risk of suicide attempts as a function of years since starting hormonal treatment.* They somehow *failed to publish this essential finding.* [Note: more potential evidence of deception, research fraud, or licensing violations.] In their key analysis, allegedly showing that gender-affirming surgery decreases risk for psychiatric treatment and suicide attempts, they relate these negative outcomes to the number of years since surgery. *Contrary to what the authors repeatedly claim, they do not employ a longitudinal design but conduct a retrospective analysis unfit for their research question.* First, the authors include only persons who were alive in 2014. *That means that those who died by suicide before 2014—and hence were at highest risk for suicide attempt—are excluded from the data and confound the results.* [Note: this appears to be still more potential evidence of deception, research fraud, and/or licensing violations.] Second, any analysis starting with a negative event is bound to find a decreased risk for related negative outcomes with increasing time after the event. To exemplify this point, *the rate of antidepressant treatment would decrease with time after a suicide attempt. This does not mean that suicide attempts cause a decrease in risk of antidepressant*

treatment; it is merely a case of regression toward the mean. Third, persons undergoing gender transition have, by definition, contact with mental health services in Sweden. After the transition, persons are followed up by endocrinologists and sometimes general practitioners; only those with persistent mental health issues are followed in psychiatric care. The authors' finding of lower rates of mental health treatment with increasing time after surgery is therefore not only a case of regression toward the mean, but it also follows from the standards of care and is not a proxy for improved mental health. Because the authors do not present data prior to gender affirming surgery, the study is uninformative with regard to the effects on psychiatric morbidity. Moreover, the authors miss the one conclusion that can be drawn: that the perioperative transition period seems to be associated with high risk for suicide attempt. [Note: still more potential evidence of deception, research fraud, or licensing violations.] Future research should use properly designed observational studies to answer the important question as to whether gender-affirming treatment affects psychiatric outcomes." See Landén, M. (M.D., Ph.D.) The Effect of Gender-Affirming Treatment on Psychiatric Morbidity Is Still Undecided, *Am J Psychiatry* 2020; 177:767–768; doi: 10.1176/appi.ajp.2020.19111165.

Yet another MD, PhD expert severely criticized the Branstrom, et. al. study noting: The results confirm what is already known, that is, that as a group, persons with gender dysphoria suffer from poorer psychiatric health than the general population. However, the title of the article implies that gender corrective surgery promotes mental health in this group, and the authors conclude in the Abstract section that the study “lends support to the decision to provide gender affirming surgeries to transgender individuals who seek them.” *In my opinion, this conclusion is not supported by the data presented in the article. [Note: more potential evidence of deception,*

research fraud, or licensing violations.] The most straightforward method to test whether surgery contributes to better psychological health would be to compare the health of those who underwent surgery with those who did not. Of the persons diagnosed with gender dysphoria presented in the article, 1,018 had undergone surgery, while 1,661 had not. There were 22 individuals who were hospitalized in 2015 for a suicide attempt. The authors do not state how many of these individuals had received surgery, but this may be calculated by combining the data from Table 3 and Figure 1 in the article. Figure 1 shows the proportion of persons with gender dysphoria who were hospitalized for suicide attempt in 2015, grouped according to the time that had elapsed since the last gender-corrective surgery. Table 3 shows the number of individuals with gender dysphoria, grouped according to the time elapsed since last surgical operation (“Time since last gender-affirming surgical treatment”). By combining these data, we can calculate that 10 of the suicide attempts (2.8% of 353) occurred during the same year that the last surgical correction was made (“perioperative” group in Figure 1). Two cases occurred 1 year after the last surgical correction (0.9% of 221) and one case 2–3 years after the last surgical treatment (0.5% of 198), while none occurred more than 3 years after the last surgery. Thus, 13 individuals (10 plus two plus one) of the 22 persons who were hospitalized for a suicide attempt in 2015 had undergone gender corrective surgery. Consequently, nine of them (22 minus 13) had not undergone any gender-affirmation surgery. This corresponds to an odds ratio of 2.37 (95% CI= 1.01–5.56, $p=0.047$). Hence, among the individuals examined in the study, the risk of being hospitalized for a suicide attempt was 2.4 times HIGHER if they had undergone gender-corrective surgery than if they had not. [Note this key finding was apparently hidden or not noticed by the authors ... more potential evidence of deception, research fraud, or licensing violations by the research authors.] Whether these factors involve a causal relationship (i.e., that surgery actually

worsens the poor mental health in individuals with gender dysphoria) cannot be determined from such a study. Nevertheless, *the data presented in the article do not support the conclusion that surgery is beneficial to mental health in individuals with gender dysphoria.*” See Wold, A. (M.D., Ph.D.) Gender-Corrective Surgery Promoting Mental Health in Persons With Gender Dysphoria Not Supported by Data Presented in Article, *Am J Psychiatry* 2020; 177:768; doi: 10.1176/appi.ajp.2020.19111170.

In addition, yet another pair of reviewers severely criticized the Bränström study noting: “The qualitative approximation of this curve with the reduction described by Branstrom and Panchankis (in their Figure 1) is striking. Therefore, accounting for the increase in mental health issues from 2005, together with an assumption of *increased* mental health treatment due to this surgery, fits *the data in the article and overturns the authors stated conclusions*, [Note ... more potential evidence of deception, research fraud, or licensing violations by the research authors.] suggesting that sex reassignment surgery is in fact associated with *increased* mental health treatment. See Ring, A. (PhD) and Malone, W., Confounding Effects on Mental Health Observations After Sex Reassignment Surgery, *Am J Psychiatry* 2020; 177:768–769; doi: 10.1176/appi.ajp.2020.19111169.

It should be noted, that after this very public exposure of the Branstrom debacle by multiple expert reviews, *the research authors admitted their conclusions were in error (confessed)* and that “more research” *is needed to answer the question of whether these treatments are helpful or harmful, long-term.* The authors admitted, “Studies employing prospective cohort designs are needed to better understand suicidality within this group and its associations with gender-affirming care... (and)... When comparing the mental health treatment outcomes between the two

groups (Table 1), we found *no significant difference* in the prevalence of treatment for mood disorders and *no significant difference* in the prevalence of hospitalization-suicide attempts.” and stunningly *they admitted they had failed to note that “individuals diagnosed with gender incongruence who had received gender-affirming surgery were MORE likely to be treated for anxiety disorder compared with individuals diagnosed with gender incongruence who had not received gender-affirming surgery”* and “While the design clearly establishes that individuals diagnosed with gender incongruence utilized more mental health care than the general population in 2015, especially during the perioperative period, like most extant research on the topic, *the design is incapable of establishing a causal effect* of gender affirming care on mental health treatment utilization. This retreat and mea culpa was published as Branstrom, R. and Pachankis, J., Toward Rigorous Methodologies for Strengthening Causal Inference in the Association Between Gender-Affirming Care and Transgender Individuals’ Mental Health: Response to Letters, *Am J Psychiatry* 2020; 177:769–772; doi: 10.1176/appi.ajp.2020.20050599.

(Emphases above are added.)

In sum, like the Branstrom debacle ... too many ideologically tainted and methodologically defective research studies suffer from these kinds of *serious errors, improper analyses and harmfully deceptive reports*. Such poorly designed and improperly conducted research studies continue to prevent gender transition “affirmation” treatments from being generally accepted by the relevant scientific community. Finally, the Error Rates for such unproven, experimental “treatments” as well as for the foundational politically-based transgender ideology, are unknown, un-peer-reviewed, and unpublished.

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, neonatology, 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.

82. 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 July 7, 2021.



Paul W. Hruz, M.D., Ph.D.

Curriculum Vitae

Date: 07/07/2021 05:15 PM

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Present Position

Associate Professor of Pediatrics, Endocrinology and Diabetes
Associate Professor of Pediatrics, Cell Biology & Physiology

Education

1987 BS, Chemistry, Marquette University, Milwaukee, WI
1993 PhD, Biochemistry, Medical College of Wisconsin, Milwaukee, WI
Elucidation of Structural, Mechanistic, and Regulatory Elements in 3-Hydroxy-3-Methylglutaryl-Coenzyme A Lyase, Henry Mizioro
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

**EXHIBIT
A**

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 Hospital

2000 - Pres Pediatric Endocrinologist, Inpatient Endocrinology Consult Service: 4-6 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

2020 - Pres WU ICTS Clinical and Translational Research Funding Program (CTRFP) Review Committee

Department/Division

2008 – 2016 Director, Pediatric Endocrinology & Diabetes Fellowship Program

2014 – 2017 Director, Pediatric Diabetes Research Consortium

Hospital

2000 - Pres Attending Physician, St. Louis Children's Hospital

Medical Licensure and Certifications

1997 - Pres Board Certified in General Pediatrics

2000 - Pres MO State 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

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	Endocrinology and Metabolism Clinics of North America

Community Service Contributions

2009 - 2017 Boy Scouts of America CPR Red Card Training

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
2017 - Pres	Catholic Medical Association
2018 - Pres	American College of Pediatricians
2019 - Pres	Society of Catholic Scientists

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
2018 - 2021	LEAP Innovator Challenge Novel Treatment of Fatty Liver Disease Role: Principal Investigator Total cost: \$68,500.00

Current Non-Governmental Support

2017 - 2021	Matching Micro Grant Novel Treatment of Fatty Liver Disease (CDD/LEAP) 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

Pending Non-Governmental Support

2021	WUSM ICTS Special Translation Award Request (STAR)

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 Exercise 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 Aiyegoro, 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

Journal Articles

1. Hruz PW, Narasimhan C, Mizioro 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, Mizioro 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, Mizioro 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, Mizioro HM. 3-Hydroxy-3-methylglutaryl dithio-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, Mizioro 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](#)
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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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45. Zhang Y, Higgins CB, Mayer AL, Mysorekar IU, Razani BB, Graham MJ, Hruz PW, DeBosch BJ. TFEB-dependent Induction of Thermogenesis by the Hepatocyte SLC2A Inhibitor Trehalose. *Autophagy*. 2018. PMID:[29996716](#)
46. Emfinger CH, Yan Z, Welscher A, Hung P, McAllister W, Hruz PW, Nichols CG, Remedi MS. Contribution of systemic inflammation to permanence of KATP-induced neonatal diabetes in mice. *Am J Physiol Endocrinol Metab*. 2018;315(6):E1121-E1132. PMCID:[PMC6336961](#) PMID:[30226997](#)
47. Heitmeier MR, Hresko RC, Edwards RL, Prinsen MJ, Ilagan MXG, Odom John AR, Hruz PW. Identification of druggable small molecule antagonists of the Plasmodium falciparum hexose transporter PfHT and assessment of ligand access to the glucose permeation pathway via FLAG-mediated protein engineering. *PLoS One*. 2019;14(5):e0216457. PMCID:[PMC6508677](#) PMID:[31071153](#)
48. Hruz PW. Deficiencies in Scientific Evidence for Medical Management of Gender Dysphoria. *Linacre Q*. 2020;87(1):34-42. PMCID:[PMC7016442](#) PMID:[32431446](#)
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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](#)

Book 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.

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 Hospital
2000 - Pres	Pediatric Endocrinologist, Inpatient Endocrinology Consult Service: 4-6 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

**IN THE UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF ARKANSAS
CENTRAL DIVISION**

DYLAN BRANDT, et al.,

PLAINTIFFS,

v.

No. 4:21-CV-00450-JM

LESLIE RUTLEDGE, et al.,

DEFENDANTS.

DECLARATION OF DR. PATRICK W. LAPPERT

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

I. KNOWLEDGE, TRAINING, AND EXPERIENCE

1. **Education and Training:** I received my Bachelor of Arts in Biological Sciences at the University of California, Santa Barbara, 1979. There I was engaged in research in cell membrane physiology with Dr. Philip C. Laris, studying stoichiometry of the sodium: potassium ATPase pump. I received my M.D., Doctor of Medicine degree at the Uniformed Services University of the Health Sciences, 1983 at Bethesda, Md. I served my General Surgery Residency at the Naval Hospital Oakland/UC Davis East Bay Consortium, 1987-1991 and served as Chief Resident, Department of Surgery, Naval Hospital Oakland, 1990-1991. I also served a Plastic Surgery Residency at the University of Tennessee-Memphis, 1992-1994. My professional background, experience, and publications are described in more detail in my curriculum vitae, which is attached as Exhibit A to this declaration.

2. **Board Certifications in Medicine:** I have been Board Certified in Surgery (American Board of Surgery, 1992), in Plastic Surgery (American Board of Plastic Surgery, 1997; American Board of Plastic Surgery, 2008).

3. **Medical Staff Appointments:** I served as the Staff General Surgeon at the Naval Hospital Oakland, CA 1991-1992 and as Associate Professor of Surgery, UC Davis-East Bay,



1991-1992. I also served as a Plastic and Reconstructive Surgeon, Naval Medical Center, Portsmouth, Virginia, 1994-2002 and as Chairman, Department of Plastic and Reconstructive Surgery, Naval Hospital Portsmouth, Virginia, 1996-2002. I later served as Clinical Assistant Professor, Department of Surgery, Uniformed Services University of the Health Sciences, 1995-2002 and as Founding Director, Pediatric Cleft Palate and Craniofacial Deformities Clinic, Naval Hospital Portsmouth, Virginia, 1996-2002 also as the Founding Director, Wound Care Center, Naval Hospital Portsmouth, Virginia, 1995-2002. I have also served as a Staff Plastic Surgeon in Nebraska and Alabama.

4. **U.S. Surgeon General Service:** I served as a Specialty Leader, Plastic and Reconstructive Surgery, Office of the Surgeon General-USN, 1997-2002.

5. **Faculty Appointments:** I served as Teaching Faculty at Eastern Virginia Medical School, Division of Plastic Surgery, 1995-2002. I also served on the teaching faculty of the Via College of Osteopathic Medicine, 2017-2020.

6. **Military Service:** I served as an Aviation Officer Candidate, Naval Aviation Schools Command, NAS Pensacola, 1978 and was Commissioned an Ensign, MC, USNR 1979 and Commissioned as a Lieutenant, MC, USN 1983. I served as a Designated Naval Flight Surgeon, Naval Aerospace Medical Institute, 1985, and I was Assigned Marine Fighter/Attack Squadron-451, serving as Flight Surgeon, and serving as Radar Intercept Officer in the Marine F-4S Phantom, accumulating 235 flight hours, and trained for qualification as an Air Combat Tactics Instructor. I was deployed to the Western Pacific as UDP forward deployed fighter squadron in Korea, Japan, and the Philippines. I served in the US Navy for 24 years, and I served in the USMC for 3 years. I retired with the rank of Captain, USN in 2002.

7. **Publications - Peer Reviewed Medical Journals:** Lappert PW. Peritoneal Fluid in Human Acute Pancreatitis. *Surgery*. 1987 Sep; 102(3):553-4; Toth B, Lappert P. Modified Skin Incisions for Mastectomy: The Need for Plastic Surgical Input in Preoperative Planning. *J Plastic and Reconstructive Surgery*. 1991; 87 (6): 1048-53; Lappert P. Patch Esophagoplasty. *J Plastic and Reconstructive Surgery*. 1993; 91 (5): 967-8; Smoot E C III, Bowen D G, Lappert P, Ruiz J A. Delayed development of an ectopic frontal sinus mucocoele after pediatric cranial trauma. *J Craniofacial Surg*. 1995;6(4):327–331; Lappert PW. Scarless Fetal Skin Repair: “Unborn Patients” and “Fetal Material”. *J Plastic and Reconstructive Surgery*. 1996 Nov; 98(6): 1125; Lappert PW, Lee JW. Treatment of an isolated outer table frontal sinus fracture using endoscopic reduction and fixation. *Plastic and Reconstructive Surgery* 1998; 102(5): 1642-5.

8. **Publications - Medical Textbooks:** Wound Management in the Military. Lappert PW, Weiss DD, Eriksson E. *Plastic Surgery: Indications, Operations, and Outcomes*, Vol. 1; 53-63. Mosby. St. Louis, MO 2000.

9. **Operations and Clinical Experience - Consultations and Discussions:** As a physician and surgeon, I have treated many thousands of patients in 7 states and 4 foreign nations. My practice has included Primary Care, Family Medicine, Aerospace Medicine, General Surgery, Reconstructive Surgery for combat injured, cancer reconstructive surgeries including extensive experience with microvascular surgery, Pediatric Congenital Deformity, and the care of chronic wounds. I have practiced in rural medicine, urban trauma centers, military field hospitals, university teaching hospitals, and as a solo private practitioner. In my private practice I have had occasion to treat many self-identified transgender patients for skin pathologies related to their use of high dose sex steroids, laser therapies for management of facial hair both in transi-

tioners and detransitioners. I have performed breast reversal surgeries for detransitioning patients. My practice is rated as “LGBTQ friendly” on social media. I have consulted with families with children who are experiencing gender discordance. I have given many presentations to professional meetings of educators and counselors on the subject of transgender, and the present state of the science and treatment. I have discussed the scientific issues relevant to the case with many physicians and experts over a number of years and also discussed related issues with parents and others.

10. **Retained as an Expert Witness - Compensation - Bases for Opinions:** I have been retained as an expert witness by the State of Arkansas for the defense in connection with this litigation. I have actual knowledge of the matters stated in this declaration. 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. To formulate opinions in this case I have reviewed many scientific publications, case filings, and the plaintiffs’ witness declarations.

11. **Expert Report Limitations:** My opinions and hypotheses in this matter are — as in all expert witness 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. All opinions are offered to a reasonable degree of medical certainty. 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.

II. GENDER AFFIRMING TREATMENTS ARE EXPERIMENTAL.

12. “Gender affirming” treatments remain experimental as the historic Branstrom study and National Reviews in England, Sweden, and Finland indicate. “Gender affirming” treatments (i.e., hormones and surgery) have not been proven effective, or even competently tested. Such “treatments” are not generally accepted by the relevant scientific community and have no documented error rates (See, Daubert/Kumho). Patients who experience a gender identity that is discordant with biological sex have an alarmingly high incidence of serious psychosocial morbidity including depression, anxiety, eating disorders, substance abuse, HIV infection, suicidality, and homelessness. Connolly, M. D., M. J. Zervos, C. J. Barone, C. C. Johnson, and 2nd C. L. Joseph. 2016. *“The Mental Health of Transgender Youth: Advances in Understanding.”* Journal of Adolescent Health 59:489–95. :10.1016/j.jadohealth.2016.06.012. While a need for effective treatment modalities is clear, there are currently significant deficiencies in our understanding of the etiology of this condition, of the risks and benefits of the current experimental (unproven, untested) medical interventions, and of the long-term success of various “affirmation” treatments in achieving the primary desired goal of reducing mental illness including reductions in suicide risk.

13. Multiple recent studies and reviews including the recent national science summaries and guidelines from England-NICE, Sweden, Finland, the Cochrane Review, the British Royal College of Psychiatrists and others all document significant deficits in our current understanding of these complex disorders and significant defects in the “low quality,” contradictory, and controversial existing evidence. As we strive to provide real, effective, and sustained treat-

ment to patients who experience gender dysphoria within established ethical boundaries, it is essential that we properly and scientifically research the causes of gender dysphoria as well as conduct competent, properly conducted randomized clinical trials and long-term treatment outcome studies. These basic, foundational tasks — the tasks that make experimental procedures actual, proven treatments worthy of trust — have *never been accomplished in the highly controversial field of the transgender treatment industry*. Why? Suffering and vulnerable patients and their families continue to wait for this basic, foundational scientific work to be completed. Meanwhile, affirmation “treatments” are properly viewed as experimental. (See detailed citations in the “Notes” section of this report below).

14. The science and medical world have — in just the past few years — become increasingly aware of and deeply concerned about the glaring science and ethical defects of the transgender treatment industry. For example, the very recently released 2020 Finland national science review and guidelines documented “a lack of quality evidence to support the use of hormonal interventions in adolescents with gender dysphoria.” The new strict Finnish guidance prioritizes psychological therapy over treatment with hormones or surgery, thus directly contradicting the non-science-based association protocols of WPATH. The 2020 Finland national science review and guidelines also document the ongoing lack of scientific basis for the transgender treatment industry, stating “Only limited research has been conducted on transgender identity and other gender identity conflicts, and comparative studies are very rare.” In sum, the Finland National Science Review and Guidelines, like the new Sweden Review and Guidelines, the Cochrane Review, and other reviews, and the collapse and recantation of the 2020 Branstrom long-term treatment outcome study (which proved *no benefits* to these “treatments”) claims, all

appear contrary to the opinions of plaintiffs’ experts, WPATH, and the endorsements of professional associations. (See detailed citations in the “Notes” section of this report below).

15. Meanwhile, practitioners in this troubled field continue to offer defective research and politicized endorsements from politicized, union-like associations (WPATH, APA, ACP, etc.) rather than competent, credible, valid, and reliable peer-reviewed and published scientific evidence. The plaintiffs’ experts failed to even discuss the serious defects and methodological limits of transgender medicine data and experimental practices. Fifty years of experimenting is enough. It is time for the transgender treatment industry to come up with real, competently constructed scientific evidence that they help more people than they hurt. As the recent national science reviews from England, Sweden, the Cochrane Review, and Finland have all noted, it is time to step back, slow down, and prudently investigate a range of approaches — including years of careful psychotherapy prior to experimental sterilizing “treatments” — to vulnerable patients struggling with gender discordance issues. (See detailed citations in the “Notes” section of this report below).

III. THE ETHICS OF PLASTIC SURGERY

A. “Chest Masculinization” in Natal Females is Not Ethically Equivalent to Mastectomies for Breast Cancer.

16. When mastectomy is performed for the management of breast cancer, or to mitigate the proven risk of developing breast cancer in women, it is done on the basis of objective diagnoses either by pathological examination of biopsy tissue, or as in the case of prophylactic mastectomy, on the basis of genetic analysis that shows known markers of increased risk of developing breast cancer. These tests (microscopic examination of tissue specimens, detection of cell surface markers with proven association with malignancy, and genetic screening of at-risk patients) have known positive predictive value for the diagnosis of breast cancer, and these tests

have known error rates that can be used when obtaining informed consent for mastectomy. The validity of these tests has been proven using scientific methodologies that produce high quality evidence in longitudinal population studies with control populations, and very long follow up. As the result, when a woman gives consent for mastectomy to control or prevent the potentially lethal disease, it is with a clear and proven evaluation of the risks and benefits that consent is obtained. Mastectomy is being performed based upon an objective diagnosis of a potentially lethal condition, and the surgical procedure has proven benefit in management of that condition.

17. In stark contrast, this is not the case when mastectomy is performed to “masculinize” the chest of girls and women who self-identify as transgender or who self-report symptoms of dysphoria. Otherwise healthy breasts are being removed on the basis of a diagnosis that is made by the patient since there are no tests with known error rates that can be used to predict who will benefit from this disfiguring and irreversible surgery. The claim is made that chest masculinization has proven benefit in reducing dysphoria and the associated risk of suicide. But published studies that make this claim of benefit offer evidence that is low to very low quality, typically small case collections with self-selection bias, very short follow up, and no case controls.

18. The best data presently available on the long-term effects of medical and surgical transitioning are long-term, longitudinal, population based studies. For example, Dehjne, et al., examined the putative long-term benefit of full transitioning (including hormonal and surgical treatments) found in the Swedish medical database. (See Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden; Cecilia Dhejne, Paul Lichtenstein, Marcus Boman, Anna L. V. Johansson, Niklas Långström, Mikael Landén; PLOS One February 22, 2011 <https://doi.org/10.1371/journal.pone.0016885>). That database includes

all persons in the Swedish medical system, from pre-natal to death. It reports all episodes of care and all demographic information in a uniform vocabulary. Furthermore, Sweden has been on the forefront of “gender affirmation” long before the American medical system seriously considered its claims. Because of the nature of Sweden’s database, it is possible to study a cohort of patients that exactly matches the inquiry group with regards to age, sex, economic status, etc. It is possible to ask precisely such questions as, “What is the likelihood that a fully transitioned transgender male will be hospitalized for psychiatric illness when compared to the age/sex matched control group?” or “What is the relative risk of suicide in transgender persons, when compared to age/sex matched controls?”

19. Why are such longitudinal, population based studies superior to the case-collection/case series methodology? Because confounding variables such as age, sex, and self-selection biases are removed. In the flawed case-collection methodology, the reported cases are typically only those who return for follow up. You have no way of knowing if the patient had a good outcome or didn’t return for follow up because they were in a psychiatric hospital, were incarcerated, or committed suicide. In the Swedish longitudinal study, the suicide is in the same database, as are the other issues of hospitalization, incarceration, and addiction treatment, among other rates of comorbidity. Thus the longitudinal population study can give us what is called a “hazard ratio” for a particular study population (patients who have completed transgender transition).

20. What did this Swedish study show us? It showed us that the risk of completed suicide in all transgender persons is *19.1 times higher* than in the control cohort. If you look only at patients who have transitioned — patients after “treatment” — from female to “male presentation,” the risk of completed suicide is *40 times higher* than in the general population.

(Note: this finding is consistent with the historic Branstrom 10yr follow up study, which found no benefits to “transitioning treatments” but did note an increased risk of serious suicide attempts and anxiety disorders AFTER “treatment.” (Correction to Bränström and Pachankis, *Am J Psychiatry* 177:8, August 2020; see detailed citations in the “Notes” section of this report below).

21. Another cautionary note was added to the literature review by the reputed Cochrane Review, a UK based international association of researchers who examine the quality of scientific evidence used in medical decision making. The Cochrane Review recently published findings concerning the medical evidence used to support the decision to give young women cross sex hormones as part of the transition process. The authors summarize the world literature review thus: “We found insufficient evidence to determine the efficacy or safety of hormonal treatment approaches for transgender women in transition. This lack of studies shows a gap between current clinical practice and clinical research.” (Does hormone therapy help transgender women undergoing gender reassignment to transition? See, Haupt C, Henke M, Kutschmar A, Hauser B, Baldinger S, Saenz SR, Schreiber G., Cochrane Review, 28 Nov 2020).

22. Similar issues of very poor, low quality scientific support for chest masculinization surgery can be seen in a recent article by Tolstrup et al. published in the journal *Aesthetic Plastic Surgery* (See Anders Tolstrup, Dennis Zetner, Jacob Rosenberg, Outcome Measures in Gender-Confirming Chest Surgery: A Systematic Scoping Review, *Aesthetic Plast Surg* 2020 Feb;44(1):219-228. doi: 10.1007/s00266-019-01523-1. Epub 2019 Oct 29). The article reports a comprehensive review of the world literature concerning the efficacy of “gender confirming” chest surgery in transgender patients. The authors found 849 articles on the subject, published in peer reviewed medical journals. Of these 849 articles, only 47 could be included in the review. This means that only 5.5% of all the published, peer-reviewed transgender surgery articles

demonstrated even rudimentary scientific rigor. Of those 47 articles, the authors report that only 29 of the articles addressed mental health outcomes (3.4% of all the articles). What is startling is that the mental health outcomes were judged only on the basis of uncorroborated, untested, and unassessed patient subjective reporting with descriptors that varied so widely from article to article that results could not even be compared. The authors summarize by saying, “Evaluation of outcomes in gender-confirming chest surgery showed large variations in reporting, and further streamlining of reporting is therefore required to be able to compare surgical outcomes between studies.” None of these negligent articles even bothered to examine rates of psychiatric hospitalization, substance abuse, self-harm behaviors, and suicide. This tells us that the main reason for performing these surgeries (psychological distress and suicide risk) isn’t even evaluated with regard to efficacy.

23. An example of an article with very low quality data, reckless (now banned practices), and methodology, published in a “leading journal,” and promoted as evidence for the efficacy of “chest masculinization” surgery makes this fact very clear. The lead author (Olson-Kennedy, a leading national advocate for the transgender treatment industry) is a board certified pediatrician who leads the gender clinic for the Los Angeles Children’s Hospital. The article appeared in 2018 (See J. Olson-Kennedy, J. Warus, MD1, et al., *Chest Reconstruction and Chest Dysphoria in Transmasculine Minors and Young Adults; Comparisons of Nonsurgical and Postsurgical Cohorts.*, JAMA Pediatr. 2018;172(5):431-436. doi:10.1001/jamapediatrics.2017.5440). In their summary of findings, the authors reported that “chest dysphoria” is common among “trans males” (natal females seeking to present as males), and claimed that dysphoria is “decreased by surgery.” They claim that regret for surgery is “rare.” The article reports breast removal surgery on at least one girl aged 13 years. (Note that this reckless, experimental

practice has now apparently been abandoned as unethical/experimentation on children by England, Sweden, and Finland). The average age of patients in the study was 19. Children were entered into the study through recruitment from among patients visiting the clinic and by telephone over a six month period. The authors found that of the patients recruited from among visitors to the clinic (convenience sampling) there was an abundance of non-operated patients, so they were forced to reach out to all the post-surgical patients by phone. Twenty-six percent of the clinic's post-surgical patients could not be reached for various reasons including no working phone, or failure to respond to multiple messages. The 26% drop-out rate is never even questioned by these authors. Were surgical patients lost to follow up because of dissatisfaction, psychiatric hospitalization, or *suicide*? This problem is called "self-selection bias," and it is evidence of careless study design. Of the remaining 74% of patients, only 72% completed the survey. This is a second example of self-selection bias. Why would some post-surgical patients who had been successfully contacted, not complete the survey? The authors — demonstrating multiple levels of confirmation bias — do not even ask such essential questions. (See detailed citations in the "Notes" section of this report below).

24. In the study, dysphoria was evaluated using what the author called "a novel measure," which amounted to a series of subjective questions about happiness that was in part designed by the adolescent test subjects themselves. Essentially, the methodology used an entirely unvalidated ("junk science") test instrument, with no known error rates and no proven predictive power. Furthermore, the post-surgical patients were administered the survey at widely varying time intervals post-surgery. The longest interval between surgery and the satisfaction survey was 5 years, but children less than a year post-surgery were included in this obviously flawed sample, and yet the authors claim evidence of "negligible regret." This is a remarkable, misleading, and

deceptive claim given that long-term, longitudinal population studies show that there is a dramatic rise in post-surgical problems such as depression, hospitalization, substance abuse, and suicide beginning at around 7 years post-surgery (Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden; Cecilia Dhejne, Paul Lichtenstein, Marcus Boman, Anna L. V. Johansson, Niklas Långström, Mikael Landén; PLOS One February 22, 2011 <https://doi.org/10.1371/journal.pone.0016885>). Surely the authors are familiar with the world literature on transgender outcomes?

25. Having deceptively or negligently promised in the introduction to their paper that “chest dysphoria” is reduced by surgery, at the conclusion the authors confessed to the fact that the study design and execution produced very low quality data that is not useful for patient selection, or prediction of outcomes. They even confessed that the study does not address the efficacy of surgery in improving outcomes regarding the single most compelling reason for performing the operation: mitigation of depression and suicide. The authors write: “An additional limitation of the study was the small sample size. The nonsurgical cohort was a convenience sample, recruited from those with appointments during the data collection period. There could be unknown imbalances between the nonsurgical and postsurgical cohorts that could have confounded the study findings.”

26. Finally, the authors did not even bother to validate their “Chest Dysphoria Scale.” Such a “made-up” scale is unlikely to accurately represent distress or correlate with properly validated measures of quality of life, depression, anxiety, or functioning.” Their own analysis at the conclusion of the paper directly contradicts their own deceptive claim made in their introduction.

27. This is the kind of “junk science” that is used to support transgender medicine and surgery. It was written by board certified physicians who practice in one of the nation’s largest pediatric gender clinics and published in a peer-reviewed medical journal. It is essentially useless in making any clinical decisions regarding who should be offered surgery, what is the likelihood they will benefit from it, what is the likelihood they will regret their decision, and most importantly, whether their risk of suicide would be reduced.

28. Because of the very low quality scientific support for mastectomy in the management of gender dysphoria, valid consent would require that these procedures be described as experimental, would need the approval of ethics panels to monitor human experimentation, and would require the use of valid controls found in long-term, longitudinal population based study models. These are the kinds of patient protections now endorsed in England, Sweden and Finland but still ignored in the US environment where proper scientific critiques of such studies can get faculty “cancelled.” (See detailed citations in the “Notes” section of this report below).

29. Even though the transgender treatment industry has been performing these surgeries for over 50 years, gender treatment centers continue to publish the same low quality, methodologically defective studies based upon collected cases that are degraded in value by self-selection bias, confirmation bias, and short-term follow-up, while continuing to deceptively claim that such defective research provides a sufficient scientific basis for performing irreversible, disfiguring, and ultimately sterilizing hormonal treatments and surgeries. (See detailed citations in the “Notes” section of this report below).

B. “Chest Masculinization” in Natal Females is Not Ethically Equivalent to Gynecomastectomy.

30. Gynecomastectomy is the surgical treatment of gynecomastia, a fairly common condition in which males develop female-type breast gland tissue. Proponents of “masculinization” mastectomy in natal females erroneously equate the ethics of removing healthy breast tissue from these patients with the removal of abnormal breast tissue in men (gynecomastia). In the case of gynecomastectomy in male patients, the operation is performed to remove the objectively diagnosed presence of female type glandular breast tissue present in a male patient. Physical examination demonstrates the presence of a dense retro-areolar mass which is tender and sometimes disfiguring. Pathological examination of the removed tissue will demonstrate the presence of female-type fibroglandular tissue in a male patient. This is an objectively abnormal condition. It should further be noted that in the absence of such abnormal, female-type fibroglandular tissue, chest recontouring is considered to be cosmetic, and is typically not paid for by third-party payors.

31. I have never read a peer reviewed journal article which discusses the indications for gynecomastectomy that included any claim to reduce major depression and suicide. This is because any male patient seeking removal of abnormal, female-type, breast tissue who reported suicidal ideation would be considered incompetent to give consent, and would require a psychiatric evaluation and treatment to manage suicidal thinking before being considered for surgery.

C. “Chest Masculinization” in Natal Females is Not Ethically Equivalent to Breast Reduction.

32. It should be obvious that “Chest Masculinization” surgery in natal females is not ethically equivalent to breast reduction surgery in non-transgender females. In the case of breast reduction for females with excessively large breasts (macromastia, or gigantomastia), the operation is performed to relieve a debilitating orthopedic complaint of neck, back, and shoulder pain

associated with the postural/mechanical effects of the weight of the breasts. These patients experience significant activity restriction and chronic pain that is not relieved by medical management or physical therapy. Furthermore, there is voluminous actuarial data, based upon many years of longitudinal population based study by medical insurance agencies that is used to predict who will benefit from surgery, and who will not. These physical, objective tests, based upon the actual measurement of the breasts, and the patient's overall body habitus, have known error rates that can be used to predict the likelihood that a breast reduction will relieve the orthopedic complaints of neck, back, and shoulder pain. When the tissue specimens are submitted to pathology, they are weighed in order to ensure that enough tissue has been removed so that there will be a very high likelihood that the surgery will relieve the orthopedic condition of neck, back, and shoulder pain (Accuracy of Predicted Resection Weights in Breast Reduction Surgery, Theodore A. Kung, MD, Raouf Ahmed, MBBS¹ Christine O. Kang, MPH,¹ Paul S. Cederna, MD, and Jeffrey H. Kozlow, MD; *Plast Reconstr Surg Glob Open*. 2018 Jun; 6(6): e1830.

33. Based upon that, adequate pre-operative consent can be obtained. The supporting data is based in very high quality methodology. There is no quality research data, no pre-operative test or study, and no known error rates, that can be used to predict the likelihood that any child suffering from gender dysphoria will benefit from the experimental procedures of mastectomy and chest "masculinization." As noted above, because of the very low quality data, transgender chest masculinization is at best experimental and at worst, should be viewed as a form of medical child abuse — it is important to note that Finland, Sweden, and the UK appar-

ently now all agree with this analysis, as they have all retreated from such reckless surgical procedures for minors — similar to what Arkansas’s science-informed, responsible legislature has now done. (See detailed citations in the “Notes” section of this report below).

34. It is crucial to remember that “chest masculinization” of healthy breast tissue results in a complete loss of function, that this loss is two-fold (breast feeding and erotic sensibility), and the cause of the loss is two-fold (gland removal and severing of the intercostal nerve). (See Breast Reduction with Use of the Free Nipple Graft Technique; Stephen R. Colen, MD; Aesthetic Surgery Journal, (Breast Reduction with Use of the Free Nipple Graft Technique; Stephen R. Colen, MD; Aesthetic Surgery Journal, Volume 21, Issue 3, May 2001, Pages 261–271, <https://doi.org/10.1067/maj.2001.116439>).

35. If a patient who undergoes “chest masculinization” should regret the surgery, they do have the option of breast reconstruction. But all that will be produced is the appearance of a breast. The patient will have lost the function of breast feeding. Additionally, the most commonly performed “masculinization” surgery involves the removal of the nipples, and subsequent re-attachment in the form of a nipple graft. Those nipples will have lost their native nerve connections that provoke erotic sensibility. All that can be hoped for is the eventual random ingrowth of local skin sensation, but there will never be erotic sensation because the particular branch of the fourth intercostal nerve which communicates with particular centers in the brain responsible for oxytocin release and erotic provocation will have been permanently severed. This means that breast function has been completely and irreversibly sacrificed for the sake of producing a cosmetic result (a masculine appearing chest). This is the exact opposite of the goals of any reconstructive surgery. It must therefore be understood that “chest masculinization”

is a cosmetic procedure that has violated the most essential principle of cosmetic surgery: never sacrifice function for the sake of a cosmetic result.

D. Masculinizing and Feminizing Chest Surgeries are Not “Medically Necessary.”

36. Supporters of “transitioning” treatments justify surgical treatment based upon “medical necessity.” They claim that gender dysphoria can lead to debilitating anxiety and depression, as well as serious incidents of self-harm, including self-mutilation, suicide attempts, and suicide. Yet with only a single exception, in the studies they cite no measures are made of the effects of surgery on what is claimed to constitute the “medical necessity” for these procedures.

37. In contrast, the Branstrom study cited in detail in the Notes Section of this declaration documented no reliable benefits for transgender surgery/hormonal treatments and no reduction in suicide and even an *increase* in serious suicide attempts requiring hospitalization in patients receiving surgery. These recent, long-term, published, peer reviewed, credible research findings are quite contrary to the claims of supporters of “transitioning treatments” — as are the National Science Reviews in this area from England-NICE, Sweden, and Finland. (See detailed citations in the Notes section in this declaration).

38. Scientific rigor would demand an examination of such outcomes as: rates of substance abuse, psychiatric hospitalization, self-harm, or suicide, and how they were changed by surgery. One paper does ask these crucial questions concerning efficacy in a very comprehensive, long term, longitudinal population cohort study which actually shows the opposite of what plaintiffs’ experts’ claims for these patient outcomes. When followed beyond 8 years post-operatively, this paper shows patients receiving plaintiffs’ experts’ treatments have the same alarmingly high rates of hospitalization, substance abuse, self-harm, and completed suicide as persons

who have had no medical or surgical intervention. The fact that the citation is included by plaintiffs' experts, but never discussed in his opinion regarding efficacy is troubling. In summary, on the issue of the safety and efficacy of these surgeries, the scientific support is very weak, while the scientific evidence rejecting the hypothesis of efficacy is remarkably strong (See Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden; Cecilia Dhejne, Paul Lichtenstein, Marcus Boman, Anna L. V. Johansson, Niklas Långström, Mikael Landén; PLOS One February 22, 2011 <https://doi.org/10.1371/journal.pone.0016885>)

39. The surgical removal of the breasts, and the re-contouring of the chest through liposuction is a common procedure for women who seek to present as men. These operations are performed in both men and women, for a variety of reasons, are very safe, and typically performed in the outpatient setting. It is important to understand that the only way of distinguishing cosmetic breast surgery from "medically indicated" surgery is based upon the diagnosis of underlying pathology. For example, breast reduction may be cosmetic, or it may be medically indicated. In both cases, the patient presents with a complaint that her breast are too big. The distinction between cosmetic breast reduction and medically indicated breast reduction is based upon the presenting symptoms of orthopedic problems caused by the weight of the breasts, but even then, the weight of the removed tissue is factored into the objective verification that the surgery was "medically necessary."

40. The same issues are at stake in breast enhancement for men seeking to present as women. Cross-sex hormones will have caused varying degrees of gynecomastia (breast enlargement in men). Surgical enhancement procedures are exactly the same in both men and women.

Medically necessary surgery in women is based upon the diagnosis of an objective medical condition, such as Poland's syndrome (congenital absence of a breast), surgical absence of the breast following cancer care. In men, the objective diagnosis of gynecomastia might warrant surgery based upon medical necessity, but it would be a removal of tissue. A rare diagnosis of breast cancer in a man might warrant chest wall reconstruction after cancer care. On the other hand, cosmetic surgery of the breast is entirely about the subjective feelings of the patient, and that is all that we have in the case of the self-identified transgender patient.

41. In the case of transgender chest surgery, the diagnosis is based on the patient's subjective report of dysphoria, but the medical necessity is based on the expectation that surgery will relieve the patient of the risk of, among other things, major depression, self-harm behaviors, and suicide. None of the papers typically cited by supporters of "transitioning treatments" address themselves to the question of medical necessity for either masculinizing surgery, or feminizing surgery. They only address technical issues, management of complications, and subjective outcomes that employ precisely the same language that is used to assess cosmetic surgery of the breast. In summary, the medical necessity of transgender chest surgery is not supported by scientific evidence, and appears to be firmly in the category of cosmetic surgery.

E. Virtually All Transgender Patients are Born with Normal, Healthy Sex Organs and No Scientifically Validated Reason to Surgically Damage Them.

42. Sex is not "assigned at birth" but permanently "assigned" at conception by DNA. Medical technology can be used to determine a fetus's sex before birth. It is thus not scientifically correct to talk of doctors "assigning" the sex of a child at birth; almost anyone can accurately and reliably identify the sex of an infant by genital inspection with approx 99.9% accuracy. Every nucleated cell of an individual's body is chromosomally identifiably male or female—XY or XX. Claims that patients can — via hormonal and surgical treatments — obtain a

“sex change” or a “gender transition” process are misleading and scientifically impossible. In reality, the typical “transgender” gender discordant patient has normal healthy sex organs but struggles with gender discordant feelings and perceived identity — a psychiatric and not a medical problem.

F. Detransitioners are Real and Surgeons Have No Diagnostic Tools to Identify Who They Will Be.

43. The phenomenon of desistance or regret experienced later than adolescence or young adulthood, or among older transgender individuals, has to my knowledge not been quantified or well-studied. But it is a real phenomenon. I myself have worked with multiple individuals who have abandoned a trans female identity after living in it for years, and who would describe their experiences as “regret.” More dramatically, a surgical group prominently active in the sexual reassignment field has published a report on a series of seven male-to-female patients requesting surgery to transform their surgically constructed female genitalia back to their original male form. See Djordjevic ML, Bizic MR, Duisin D, Bouman MB, Buncamper M. Reversal Surgery in Regretful Male-to-Female Transsexuals After Sex Reassignment Surgery. *J Sex Med.* 2016 Jun;13(6):1000-7. doi: 10.1016/j.jsxm.2016.02.173. Epub 2016 May 4. PMID: 27156012. Further, there is an increasingly visible online community of young women who have desisted after claiming a male gender identity at some point during their teen years. See, e.g., <https://our-duty.group/2020/04/29/the-detransition-advocacy-network/>. Given the rapid increase in the number of girls presenting to gender clinics within the last few years, the phenomena of regret and desistance by young women deserves careful attention and study.

44. Transgender surgeons have no objective, reliable means of evaluating the diagnostic error rate because there is no body of reliable scientific evidence that can be used to counsel the patient about what their risk of regret is. The ever growing population of de-transitioning

patients suggests that the error rate may be considerable, and the future medico-legal consequences may be proportionate.

45. Valid surgical consent requires that the surgeon is ultimately responsible for the accuracy of the diagnosis. For example, if an endocrinologist refers a patient for thyroidectomy because they have diagnosed a malignant thyroid nodule, the operating surgeon is still obliged to ensure the validity of the diagnosis. He has to entertain alternative diagnoses. Is it a benign nodule? Can it be treated with non-surgical means at lower risk to the patient? What do the scans show? What do the hormone levels show? Having evaluated all the alternative possibilities in the differential diagnosis, the surgeon can then counsel the patient and their family on the options of care, the likelihood of cure, and proper informed consent can be obtained.

46. But the transgender treatment industry, employing scientifically unsupported WPATH guidelines essentially (and unethically) excuse the surgeon from any responsibility for the diagnostic process or its consequences if the diagnosis is incorrect. The 7th edition of the WPATH guidelines requires only two letters written by psychologists, and a period of social transition. There is no action taken to verify the diagnosis on the part of the surgeon. The surgeon has no objective, reliable means by which to anticipate who might benefit or who might be harmed by surgery.

47. By the time a patient presents to a transgender surgeon, they have been the subject of affirmation processes that include everything from social transitioning, to hormonal manipulation. The surgeon is performing permanently life-altering surgical interventions to cure a psychological condition that was diagnosed by the patient, and sometimes the patient made the diagnosis before they even entered puberty. Since the abandonment of frontal lobotomies in 1967, there has been no other psychological-psychiatric condition for which surgery is performed, and

there is no other area of surgical care where the diagnostician is the patient themselves, and the surgeon has no objective, reliable means of confirming or rejecting the diagnosis.

G. I Do Not Engage in Experimental Treatments Lacking Reliable, Credible Scientific Support.

48. As multiple national science reviews and multiple peer reviewed science publications demonstrate, the relevant scientific community has never accepted the reliability, validity, safety or effectiveness of “gender affirmation” treatment procedures — including surgical procedures. Significant medical, ethical, and potential legal problems are created when health care providers employ experimental, unproven, treatment including surgical procedures. Due to the well-documented lack of scientific support and only low quality evidence of efficacy and safety, I will not personally engage in the delivery of experimental gender affirming medical interventions to patients of any age. I will not consider doing such invasive, potentially harmful surgical procedures — that can lead to life-long sterilization of vulnerable patients — until reliable, valid scientific research supports such methods.

49. The transgender treatment industry generates considerable income for hospitals, clinicians, and pharmaceutical companies. Members of the transgender treatment industry have a vested interest in believing that science has already justified their existence. Further, as sterilization is the expected adult outcome of endocrine and surgical treatments of the procedures undertaken in youth prior, the transgender treatment industry must have developed strong rationalizations to justify creating infertility. Will one day the medical profession look at support for transitioning youth in the same manner the eugenics movement is now regarded? (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

50. In summary, proponents of “affirmation care” for self-identified transgender patients have no body of quality scientific evidence that proves benefit from their interventions. They rely on low to very low quality data when they recommend affirmation therapy. Consensus statements by professional bodies are based upon the lowest category of evidence available. Advocates of “affirmation care” have no long term data to support their therapeutic recommendations, and they never compare their data to the historically proven approach of “watchful waiting.” Advocates for “affirmation care” including medical and surgical intervention, have no objective test, with published error rates, that can be employed to determine who will benefit from their treatments. They rely only on subjective reporting by the patient. Transgender surgery, including “chest masculinization” does not meet the criteria for reconstructive surgery. Because the sole aim of the surgery is the claimed, but unsupported, emotional benefit, it is *by definition* aesthetic (feelings) or cosmetic (appearance) surgery. Chest “masculinization” surgery fails on professional moral grounds because informed consent is impossible (given that there is no way to predict who will benefit), and because function is utterly destroyed in order to achieve a counterfeit form.

IV. PLASTIC SURGERY IS CONCERNED WITH PSYCHOLOGY.

A. Why is Plastic Surgery Concerned with Psychology?

51. Plastic surgery has two areas of activity with broad overlap. The practice of plastic surgery includes reconstructive as well as aesthetic (often called cosmetic) surgery.

52. Reconstructive surgery is ordered to the establishment, or restoration, of normal body structures and their associated functions. The reconstructive process aims at deformities caused by trauma, disease or the management of disease such as cancer surgery, and congenital

deformities. The goal is the restoration of form and function. Sometimes functional restoration is given priority over form, as with the reconstruction of a hand injury in a man. Sometimes functional restoration is impossible, and all that can be offered is aesthetic, as with reconstruction of a facial wound that has resulted in the loss of an eye, where vision cannot be restored, and all that can be offered is a prosthetic eye.

53. Aesthetic (cosmetic) surgery on the other hand is surgery to modify the appearance of an area of the body that is functionally normal, and that has an appearance that, even though it is within the range of normal, causes some degree of annoyance or discomfort to the patient. (For example, prominent ears on a boy.) The ears are functionally normal, and their prominence may even be a recurring family trait, but their prominence is a daily annoyance to the boy; he may even have been given a pejorative nick name. A simple and safe procedure can be performed that reduces the prominence of his ears *without sacrificing any function*, and his daily annoyance is resolved. Form is changed within the range of normal, function is preserved, and the aesthetic (feelings) problem is solved.

54. In the clinical training of plastic surgeons, we learn to carefully evaluate aesthetic patients, not only for the sake of surgical planning, but because we have to understand their motivation for the surgery and how to anticipate potential complications. It is axiomatic in plastic surgery that the most avoidable complication in aesthetic surgery is disappointment and regret on the part of the patient. We are taught that disappointment is first and foremost managed by ensuring that the doctor understands what the patient is seeking to achieve, that the goal is worthy of pursuing, and that the surgeon is likely to achieve the goal.

55. Plastic surgeons are trained to recognize a particular subset of aesthetic patients who at first appear to be seeking some ordinary improvement in appearance, but upon further

evaluation discovers that the patient is seeking cosmetic surgery because they are convinced they are horribly disfigured — and *this* is the reason they feel alone, isolated and depressed. If such a patient has an otherwise normal physical appearance, then the diagnosis of Body Dysmorphic Disorder must be entertained. See (5) Body Dysmorphic Disorder, Andri S. Bjornsson, PhD, Elizabeth R. Didie, PhD, Katharine A. Phillips, MD; Dialogues Clin Neurosci. 2010 Jun; 12(2): 221–232; and Body Dysmorphic Disorder and Cosmetic Surgery Crerand, Canice E. Ph.D.; Franklin, Martin E. Ph.D.; Sarwer, David B. Ph.D. Plastic and Reconstructive Surgery: December 2006 - Volume 118 - Issue 7 - p 167e-180e.

56. Persons who suffer with this condition are seeking a physical explanation for a psychological wound. They are trying to explain their isolation, anxiety, depression, and despair by pointing to their appearance as the cause of their sorrows. Plastic surgeons learn that such patients may be elated at first with their surgery, but they return with complaints that “you didn’t do the surgery right.” They are disappointed because they still experience the anxiety, isolation, depression, and despair, which should not be surprising given the obvious fact that *you cannot heal a psychological wound with cosmetic surgery*.

57. Indeed, to offer cosmetic surgery to a person suffering from Body Dysmorphic Disorder is considered a failure of diagnosis. *To know that a person is suffering from body dysmorphic disorder, and to offer them surgery in spite of that knowledge is malpractice*. The surgeon is taking advantage of a psychologically vulnerable patient for the sake of financial gain. See Cosmetic Surgery and Body Dysmorphic Disorder – An Update B S. Higgins, MD and A. Wysong, MD, MS, Int J Womens Dermatol. 4(1); March 2018.

58. Gender dysphoria is a diagnosis that is based upon the subjective reporting of the affected child. There is no objective test, with known error rates, that can be employed to confirm the diagnosis, or predict who will benefit from any putative therapeutic interventions. There is no chromosomal study, no genetic marker, no gene product, no hormonal abnormality, or any dynamic brain scan that can be used to confirm the diagnosis. Essentially, the transgender treatment industry is offering permanently life altering hormonal manipulation and irreversible surgery based upon a diagnosis that is made by an emotionally stressed adolescent, or even prepubertal child who is being socially transitioned. (See Deficiencies in Scientific Evidence for Medical Management of Gender Dysphoria Paul Hruz, MD, PhD. Linacre Quarterly 2020 Feb 87 (1)34-42. doi10.1177/0024363919873762. Epub 2019 Sep 20.)

B. Gender Dysphoria or Gender Identity Disorder is a Logical Subcategory of Body Dysmorphic Disorder.

59. Body dysmorphic disorder is a subcategory of obsessive compulsive disorder. What distinguishes gender identity disorder from other forms of body dysmorphic disorder is that the content of the obsessive thought is the sexed appearance of the patient. The obsessive thought is that they have the wrong genitalia, that they are really the other sex, and if they could change that, their anxiety, isolation, depression, and despair would resolve. Given that the patient is physically normal, and that the patient is seeking a change in appearance in order to resolve a feeling (aesthetic), all transgender surgery, by definition, is cosmetic surgery.

60. To call a “chest masculinization” mastectomy a “chest reconstruction” is not just an imprecision of language. It is intentional deception. Such mastectomy is in no way a restoration of form and function. It is rather the willful destruction of function for the purposes of producing a counterfeit form. What is more, because these mastectomies involve the irreversible destruction of normally functional parts, with associated loss of function, these operations violate

the first and most important principle of plastic surgery: It is bad surgical planning if you compromise function for the sake of a cosmetic result. In this case the compromise of function is actually a 100% loss.

C. There Are Multiple Pathways to Gender Dysphoria.

61. The diagnosis of “gender dysphoria” encompasses a diverse and controversial array of conditions, with widely differing pathways and characteristics depending on age of onset, the complexities introduced by co-occurring mental illnesses, social contagion and other environmental factors, among other things. Data from one population (e.g. adults, those struggling with complex mental illnesses) should not naively be assumed to be easily applicable to others (e.g. children, those changed by social contagion) and other factors. The developmental and mental health patterns for these groups are sufficiently different that data developed in connection with one of them cannot be assumed to be reliably applicable to another. See K. Zucker (2018), The Myth of Persistence: Response to “A Critical Commentary on Follow-Up Studies & ‘Distress’ Theories about Transgender & Gender Non-Conforming Children” by Temple Newhook et al., *Intl J. of Transgenderism* at 10, DOI: 10.1080/15532739.2018.1468293 (“Myth of Persistence”).

V. OPINIONS REGARDING THE SHOCKING OMISSIONS OF PLAINTIFFS’ REPORTS

62. As a physician and surgeon for decades, I have dedicated my life to helping the injured, the wounded, the sick, the vulnerable, and those in distress. As a physician and surgeon, I have a duty to carefully assess the available scientific research literature and determine what surgical procedures have been scientifically proven safe and effective for use on patients — and which procedures are still experimental, potentially dangerous, and may well do more harm than good for patients. Such an assessment requires the prudential review of scientific publications and my being familiar with the ongoing methodological and scientific debates in the field.

63. I have reviewed the plaintiffs’ declarations from Drs. Adkins and Antommara in this case. Those declarations demonstrate a stunning lack of knowledge or candor regarding the ongoing, raging, international scientific debates over the safety and effectiveness of “gender affirming” medical procedures. Those reports offer no proper disclosure of these controversies and demonstrate no apparent awareness of the serious methodological and ethical defects and controversies exposing the lack of scientific foundations for the transgender treatment industry. Over the past few years, multiple methodological exposes and national reviews in England (NICE), Sweden, and Finland, plus other reviews (e.g., Cochrane, Griffin, Carmichael, etc), have all raised urgent warnings and serious questions about the quality and the integrity of the scientific foundation for this very controversial field.

64. It is troubling that the plaintiffs’ experts both appear to have significant financial and professional conflicts of interest as they themselves have reported in their appended curriculums vitae that much of their practices and incomes are derived from these experimental, unproven, potentially harmful methods and procedures of “gender affirmation transitioning” medical treatments. Further, not only their incomes but their professional reputations, academic positions, journal publications, and association memberships would all collapse if the transgender treatment industry collapsed due to widely noted missing evidence of safety and effectiveness.

65. The following are among the shocking errors, omissions, and failures of the plaintiffs’ expert reports.

A. Failure to Disclose Multiple International Controversies and the Poor Quality of the Evidence

66. The plaintiffs’ experts failed to properly disclose and discuss the international debates and controversies surrounding transgender affirmation methods and procedures discussed above. Indeed, it is difficult to imagine a more inaccurate summary of the state of the embattled,

experimental transgender treatment industry that that reflected in their reports. (See detailed citations in the “Notes” section of this report below).

67. The plaintiffs’ experts failed to properly disclose and discuss multiple peer-reviewed, published exposés of significant methodological defects in research on transgender affirmation methods and procedures. Further, the plaintiffs’ experts failed to properly disclose and discuss recent scientific studies and reviews including the Cochrane Review, the Carmichael study, the Griffin review and the devastating scientific critiques of the ill-fated and recanted Branstrom, et al. study, including the many multiple, detailed, methodologically sophisticated letters to the editor. (See detailed citations in the “Notes” section of this report below).

B. Failure to Acknowledge Comorbidities

68. Plaintiffs’ experts fail to recognize how the existence of comorbidities complicate the treatment of gender dysphoric patients. It is well established in peer-reviewed medical literature that children who experience gender discordance have a very high likelihood of major anxiety disorders, major clinical depression, self-harming behaviors such as cutting, substance abuse. They also have a greater than 30% likelihood of being on the autism spectrum. Under the “affirmation care” model, these issues are more often than not ignored, ascribing all of the child’s problems to their self-diagnosed gender dysphoria. (See Elevated rates of autism, other neurodevelopmental and psychiatric diagnoses, and autistic traits in transgender and gender-diverse individuals, Varun Warriar, David M. Greenberg, Elizabeth Weir, Clara Buckingham, Paula Smith, Meng-Chuan Lai, Carrie Allison & Simon Baron-Cohen ; Nature Communications volume 11, Article number: 3959 (2020), <https://www.nature.com/articles/s41467-020-17794-1>).

C. Failure to Acknowledge the Radically Changing Patient Demographics and Problems for the “Affirmative” Model

69. Plaintiffs’ experts fail to recognize that the demographics of transgender patients have seen a radical transformation in the last several years. Historically, the condition was rare (less than 0.2% of children), had initial presentation in pre-puberty, was almost exclusively boys, and showed a desistance (i.e., abandonment of cross-sex self-identification) rate of over 80% by mid-adolescence, and over 90% when followed into adulthood. See A Follow-Up Study of Boys With Gender Identity Disorder; Devita Singh, Susan J. Bradley, and Kenneth J. Zucker, *Front. Psychiatry*, 29 March 2021.

70. Currently, the majority of newly diagnosed transgender children are natal females (over 50%), initial presentation is in early adolescence to young adulthood, and some reports have the overall prevalence rate rising to somewhere between 2 and 10% of school age children. See Evidence for a Change in the Sex Ratio of Children Referred for Gender Dysphoria: Data From the Gender Identity Development Service in London (2000-2017) Nastasja M de Graaf , Polly Carmichael , Thomas D Steensma , Kenneth J Zucker, *J Sex Med* 2018 Oct;15(10):1381-1383 and also Characteristics of Referrals for Gender Dysphoria Over a 13-Year Period Melinda Chen, M.D., John Fuqua, M.D., and Erica A. Eugster, M.D *J Adolesc Health*. 2016 Mar; 58(3): 369–371. doi: 10.1016/j.jadohealth.2015.11.010). This means that the diagnosis among females has risen by nearly 50-fold in the last five years (See Gender dysphoria in adolescence: current perspectives, Riittakerttu Kaltiala- Heino, Hannah Bergman, Marja Työläjäarvi, and Louise Frisén; *Adolesc Health Med Ther*. 2018; 9: 31–41. Published online 2018 Mar 2. doi: 10.2147/AHMT.S135432).

71. Additionally, there appear to be “outbreaks” of clusters of adolescent females that are connected either by school, or social media that suddenly appear. This was first reported by

Dr. Lisa Littman of Brown University in her 2018 paper which coined the diagnostic term of Rapid Onset Gender Dysphoria. (See Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria, Littman, L. PLOS One, August 16, 2018; <https://doi.org/10.1371/journal.pone.0202330>). She found evidence suggesting that these subjects developed transgender self-identification through a social contagion process that included highly rehearsed speech to be used when speaking to psychologists, counselors, pediatricians, and surgeons. A moment's reflection on this single fact should be enough to dissuade anyone from the idea that transgender self-identification is a biologically determined condition. Has there been a mass mutation in the human genome that would cause a fifty-fold increase among girls? Is there some substance abroad in the world that has radically and swiftly altered childhood brain development? The numbers of affected children would easily place this in the category of a pandemic, given the geographic range of the condition in the western world.

72. The transgender treatment industry has not shown the slightest interest in examining alternative causes, and it offers precisely the same treatment model to children whether they experience gender dysphoria from their first days of character formation in early childhood or at age 14 when their psychosexual development is under the tremendous pressures of puberty. All patients are given “affirmation care” in spite of the fact that we are dealing with wildly different psychological processes. The only variation in treatment plan, from the youngest patient to the oldest, is where along that single line of care they are brought in: social transition, puberty blockers, cross-sex hormones, then surgery.

73. Psychological evaluation and treatment, even of the known psychological comorbidities such as depression and anxiety, bipolar disorder, etc., is a priori decried by the American Psychological Association and other political allies as “conversion therapy,” even if the therapy

is used to reduce depression and anxiety. Therapists are *barred* by “political correctness” from seeking alternative causal explanations and thus less able to avoid confirmation bias. Properly exploring the possibility of alternative diagnoses, such as anxiety disorder, major depression, or autism spectrum, even though part of the standard of care, is labelled as “trans-phobic.”

74. Because the alternative causal explanations identify disorders that are far more treatable, cross-sex identification may, for many patients, be treatable using safe, proven methodologies such as Cognitive Behavioral Therapy (CBT). Instead, “affirmation” advocates claim that CBT — the most tested and validated form of psychotherapy for depression and anxiety relief — is nothing more than “conversion therapy”, or even “psychological torture.” (See APA Resolution on Gender Identity Change Efforts Feb. 2021 <https://www.apa.org/about/policy/resolution-gender-identity-change-efforts.pdf>). The transgender treatment industry maintains emotional chaos in these vulnerable patients, giving rise to a continuing “need” for irreversible, sterilizing, unproven, controversial “transitioning” treatments.

D. The Existence of the “Watchful Waiting” Model of Care

75. Plaintiffs’ expert witnesses failed to acknowledge even the very existence of the “watchful waiting” model of care.

76. Historically, Gender Identity Disorder (now called Gender Dysphoria) was recognized as a sub-category of Obsessive Compulsive Disorder where the child has a persistent, intrusive thought that they are the wrong sex. This makes sense because the content of the thought meets the three criteria of a delusional thought: It is 1) held with absolute certainty, 2) unpersuadable by contrary evidence, and 3) impossible. In the case of the gender discordant child, the content of the delusional thought relates to their sexed self. These children typically presented in pre-puberty, and care were directed at several important issues: Experiences or perceptions that have provoked fear or anxiety (e.g. child abuse including sexual assault) that might be causing

the child to seek safety in the opposite sex presentation; misinterpretation of family dynamics that may have caused a desire to be the other sex; actual abuse events that may have provoked and habituated the obsessive thought.

77. Individual and family counseling directs the child's thoughts and coping processes in the direction of the truth of their nature, which includes their biological sex. Historically, this "watchful waiting" approach resulted in a complete resolution of symptoms in 80% of children by mid-adolescence, and over 90% resolution by early adulthood. (See Psychosexual outcome of gender-dysphoric children. Madeleine S. C. Wallien, P. Cohen-Kettenis 2008 Psychology, Medicine Journal of the American Academy of Child and Adolescent Psychiatry 10.1097/CHI.0b013e31818956b9; and A Follow-up Study of Girls with Gender Identity Disorder, Kelley D Drummond 1, Susan J Bradley 2, Michele Peterson-Badali 1, Kenneth J Zucker; Dev Psychol. 2008 Jan;44(1):34-45. doi: 10.1037/0012-1649.44.1.34).

78. The "watchful waiting" approach is based upon a recognition that at the heart of the transgender process lies a psychological problem, and this perspective finds strong support in both its natural history (80+% resolution without medical or surgical intervention), and the fact that no objective test, having known error rates, has yet been found that can affirm or reject a "transgender" diagnosis.

79. In contrast to the highly successful results of "watchful waiting," we have the presently regnant "affirmation" model. Under the "affirmation" model, the treating physician is essentially forbidden to consider the transgender condition to be a psychological disturbance apart from the unhappiness and associated impaired social functioning caused by the discordance between their objective biological sex and their interior sense of their gender. Treating profes-

sionals, including pediatricians, endocrinologists, psychologists, and surgeons are strongly discouraged from examining alternate theories concerning the diagnosis and causes, such as clinical anxiety apart from gender discordance, major depression, or the social contagion model of causation. The affirmation model proposes that the child's interior sense of their gender is "their true self," and that the problem demands that the appearance of the body must be radically changed so that it "aligns" with the child's subjective sense of being the opposite sex.

80. The startling difference in outcomes between "watchful waiting" and "affirmation" provides a compelling counter argument to the WPATH guidelines. As stated above, "watchful waiting," which includes individual and family counseling, yields successful resolution of gender discordance by natural maturation in over 80% of children by mid adolescence, and over 90% by young adulthood. This is in stark contrast, with "affirmation care" where we find that children who are enrolled in gender clinics are nearly 100% likely to persist in their cross-sex self-identification through childhood into adulthood. Essentially, at least 80% of affected children who would have resolved their problem and gone onto gender congruence, are instead trapped in the transgender treatment enterprise. The proponents of "affirmation care" have no proven test, with known error rates, by which to distinguish the 90% that will resolve their problem from the 10% that will experience persistence of symptoms into adulthood. The probability of misdiagnosis — the error rate for this process — is 90%. This places the transgender treatment enterprise, including endocrinologists and surgeons, in the category of gross malpractice.

81. Plaintiffs' experts claim that in the case of transgender patients, it would be unethical to randomize patients into control groups and treatment groups, given the high rate of self-harm. This is a specious argument for two reasons. First, randomized case/control studies are

not the only alternative to unreliable, retrospective, biased collected case reports with short follow up on which the transgender industry rests. Longitudinal, population based, long term data is available in the world literature that allows us to evaluate the claims made by the gender affirmation treatment model. (See Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden; Cecilia Dhejne, Paul Lichtenstein, Marcus Boman, Anna L. V. Johansson, Niklas Långström, Mikael Landén; PLOS One February 22, 2011 <https://doi.org/10.1371/journal.pone.0016885>). In fact, that long-term population based data is very the reason why the Tavistock Institute in London and the Karolinska Institute Hospital in Sweden — in a dramatic change — have *restricted* the use of puberty blockers, cross-sex hormones, and transgender surgery in minors. The famed Swedish hospital’s new patient protections require the involvement of research monitoring to protect children from “transitioning” experimental procedures. (See detailed citations in the “Notes” section of this report below).

82. Essentially, the “control group” already exists in the world literature, however the transgender treatment industry ignores this control group, and continues to publish low-quality case-collection studies without controls, with short follow up and massive self-selection biases.

83. Secondly, there is a very long history of results from the “watchful waiting” model against which the “affirmation model” can be compared. But Plaintiffs’ experts entirely ignore this data which shows that the historically proven “watchful waiting” model has a “cure” rate of approximately 90%. The “affirmation care” model hasn’t even proven basic efficacy, much less high rates of efficacy, given the low to very low quality evidence that they continue to rely on. Its proponents publish only subjective results to which they assign numerical values using unproven test instruments that have no known error rates or predictive value. (E.g., as noted

above, the historic Branstrom study and recantation documented no reliable benefits to patients in a 10yr+ follow-up study.) (See detailed citations in the “Notes” section of this report below).

E. Failure to Acknowledge that Relying on “Consensus Statements” is Not Relying on Evidence.

84. As can be seen in the Complaint in this case and the plaintiffs’ expert reports, the primary supports for the “affirmative” approach are the repeated references to “consensus statements” from medical and other associations and the WPATH guidelines. It should be noted that the quality of scientific evidence in medicine can be graded based upon the methodology employed. The methodology of professional consensus seeking is in the lowest category. (See The Levels of Evidence and their role in Evidence-Based Medicine Patricia B. Burns, MPH, Rod J. Rohrich, MD, and Kevin C. Chung, MD, MS. *Plast Reconstr Surg*. 2011 Jul; 128(1): 305–310.)

85. It should further be noted that consensus statements from such organizations as the American Pediatric Association and the Endocrine Society are not obtained by polling the membership of the entire society, but are instead the product of consensus seeking methodology applied to a very small, self-selected sample of members that happen to be on that particular policy committee. Nonetheless, the “consensus statement” is incorrectly presented as though there is majority if not universal agreement by pediatricians and endocrinologists.

86. Furthermore, WPATH intentionally mis-labels its guidelines, calling them “Standards of Care” (See <http://www.wpath.org/publications/soc>). Guidelines are a suggested course of treatment that may or may not produce the desired results, and are therefore not mandatory. Labeling their document as “Standards of Care” implies that they are proven treatment methods of very high efficacy that must be adhered to in order to achieve a known and positive outcome, and that deviations from the “standards of care” has a high probability of a poor outcome, and possible legal consequences.. Given that the guidelines offer no scientifically verified

evidence that their outcomes are consistently and overwhelmingly positive, this is a clear misrepresentation of their actual value. For this reason, whenever the acronym “WPATH” is used in conjunction with the words “standards of care,” the author of such words is intentionally misleading the reader.

87. The WPATH guidelines also seek to define a “professional” in transgender health. In order to be classified as a “professional” you must simply agree with what the WPATH documents state. (See WPATH Standards of Care section VI p.13 – section VII p.33 (defining the “professional” in terms of compliance with WPATH “standards of care”)). This is more characteristic of a cult than a scientific body. Science demands unflinching, ongoing, debate and re-evaluation of hypotheses, quality of data, methodologies, and best practices. In contrast, WPATH demands consensus and compliance with a single, unproven model of care, even when the patients have wildly differing presentations (pre-pubertal vs. adult, co-morbid association with other illness such as autism spectrum etc.).

88. As it happens, among the lead authors of the WPATH guidelines, and their board members, are physicians and surgeons whose practices largely depend on the revenue stream found in transgender services. (WPATH Standards of Care. Pp.109-112 (describing the composition of the committee members, and their consensus methodology used in generating the document)). Essentially, they are saying, “mastectomy is justified in transgender teenage natal females because I said so in the WPATH document that I wrote.” This is a classic *ipse dixit* opinion.

VI. CONCLUDING OPINIONS

89. There are no currently no competently conducted, 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.

90. 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.

91. 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.

92. 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.

93. 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.

94. A currently unknown percentage and number of patients reporting gender dysphoria are suffering social contagion and social pressure processes brought on by a peer group, social media, YouTube role modeling, and/or family dynamics.

95. 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.

96. 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 “affirmative” treatments.

97. 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.

98. 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.

99. Affirmation medical treatments — hormones and surgery — for gender dysphoria and “transitioning” have not been accepted by the relevant scientific communities (biology, genetics, neonatology, medicine, psychology, etc.).

100. “Gender affirmation” assessments and treatments — hormones and surgery — for gender dysphoria and “transitioning” have no known, peer reviewed and published error rates.

101. Political advocates, activist physicians, and 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 are easily swayed by political ideologies rather than evidence-based scientific methodologies.

102. Experts in legal cases have an ethical obligation to honestly, fairly, and accurately disclose and discuss the international controversies regarding the safety, effectiveness, reliability, and credibility of the gender transition industry. It is astonishing that in their expert declarations, Plaintiffs' experts failed to disclose and discuss the serious controversies, complex issues, debates, and contrary national science review recommendations in this field. It is difficult to imagine a more inaccurate summary of the state of the embattled, experimental transgender treatment industry. (See detailed citations in Notes section below).

VII. RESEARCH NOTES

To assist in my testimony in this case, I include my notes, references and citations documenting the depth and breadth of the serious controversies in this field. Over the past few years, the glaring defects in the research foundations of the gender transition industry have been exposed for all the world to see.

See, Vrouenraets et al, Early Medical Treatment of Children and Adolescents With Gender Dysphoria: An Empirical Ethical Study, *Journal of Adolescent Health* 57 (2015) 367e373. ...”no consensus exists whether to use these early medical interventions.” The study shows that there is no agreement concerning the causes of gender dysphoria, which give rise to very different treatment strategies that are at times in diametric opposition. As a result of this confusion of explanations, “consensus” regarding treatment is ipso facto impossible. Results: Seven themes give rise to different, and even opposing, views on treatment: (1) the lack of an explanatory model for GD; (2) the unknown nature of GD (normal variation?, social construct?, or mental illness?); (3) the role of physiological puberty in developing gender identity; (4) the role of comorbidity [with severe mental illnesses] ; (5) unknown possible physical or psychological effects of (refraining from) early medical interventions; (6) child competence and decision making authority [to give truly informed consent to be sterilized for experimental procedures?]; and (7) the role of social context ...how GD is perceived. Strikingly, the guidelines are debated both for being too liberal and for being too limiting. Conclusions: As long as debate remains on these seven themes and only limited long-term data are available, there will be no consensus on treatment. Therefore, more systematic interdisciplinary and (worldwide) multi-center research is required. It is striking that plaintiffs’ experts somehow both failed to properly report this ongoing international debate within their claimed filed of expertise.

See, Dhejne et al. (2011), Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden, PLOS ONE 6(2) e16885 (“Long Term”); See also, R. K. Simonsen et al. (2016), Long-Term Follow-Up of Individuals Undergoing Sex Reassignment Surgery: Psychiatric Morbidity & Mortality, Nordic J. of Psychiatry 70(4). Swedish follow-up study of patients who underwent sex-reassignment surgery over a 30-year period found a suicide rate in the post-Sex Reassignment Surgery (SRS) population 19.1 times greater — after affirmation treatment — than that of the controls; both studies demonstrated elevated mortality rates from medical and psychiatric conditions.

See, 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. Self-harm did NOT improve and “no changes in psychological function,” meaning no improvement. (Also, “YSR [Youth Self Report] data at 36 months (n = 6) were not analyzed.” No significant effect on their psychological function, thoughts of self-harm, or body image, a study has found... children experienced reduced growth in height and bone strength by the time they finished their treatment at age 16. The findings, from a study of 44 children treated by the Gender Identity Development Service (GIDS) run by the Tavistock and Portman NHS Foundation Trust in London, have emerged as the trust prepares to appeal against a High Court ruling that led NHS England to pause referrals of under 16s for puberty blockers.

Demographics: no biological explanation. The radical change in patient demographics from early onset in boys to teen girls with rapid onset— has been termed late-, adolescent-, or

rapid-onset gender dysphoria — has now been seen in every gender clinic in the western world, and there has been a huge surge in the number of cases. "National College Health Assessment: ACHA-NCHA [s://www.acha.org/NCHA/ACHANCHA_Data/Publications_and_Reports/NCHA/Data/Publications_and_Reports.aspx?hkey=d5fb767c-d15d-4efc-8c41-3546d92032c5](https://www.acha.org/NCHA/ACHANCHA_Data/Publications_and_Reports/NCHA/Data/Publications_and_Reports.aspx?hkey=d5fb767c-d15d-4efc-8c41-3546d92032c5) See, Kalliala-Heino, Riittakerttu, Hannah Bergman, Marja Työläjäarvi, and Louise Frisen. "Gender Dysphoria in Adolescence: Current Perspectives." *Adolescent Health, Medicine and Therapeutics* Volume9 (March 2018): 31–41. <https://doi.org/10.2147/AHMT.S135432> See, Vries, Annelou L.C. de. "Challenges in Timing Puberty Suppression for Gender-Nonconforming Adolescents." *Pediatrics* 146, no. 4 (October 2020): e2020010611. <https://doi.org/10.1542/peds.2020-010611>. See, Zucker, Kenneth J. "Adolescents with Gender Dysphoria: Reflections on Some Contemporary Clinical and Research Issues." *Archives of Sexual Behavior* 48, no. 7 (October 2019): 1983–92. <https://doi.org/10.1007/s10508-019-01518-8>.

Great Britain (NICE), Deborah Cohen and Hannah Barnes, Evidence for puberty blockers use very low, says NICE at <https://www.bbc.com/news/health-56601386> ["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"

See, Asscheman H, Giltay EJ, Megens JA, et al. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. *Eur J Endocrinol*. 2011;164:635-642. *"There is no evidence that transition reduces suicide when we look past 10 years, and there is some suggestion that **suicide rates may actually increase after the transition***

honeymoon phase is over," says Malone, stressing the importance of providing proper evaluation and appropriate psychological treatment for any suicidal tendencies. (Supports the Branson conclusions after recantation and correction).

Sweden - Review of Gender dysphoria in children and adolescents: an inventory of the literature, SBU Policy Support no 307, 2019 www.sbu.se/en • registrator@sbu.se Contact SBU: Jan Adolfsson, Medical Advisor, Project Manager, jan.adolfsson@sbu.se, English Proofreading: Project group and Jan Adolfsson, SBU [“ No relevant randomized controlled (treatment outcome) trials in children and adolescents were found.”] ; See, also e.g., FINLAND Issues Strict Guidelines for Treating Gender Dysphoria at <https://genderreport.ca/finland-strict-guidelines-for-treating-gender-dysphoria/>. In 2020, Finland reportedly became the first country in the world to issue new guidelines for this group of patients when it concluded similarly to the UK High Court that there is a lack of quality evidence to support the use of hormonal interventions in adolescents with gender dysphoria.... they also issued the guideline ordering “No surgical interventions are allowed for children under the age of 18”.). As the *methodological quality of the studies was already poor* based on the type of study, thus no actual quality assessment or determination of the degree of evidence was performed.”] ;

See, Cochrane Review (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.)

See, 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, the authors noted the hazardous error of mandating “affirmation treatments” — thus requiring the negligent practice of Confirmation Bias — rather than properly and carefully exploring alternative hypotheses — the standard, required ethical, medical standard of practice. As Griffin discussed, “Attempts to properly explore, formulate and treat coexisting mental illness in gender dysphoric populations, including that relating to childhood trauma, might be considered tantamount to ‘conversion therapy’. Although mental illness is overrepresented in the trans population it is important to note that gender non-conformity itself is not a mental illness or disorder. 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. Taking a supportive, exploratory (psychotherapy) approach with gender-questioning patients should not be considered conversion therapy.” 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, Dyer, C., Puberty blockers do not alleviate negative thoughts in children with gender dysphoria, finds study BMJ 2021; 372 doi: <https://doi.org/10.1136/bmj.n356> (Published 08 February 2021), BMJ 2021;372:n356 (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, Bränström and Panchankis long term surgical results. NO benefit (data suggests and suggests an increased risk of serious suicide attempts). See, Kalin, N.H., Reassessing Mental Health Treatment Utilization Reduction in Transgender Individuals After Gender-Affirming Surgeries: A Comment by the Editor on the Process by the Editor-in-Chief The American Journal of Psychiatry, Am J Psychiatry 2020; 177:7 64; doi: 10.1176/appi.ajp.2020.20060803; See also, Anckarsäter, H., and Gillberg, C., Methodological Shortcomings Undercut Statement in Support of Gender-Affirming Surgery, Am J Psychiatry 2020; 177:764–765; doi: 10.1176/appi.ajp.2020.19111117.

See, e.g., Wold, A. (M.D., Ph.D.) Gender-Corrective Surgery Promoting Mental Health in Persons With Gender Dysphoria Not Supported by Data Presented in Article, Am J Psychiatry 2020; 177:768; doi: 10.1176/appi.ajp.2020.19111170. [among the individuals examined in the Branstrom study discussed here, the risk of being hospitalized for a suicide attempt was 2.4 times HIGHER if they had undergone gender-corrective surgery than if they had not.... the data presented in the Branstrom article do not support the conclusion that surgery is beneficial to mental health in individuals with gender dysphoria.”]

“Therefore, ... the data in the article ... *OVERTURNS the authors’ stated conclusions, suggesting that sex reassignment surgery is in fact associated with INCREASED mental health*

treatment See, Ring, A. (PhD) and Malone, W. , Confounding Effects on Mental Health Observations After Sex Reassignment Surgery, *Am J Psychiatry* 2020; 177:768–769; doi: 10.1176/appi.ajp.2020.19111169.

See, See, Van Mol, A., Laidlaw, M. K., Grossman, M., McHugh, P., Gender-Affirmation Surgery Conclusion Lacks Evidence, *Am J Psychiatry* 177:8, August 2020 ajp.psychiatryonline.org 765. “The study confirms the strong association between psychiatric morbidity and the experience of incongruity between gender identity and biological sex. However, the study does NOT demonstrate that either hormonal treatment or surgery has ANY effect on this morbidity. It seems that the main message of this article is that the incidence of mental health problems and suicide attempts is especially HIGH in the year AFTER the completion of gender-affirming surgery [It is telling that the authors somehow ignored this most essential finding] ...” See, Curtis, D., Study of Transgender Patients: Conclusions Are Not Supported by Findings, *Am J Psychiatry* 2020; 177:766; doi: 10.1176/appi.ajp.2020.19111131.

See, Malone, W. and Roman, S., Calling Into Question Whether Gender-Affirming Surgery Relieves Psychological Distress, *Am J Psychiatry* 2020; 177:766–767; doi: 10.1176/appi.ajp.2020.19111149. “Bränström and Pachankis study on mental health treatment and suicide attempts ... is misleading because the study design is flawed.” “The authors first found what was already known ... the rate of psychiatric morbidity is much higher in persons with gender dysphoria compared with the general population (both before AND after “transitioning”). The authors then explored if the risk for mental health treatment changes as a function of years since starting HORMONAL treatment. They find NO effect (odds ratio = 1.0), but they do find a trend toward INCREASED risk of suicide attempts as a function of years since starting

[gender affirmation] HORMONAL treatment. They somehow failed to publish this essential finding.

See, Landén, M. (M.D., Ph.D.) The Effect of Gender-Affirming Treatment on Psychiatric Morbidity Is Still Undecided, Am J Psychiatry 2020; 177:767–768; doi: 10.1176/appi.ajp.2020.19111165. This conclusion is not supported by the data presented in the article.

See, Bränström, R. and Pachankis, J., Toward Rigorous Methodologies for Strengthening Causal Inference in the Association Between Gender-Affirming Care and Transgender Individuals 'Mental Health: Response to Letters, Am J Psychiatry 2020; 177:769–772; doi: 10.1176/appi.ajp.2020.20050599.

2020 - Sweden, following a national review of transgender science, published a new guideline that is NOT consistent with WPATH protocols nor the opinions of the plaintiffs' experts in this case. <https://genderreport.ca/finland-strict-guidelines-for-treating-gender-dysphoria/> The Swedish National Guidelines appear quite contrary to the opinions of Plaintiffs Experts and WPATH.

2020 - Finland following a review of transgender science, became the first country in the world to issue new guidelines for this group of patients when it concluded similarly to the UK High Court that *there is a* lack of quality evidence to support the use of hormonal interventions in adolescents with gender dysphoria. This new Finnish guidance prioritizes psychological therapy over treatment with hormones or surgery and suggests different care plans for early-onset vs late-onset childhood gender dysphoria. The 2020 Finland guidelines state "Only limited research

has been conducted on transgender identity and other gender identity conflicts, and comparative studies are very rare.”] The Finland National Guidelines appear quite contrary to the opinions of Plaintiffs Experts and WPATH.

See, <https://genderreport.ca/finland-strict-guidelines-for-treating-gender-dysphoria/> Finland Clinical Guidelines and Conclusions Three reports were created by COHERE in Finland. The report “Medical treatment methods for dysphoria associated with variations in gender identity in minors – recommendation” clarifies the roles of different healthcare providers in a situation where a minor is uncertain about their gender identity. They also produced general recommendations for the treatment of transgender people, which applies to adults. And interestingly, a third and separate set of recommendations for the treatment of gender dysphoria related to non-binary people and people with gender identities other than opposite-sex gender identities.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on July 8, 2021.



Patrick W. Lappert, MD

Curriculum Vitae

Patrick W. Lappert, MD
Board Certified in Surgery and Plastic Surgery
Decatur, AL 35603

Education and Training :

— Bachelor of Arts in Biological Sciences at the University of California, Santa Barbara, 1979. Research in cell membrane physiology with Dr. Philip C. Laris, studying stoichiometry of the sodium: potassium ATPase pump.

— M.D., Doctor of Medicine degree at the Uniformed Services University of the Health Sciences, 1983 at Bethesda, Md.

— General Surgery Residency at the Naval Hospital Oakland/ UC Davis East Bay Consortium, 1987-1991

— Chief Resident, Department of Surgery, Naval Hospital Oakland, 1990-1991.

— Plastic Surgery Residency at the University of Tennessee- Memphis, 1992-1994.

Board Certifications in Medicine :

— Board Certified in Surgery — American Board of Surgery, 1992, in

— Board Certified in Plastic Surgery — American Board of Plastic Surgery, 1997; American Board of Plastic Surgery, 2008.

Medical Staff Appointments :

EXHIBIT A

— Staff General Surgeon at the Naval Hospital Oakland, CA 1991-1992

— Associate Professor of Surgery, UC Davis-East Bay, 1991-1992.

— Plastic and Reconstructive Surgeon, Naval Medical Center, Portsmouth, VA
1994-2002

— Chairman, Department of Plastic and Reconstructive Surgery, Naval Hospital
Portsmouth, VA 1996-2002.

— Clinical Assistant Professor, Department of Surgery, Uniformed Services University of
the Health Sciences, 1995-2002

— Founding Director, Pediatric Cleft Palate and Craniofacial Deformities Clinic, Naval
Hospital Portsmouth, VA 1996-20002

— Founding Director, Wound Care Center, Naval Hospital Portsmouth, VA 1995-2002.

— Staff Plastic Surgeon in Nebraska, and Alabama.

U.S. Surgeon General Service:

— Specialty Leader, Plastic and Reconstructive Surgery, Office of the Surgeon General-
USN, 1997-2002

Faculty Appointments:

— Teaching Faculty at Eastern Virginia Medical School, Division of Plastic Surgery,
1995-2002

Military Service :

- Aviation Officer Candidate, Naval Aviation Schools Command, NAS Pensacola, 1978
- Commissioned an Ensign, MC, USNR 1979 and Commissioned as a Lieutenant, MC, USN 1983 .

- Designated Naval Flight Surgeon, Naval Aerospace Medical Institute, 1985
- Flight Surgeon, Marine Fighter/ Attack Squadron-451
- Radar Intercept Officer in the Marine F-4S Phantom, accumulating 235 flight hours, and trained for qualification as an Air Combat Tactics Instructor.

- Deployed to the Western Pacific as UDP forward deployed fighter squadron in Korea, Japan, and the Philippines.

- Service in the US Navy for 24 years
- Service in the US Marine Corp. for 3 years.
- Retired with the rank of Captain, USN in 2002

Military Awards:

- Navy Commendation Medal - For service with Marine Fighter/Attack Squadron - 451
- Meritorious Unit Citation- 3rd award
- Humanitarian Service Medal - For service in the aftermath of the Loma Prieta earthquake.

Publications - Peer Reviewed Medical Journals :

- Lappert PW. Peritoneal Fluid in Human Acute Pancreatitis. Surgery. 1987 Sep;102(3):553-4

— Toth B, Lappert P. Modified Skin Incisions for Mastectomy: The Need for Plastic Surgical Input in Preoperative Planning. *J Plastic and Reconstructive Surgery*. 1991; 87: 1048-53

— Lappert P. Patch Esophagoplasty. *J Plastic and Reconstructive Surgery*. 1993; 91 (5): 967-8

— Smoot E C III, Bowen D G, Lappert P, Ruiz J A. Delayed development of an ectopic frontal sinus mucocele after pediatric cranial trauma. *J Craniofacial Surg*. 1995;6(4):327–331.

— Lappert PW. Scarless Fetal Skin Repair: “Unborn Patients” and “Fetal Material”. *J Plastic and Reconstructive Surgery*. 1996 Nov;98(6):1125

— Lappert PW, Lee JW. Treatment of an isolated outer table frontal sinus fracture using endoscopic reduction and fixation. *Plastic and Reconstructive Surgery* 1998;102(5):1642-5.

Publications - Medical Textbooks:

— Wound Management in the Military. Lappert PW, Weiss DD, Eriksson E. *Plastic Surgery: Indications, Operations, and Outcomes*, Vol. 1; 53-63. Mosby. St. Louis, MO 2000

Operations and Clinical Experience - Consultations and Discussions : As a physician and surgeon, I have treated many thousands of patients in 7 states and 4 foreign nations. My practice has included Primary Care, Family Medicine, Aerospace Medicine, General Surgery, Reconstructive Surgery for combat injured, cancer reconstructive surgeries including extensive experience with microvascular surgery, Pediatric Congenital Deformity, and the care of chronic wounds. I have practiced in rural medicine, urban trauma centers, military field hospitals, university teaching hospitals, and as a solo private practitioner. In my private practice I have had

occasion to treat many self-identified transgender patients for skin pathologies related to their use of high dose sex steroids, laser therapies for management of facial hair both in transitioners and detransitioners. I have performed breast reversal surgeries for detransitioning patients. My practice is rated as "LGBTQ friendly" on social media. I have consulted with families with children who are experiencing gender discordance. I have given many presentations to professional meetings of educators and counselors on the subject of transgender, and the present state of the science and treatment. I have discussed the scientific issues relevant to the case with many physicians and experts over a number of years and also discussed related issues with parents and others.



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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

EXHIBIT

5

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Concepts

Suppression treatment	Pubertal suppression with GnRH analogues (drugs that inhibit gonadotropin-releasing hormone activity) to halt the development of secondary sex characteristics of the biological sex.
Cisgender/Cis person	A person whose gender identity matches the sex determined at birth (identifies, and is satisfied with, the sex determined at birth and generally expresses his/her gender accordingly).
Other gender identity	A person who does not identify as a man or a woman, but rather somewhere along the continuum or outside of it; genderless, nonbinary, or multigendered.
Transgender	A person whose gender identity differs from the legal and biological sex determined at birth but instead aligns with the opposite sex.



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1. Basis for Preparing These Recommendations

As the number of patients, including minors, referred to the Helsinki University Hospital (HUS) and the Tampere University Hospital (TAYS) multidisciplinary outpatient clinics for assessment and treatment of gender dysphoria has increased, PALKO (Council for Choices in Healthcare in Finland / COHERE Finland) decided to prepare recommendations for medical treatments of gender dysphoria, i.e., distress which is associated with a minor's gender variance and impairs function. Gender variance refers to a spectrum of gender experience anywhere on the male-female identity continuum or outside it, and is not exclusively confined to the dichotomized male/female conception of gender. Not all patients with gender variance experience significant suffering or functional impairments, and not all seek medical treatment.

These recommendations are based on the legislation in force at the time of the adoption of the recommendation, the available research evidence, and the clinical experience of multidisciplinary teams with expertise in gender dysphoria assessment and treatment at HUS and TAYS. The knowledge base supporting these recommendations is detailed in a separate Preparatory Memorandum and appendices and includes a description of planning and implementation of medical treatments, a literature review of medical treatments, an extensive ethical analysis, and feedback following meetings with patients and the advocacy groups who represent them.

Finnish legislation defines the requirements for the legal gender recognition of transsexuals (Act on Legal Recognition of the Gender of Transsexuals (Trans Act) 536/2002). The detailed requirements for providing the assessment and treatment to enable legal gender recognition are spelled out further in a Decree of the Ministry of Social Affairs and Health (1053/2002). The Trans Act and the related Decree apply to adults. For those who are not of legal age, there are no laws governing the provision and needs of transgender healthcare; however, these are subject to the Health Care Act of Finland (1326/2010), in particular section 7 (criteria for integrated care), section 7a (criteria for treatment options), section 8 (evidence-based, high quality, safe and appropriate care) and section 10 (rationale for centralization); and also to the Constitution of Finland (731/1999)'s section 6 on equality and section 19 on the right to adequate social and healthcare services. Finland's Act on the Status and Rights of Patients, (785/1992), and especially sections 5, 6, and 7, are also relevant.



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2. Recommendations' Target Population

These recommendations apply to minors suffering from dysphoria related to gender variance who are seeking a consultation regarding an evaluation of medical examination and treatment needs; the children and adolescents may identify with the opposite sex (transgender), or may identify as genderless, non-binary, or anywhere along or outside the male/female gender identity continuum (other gender).

3. Procedures Assessed

These recommendations focus on medical treatment procedures that aim to decrease suffering and functional impairment of gender-dysphoric minors.

4. Current Care

Cross-sex identification in childhood, even in extreme cases, generally disappears during puberty. However, in some cases, it persists or even intensifies. Gender dysphoria may also emerge or intensify at the onset of puberty. There is considerable variation in the timing of the onset of puberty in both sexes. The first-line treatment for gender dysphoria is psychosocial support and, as necessary, psychotherapy and treatment of possible comorbid psychiatric disorders.

Consultation appointments (for parents / caregivers) regarding pre-pubescent children's cross-sex identification or gender dysphoria are provided by the research group on the gender identity of minors at TAYS or HUS. However, ongoing support or other treatment of psychiatric disorders are provided through the local municipal services.

In clear cases of pre-pubertal onset of gender dysphoria that intensified during puberty, a referral can be made for an assessment by the research group at TAYS or HUS regarding the appropriateness for puberty suppression. If no contraindications to early intervention are identified, pubertal suppression with GnRH analogues (to suppress the effect of gonadotropin-releasing hormone) may be considered to prevent further development of secondary sex characteristics of the biological sex.

Adolescents who have already undergone puberty, whose gender dysphoria occurs in the absence of co-occurring symptoms requiring psychiatric treatment, and whose experience of transgender identity failed to resolve following a period of reflection, can be referred for assessment by the research group on the gender identity of minors at TAYS or HUS. Hormone therapy (testosterone/estrogen and anti-androgen) can be started after the diagnostic evaluations, but no earlier than age 16. Additionally, patients under 18 receive three to six months of GnRH analogue treatment prior to the initiation of cross-sex hormones in order to suppress the hormonal activity of the gonads. No gender confirmation surgeries are performed on minors.



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5. Risks, Benefits and Uncertainty

The literature review identified two studies with the total of 271 persons diagnosed with childhood-onset gender identity disorder and associated gender or body dysphoria that intensified after the onset of puberty (Preparatory Memorandum Appendix 1, Tables 15 and 16, pages 46-48).

In a smaller study of 70 adolescents, puberty was suppressed with the GnRH analogue at the average age of 14.8 (12-18 years) and puberty blockade continued for an average of 2 years. During the treatment period, the adolescents' mood improved, and the risk of behavioral disorders diminished, but gender dysphoria itself did not diminish, and there were no changes in body image. In a larger study consisting of 201 adolescents, 101 patients with the average age of 15.5 (12-18 years) started an 18-month psychological supportive intervention, and, additionally at six months, pubertal development was suppressed by starting GnRH analogue treatment. The other cohort of 100 only received psychological supportive intervention for 18 months. In both groups, statistically significant increases in global psychosocial functioning were found at 12 and 18 months; among those having received psychological intervention alone, the improvement in global functioning was already significant at the 6-month mark. Both studies lack long-term treatment follow-up into adulthood.

A recent Finnish study, published after the completion of this literature review, reported on the effect of initiating cross-sex hormone therapy on functioning, progression of developmental tasks of adolescence, and psychiatric symptoms. This study found that during cross-sex hormone therapy, problems in these areas did not decrease.

Potential risks of GnRH therapy include disruption in bone mineralization and the as yet unknown effects on the central nervous system. In trans girls, early pubertal suppression inhibits penile growth, requiring the use of alternative sources of tissue grafts for a potential future vaginoplasty. The effect of pubertal suppression and cross-sex hormones on fertility is not yet known.

6. Ethical Assessment

Although the ethics analysis did not systematically address the issues pertaining to children and adolescents, they have been discussed in several areas in the related documents (Preparatory Memorandum pages 52-62; Appendix 5).

According to the Health Care Act (section 8), healthcare services must be based on evidence and recognized treatment and operational practices. As far as minors are concerned, there are no medical treatment that can be considered evidence-based. At the same time, the numbers of minors developing gender dysphoria has increased. In this situation, it is vital to assure that children and young people are able to talk about their feelings, and that their feelings are acknowledged. The opportunity to reflect on one's experience should be easily accessible through the local health system (i.e., school or student health care, primary care). A young

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person's feelings should not be interpreted as immediately requiring specialized medical examinations or treatments.

In cases of children and adolescents, ethical issues are concerned with the natural process of adolescent identity development, and the possibility that medical interventions may interfere with this process. It has been suggested that hormone therapy (e.g., pubertal suppression) alters the course of gender identity development; i.e., it may consolidate a gender identity that would have otherwise changed in some of the treated adolescents. The reliability of the existing studies with no control groups is highly uncertain, and because of this uncertainty, no decisions should be made that can permanently alter a still-maturing minor's mental and physical development.

From the point of view of patient advocacy groups, halting puberty is providing young people with a period of reflection, rather than consolidating their gender identity. This is based on the premise that halting the development of one's permanent sex characteristics will improve the minor's social interactions, while allowing more time for diagnostic evaluations. Additionally, patient advocacy groups assert that early intervention with hormonal treatments will lead to improved outcomes for the patients who do eventually pursue gender reassignment. Professionals, for their part, consider it important to ensure that irreversible interventions, which may also have significant adverse effects, both physical and mental, are only performed on individuals who are able to understand the permanence of the changes and the potential for harm, and who are unlikely to regret such interventions. It is not known how the hormonal suppression of puberty affects young people's judgement and decision-making.

The Act on the Status and Rights of Patients (1992/785) states that the patient shall be provided with information about his/her state of health, the significance of the treatment, various alternative forms of treatment and their effects, and about other factors concerning treatment that have an effect on treatment decision-making. In a situation where a minor's identification with the opposite sex causes long-term and severe dysphoria, it is important to make sure that he/she understands the realistic potential of gender reassignment treatments to alter secondary sex characteristics, the reality of a lifelong commitment to medical therapy, the permanence of the effects, and the possible physical and mental adverse effects of the treatments. Although patients may experience regret, after reassignment treatments, there is no going back to the non-reassigned body and its normal functions. Brain development continues until early adulthood – about age 25, which also affects young people's ability to assess the consequences of their decisions on their own future selves for rest of their lives.

A lack of recognition of comorbid psychiatric disorders common among gender-dysphoric adolescents can also be detrimental. Since reduction of psychiatric symptoms cannot be achieved with hormonal and surgical interventions, it is not a valid justification for gender reassignment. A young person's identity and personality development must be stable so that they can genuinely face and discuss their gender dysphoria, the significance of their own feelings, and the need for various treatment options.

For children and adolescents, these factors are key reasons for postponing any interventions until adulthood.

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7. Conclusions

The first-line intervention for gender variance during childhood and adolescent years is psychosocial support and, as necessary, gender-explorative therapy and treatment for comorbid psychiatric disorders. Uncertainty related to gender identity should be dealt with according to the severity of symptoms and the need for treatment and should be handled at the school / student health care, primary health care at the local level, or in specialty care.

In adolescents, psychiatric disorders and developmental difficulties may predispose a young person to the onset of gender dysphoria. These young people should receive treatment for their mental and behavioral health issues, and their mental health must be stable prior to the determination of their gender identity.

Clinical experience reveals that autistic spectrum disorders (ASD) are overrepresented among adolescents suffering from gender dysphoria; even if such adolescents are presenting with gender dysphoria, rehabilitative interventions for ASD must be properly addressed.

In light of available evidence, gender reassignment of minors is an experimental practice. Based on studies examining gender identity in minors, hormonal interventions may be considered before reaching adulthood in those with firmly established transgender identities, but it must be done with a great deal of caution, and no irreversible treatment should be initiated. Information about the potential harms of hormone therapies is accumulating slowly and is not systematically reported. It is critical to obtain information on the benefits and risks of these treatments in rigorous research settings.

At a minimum, a consultation for a pre-pubescent child at the specialist setting at the TAYS includes an extensive assessment appointment costing EUR 369. If necessary, a day-long outpatient consultation can be arranged, costing EUR 1,408.

The consultation and assessment process for minors at the specialist settings of TAYS or HUS costs EUR 4,300. If it is determined that this process would be untimely, the minimum cost is EUR 640. An initial assessment / consultation by phone costs EUR 100.

The planning and monitoring costs for pubertal suppression are EUR 2,000 for the first year, and EUR 1,200 for subsequent years. The costs for the planning and monitoring of hormone treatments are a minimum of EUR 400 per year.

These costs do not take into account the additional costs of psychosocial support provided in the local level, the possible need for psychiatric treatment, or hormone treatment medication costs.

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8. Summary of the Recommendations

PALKO / COHERE maintains the following:

1. For the treatment of gender dysphoria due to variations in gender identity in minors, psychosocial support should be provided in school and student healthcare and in primary healthcare, and there must be sufficient competency to provide such support.
2. Consultation with a child or youth psychiatrist and the necessary psychiatric treatment and psychotherapy should be arranged locally according to the level of treatment needed.
3. If a child or young person experiencing gender-related anxiety has other simultaneous psychiatric symptoms requiring specialised medical care, treatment according to the nature and severity of the disorder must be arranged within the services of their own region, as no conclusions can be drawn on the stability of gender identity during the period of disorder caused by a psychiatric illness with symptoms that hamper development.

PALKO / COHERE considers that the consultation, periods of assessment, and treatments by the research group on the gender identity of minors at TAYS or HUS must be carried out according to the following principles:

1. Children who have not started puberty and are experiencing persistent, severe anxiety related to gender conflict and/or identification as the other sex may be sent for a consultation visit to the research group on the gender identity of minors at TAYS or HUS. Any need for support beyond the consultation visit or need for other psychiatric treatment should be addressed by local services according to the nature and severity of the problem.
2. If a child is diagnosed prior to the onset of puberty with a persistent experience of identifying as the other sex and shows symptoms of gender-related anxiety, which increases in severity in puberty, the child can be guided at the onset of puberty to the research group on the gender identity of minors at TAYS or HUS for an assessment of the need for treatment to suppress puberty. Based on these assessments, puberty suppression treatment may be initiated on a case-by-case basis after careful consideration and appropriate diagnostic examinations if the medical indications for the treatment are present and there are no contraindications. Therapeutic amenorrhea, i.e. prevention of menstruation, is also medically possible.
3. A young person who has already undergone puberty can be sent to the research clinic on the gender identity of minors at TAYS or HUS for extensive gender identity studies if the variation in gender identity and related dysphoria do not reflect the temporary search for identity typical of the development stage of adolescence and do not subside once the young person has had the opportunity to reflect on their identity but rather their identity and personality development appear to be stable.
4. Based on thorough, case-by-case consideration, the initiation of hormonal interventions that alter sex characteristics may be considered before the person is 18 years of age only if it can be ascertained that their identity as the other sex is of a permanent nature and causes severe dysphoria. In addition, it must be confirmed that the young person is able to understand the significance of irreversible treatments and the

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benefits and disadvantages associated with lifelong hormone therapy, and that no contraindications are present.

5. If a young person experiencing gender-related anxiety has experienced or is simultaneously experiencing psychiatric symptoms requiring specialized medical care, a gender identity assessment may be considered if the need for it continues after the other psychiatric symptoms have ceased and adolescent development is progressing normally. In this case, a young person can be sent by the specialized youth psychiatric care in their region for an extensive gender identity study by the TAYS or HUS research group on the gender identity of minors, which will begin the diagnostic studies. Based on the results of the studies, the need for and timeliness of medically justified treatments will be assessed individually.

Surgical treatments are not part of the treatment methods for dysphoria caused by gender-related conflicts in minors. The initiation and monitoring of hormonal treatments must be centralized at the research clinics on gender identity at HUS and TAYS.

9. Additional Evidence Gathering and Monitoring the Effectiveness of Recommendations

Moving forward, the following information must be obtained about the patients diagnosed and receiving treatments in Finland before re-evaluating these recommendations:

- Number of new patient referrals
- Number of patients starting the assessment period, and numbers of new transgender (F64.0) vs “other gender” (F64.8) diagnoses
- Whether the diagnosis remains stable or changes during the assessment phase
- Number of patients discontinuing the assessment period and the reasons for the discontinuation
- Adverse effects of treatments (especially long-term effects and effect on fertility)
- Number of patients regretting hormone therapy
- Analysis of the effects of the assessment and the treatment period on gender dysphoria outcomes, as measured by the Gender Congruence and Life Satisfaction Scale (GCLS)
- Analysis of the effects of the assessment and the treatment period on functional capacity and quality of life
- The prevalence of co-occurring psychiatric diagnoses (especially neurodevelopmental diagnoses F80-F90) among those diagnosed with / seeking treatment for gender dysphoria, and whether the presence of these co-occurring diagnoses impacts the ability to achieve the desired outcome (e.g. decreased dysphoria) in the assessment or the treatment phase.
- Whether the assessment and treatment periods lead to a reduction of suicide attempts
- Whether the assessment and treatment periods lead to a reduction in depression and distress



PALVELUVALIKOIMA

Tjänsteutbudet | Choices in health care

Recommendation

11(14)

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10. Appendices

Preparatory Memorandum, with Appendices 1-5.



Gender dysphoria in children and adolescents: an inventory of the literature

A systematic scoping review

SBU POLICY SUPPORT | EVIDENCE ASSESSMENT TO SUPPORT DECISION MAKERS IN SWEDEN

DECEMBER 2019 | WWW.SBU.SE/307E

Executive summary

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.

Conclusions

- ▶ We have not found any scientific studies which explains the increase in incidence in children and adolescents who seek the health 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.
- ▶ The scientific activity in the field seems high. A large part of the identified studies are published during 2018 and 2019.
- ▶ Almost all identified studies are observational, some with controls and some with evaluation before and after gender affirming treatment. No relevant randomised 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
 - the proportion starting endocrine treatment to delay puberty
 - the proportion starting gender affirming hormonal treatment
 - the proportion subjected to different gender affirming surgery

Background

The number of persons below age 18 who seeks the health care for gender dysphoria in Sweden has increased during the last decade. There is a debate as to why this happens and how it should be managed.

Aim

To assess the scientific literature for explanations of the increased number of children and adolescents seeking for gender dysphoria and to make an inventory of the literature on management and long-term effects.

Method

The following questions were assessed.

Are there any scientific studies explaining the increase in numbers seeking for gender dysphoria?

Population: Children and adolescents with gender dysphoria up to 18 years of age.

Intervention: Not applicable.

Control: Not applicable.

Outcome: Studies on incidence and prevalence of gender dysphoria and pattern of self-referral or referral.

EXHIBIT

6

Are there any scientific studies on long-term effects of treatment for gender dysphoria?

Population: Persons with gender dysphoria.

Intervention: Treatment for gender dysphoria.

Control: Any.

Outcome: Studies reporting long-term effects such as mental health, suicide attempts, suicide, cardiovascular effects, cancer development, bone health and regrets.

What scientific papers on diagnosis and treatment of gender dysphoria has been published after the National Board of Health and Welfare in Sweden issued its national support for managing children and adolescents with gender dysphoria in 2015?

Population: Children and adolescents with gender dysphoria up to 18 years of age.

Intervention: Diagnosis and treatment for gender dysphoria.

Control: Any.

Outcome: Studies on diagnosis and treatment.

This review is limited to peer reviewed papers with primary data and systematic reviews following PRISMA-standards. Case studies, meeting abstracts and editorials where not included. Only studies written in English or Scandinavian languages were eligible.

A structured systematic literature search in the following databases CINAHL (EBSCO), Cochrane Library (Wiley), EMBASE (Embase.com), PsycINFO (EBSCO), PubMed (NLM), Scopus (Elsevier), SocINDEX (EBSCO). The searches were finalised September 19, 2019.

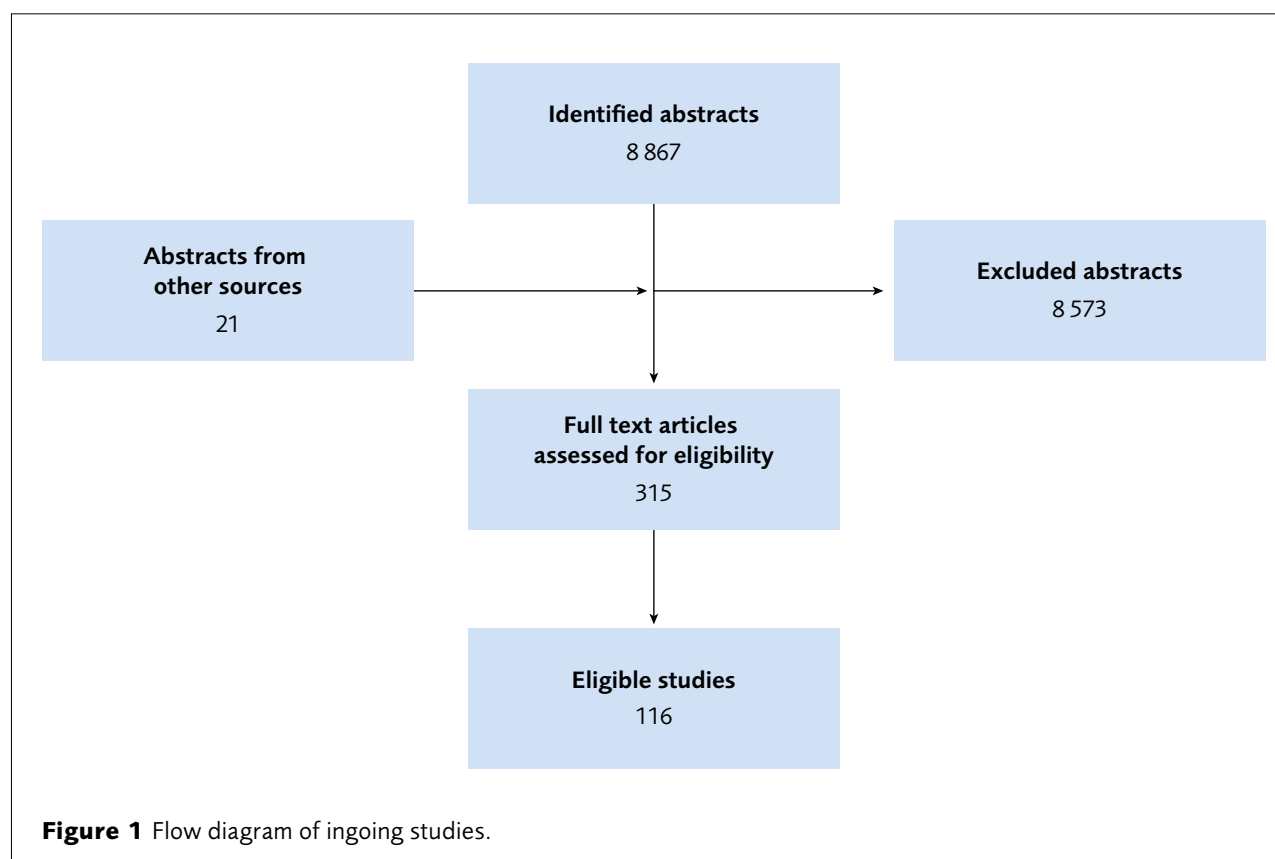
The studies were assessed for their relevance to the questions by two reviewers independently. Assessment of risk of bias, compilation of data or grading of evidence was not done.

Results/discussion

No studies explaining the increase of children and adolescents seeking for gender dysphoria were identified. The literature on management and long-term effects in children and adolescents is sparse, particularly regarding gender affirming surgery. All identified studies are observational, and few are controlled or followed-up over time. Much of the data in the literature are from the University Medical Centre in Amsterdam based on their management tradition. A large part of the literature that was considered relevant was published during 2018 and 2019.

Appendices

For search strategies, excluded articles, references and tables, see www.sbu.se/307e



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Policy Change Regarding Hormonal Treatment of Minors with Gender Dysphoria at Tema Barn - Astrid Lindgren Children's Hospital.

Background

The hormonal treatment of children and adolescents with gender dysphoria may consist of puberty-blocking treatment initiated at the onset of puberty, and cross-sex hormones initiated at the age of 16. These treatments are controversial and have recently become subject to increased attention and scrutiny both nationally and internationally. In December 2019, the SBU (*Swedish Agency for Health Technology Assessment and Assessment of Social Services*) published an overview of the knowledge base which showed a lack of evidence for both the long-term consequences of the treatments, and the reasons for the large influx of patients in recent years. These treatments are potentially fraught with extensive and irreversible adverse consequences such as cardiovascular disease, osteoporosis, infertility, increased cancer risk, and thrombosis. This makes it challenging to assess the risk / benefit for the individual patient, and even more challenging for the minors and their guardians to be in a position of an informed stance regarding these treatments.

A highly publicized court case in Great Britain shed light on this issue and in a recent ruling (December 1st, 2020), established overarching problems associated with puberty-blocking treatment. Further, the ruling specifically establishes that it is highly unlikely, if at all possible, for an individual under the age of 16 to give informed consent to this treatment. For individuals between the age of 16 and 18, the court considers it advisable to request court approval before starting hormonal treatment, since the treatment should be considered experimental. As a result of this ruling, the NHS (National Health Service) put an end to initiating hormonal treatments in new cases of individuals under 16, while recommending a thorough review of ongoing, actively treated cases. For patients between ages 16 and 18, it is recommended that the treating physician receives court approval before cross-sex hormones are initiated.

Executive Decisions

- In light of the above, and based on the precautionary principle, which should always be applied, it has been decided that hormonal treatments (i.e., puberty blocking and cross-sex hormones) will not be initiated in gender dysphoric patients under the age of 16.
- For patients between ages 16 and 18, it has been decided that treatment may only occur within the clinical trial settings approved by the EPM (*Ethical Review Agency/Swedish Institutional Review Board*). The patient must receive comprehensive information about potential risks of the treatment, and a careful assessment of the patient's maturity level must be conducted to determine if the patient is capable of evaluating, and consenting to, the treatment.

- These changes do not affect the continued psychological and psychiatric care within BUP (Public child and adolescent psychiatry) for patients under 18 years of age.
- These changes apply from April 1, 2021.

For patients currently treated with puberty blockade or cross-sex hormones, a careful individual assessment to determine whether treatment should be stopped or continued must be performed by the treating provider. During this assessment, it is important to present appropriate information about the uncertainty in the state of evidence regarding long-term effects and potential risks of the treatment, in order to make it possible for patients and guardians to make as well-informed decisions as possible about consenting to a potential continued treatment. The young patients' degree of maturity and ability to consent, as well as other indications should factor into these decisions.

Guideline Regarding Hormonal Treatment of Minors with Gender Dysphoria at Tema Barn - Astrid Lindgren Children's Hospital (ALB).

Background

The hormonal treatment of children and adolescents with gender dysphoria may consist of puberty-blocking treatment which may be initiated at the onset of puberty, and cross-sex hormones which may be initiated at the age of 16. These treatments are controversial and have recently become subject to increased attention and scrutiny both nationally and internationally.

In December 2019, the SBU (*Swedish Agency for Health Technology Assessment and Assessment of Social Services*) published an overview of the knowledge base which showed a lack of evidence for both the long-term consequences of the treatments, and the reasons for the large influx of patients in recent years. In October 2020, NICE (*The National Institute for Health and Care Excellence, UK*) also performed an evidence review of GnRHa (*puberty blocker*) and of cross-sex hormone treatments of children and adolescents with gender dysphoria. Taken together, they show that the studies conducted to date are small, uncontrolled observational studies providing low quality evidence that the treatments have the desired effect, and that we have very little knowledge about their safety in the long term.

A highly publicized court case from Great Britain has shed light on this issue and in a judgment from December 1st, 2020 the court establishes the overarching problem of puberty-blocking treatment and that informed consent for this treatment is highly doubtful, if at all possible, under 16 years of age. For ages between 16 and 18, the court considers it advisable to request a court approval before starting hormonal treatment, since the treatment should be regarded as experimental. As a result of this ruling, the NHS (*National Health Service*) discontinued initiating hormonal treatments in new cases of individuals under 16, while recommending a thorough review of ongoing actively treated cases. For patients between ages 16 and 18, it is recommended that the treating physician receives court approval before cross-sex hormones are initiated. During the Spring of 2020 the NHS changed its public stance regarding puberty blocking treatment, from considering it fully reversible, to now describing it as having uncertain long-term consequences. Following the above-mentioned ruling, the NHS changed their guidelines to no longer initiate hormonal treatment of gender dysphoria in patients under 16 years of age.

These treatments are potentially fraught with extensive and irreversible adverse consequences such as cardiovascular disease, osteoporosis, infertility, increased cancer risk, and thrombosis. This makes it challenging to assess the risk / benefit for the individual patient, and even more challenging for the minors or their guardians to be in a position of an informed stance regarding these treatments.



- In light of the above, and based on the precautionary principle, which should always be applied, the ALB will not initiate hormonal treatment (*i.e.*, *puberty blocking and cross-sex hormones*, see above) for patients with gender dysphoria.
- Hormonal treatment will only be allowed to take place in a clinical trial setting that received ethical approval by the EPM (*Ethical Review Agency/Swedish Institutional Review Board*). The patient must receive comprehensive information about potential risks of the treatment, and a careful assessment of the patient's maturity level must be conducted to determine if the patient is capable of taking an informed stance on, and consenting to, the treatment.
- These changes are effective as of May 1, 2021.

For patients currently treated with puberty blockade or cross-sex hormones, a careful individual assessment to determine whether treatment should be stopped or continued must be performed by the physician responsible for the patient. In such an assessment, it is important to present adequate information about the uncertainty in the state of evidence regarding long-term effects and potential risks of the treatment, in order to make it possible for patients and guardians to make an assessment, and an as well-informed decision as possible, about consenting to a potential continued treatment. The young patients' degree of maturity in their ability to consent, and remaining indication should factor into this decision.

Signed by:

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References:

SBU (Swedish Agency for Health Technology Assessment and Assessment of Social Services). "[Könsdysfori hos barn och unga - En kunskapskartläggning rapport 307](#)". ("[Gender Dysphoria in Children and Adolescents - An overview of the literature](#)" report 307.) Record Number: SBU 2019/427

Judgement in the Great Britain court case:

<https://www.judiciary.uk/wp-content/uploads/2020/12/Bell-v-Tavistock-Judgment.pdf>

NHS change in procedure after the ruling:

<https://www.england.nhs.uk/wp-content/uploads/2020/12/Amendment-to-Gender-Identity-Development-Service-Specification-for-Children-and-Adolescents.pdf>

NICE reports:

Evidence review: Gonadotrophin releasing hormone analogues for children and adolescents with gender dysphoria

<https://arms.nice.org.uk/resources/hub/1070905/attachment>

Evidence review: Gender-affirming hormones for children and adolescents with gender dysphoria

<https://arms.nice.org.uk/resources/hub/1070871/attachment>

Selection of articles where potential risks of the treatment are described:

Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, Rosenthal SM, Safer JD, Tangpricha V, T'Sjoen GO. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2017 Nov 1; 102(11):3869-3903. doi: 10.1210/jc.2017-01658.

Nota NM, Wiepjes CM, de Blok CJM, Gooren LJG, Kreukels BPC, den Heijer M. Occurrence of Acute Cardiovascular Events in Transgender Individuals Receiving Hormone Therapy. *Circulation*. 2019 Mar 12;139(11):1461-1462. doi: 10.1161/CIRCULATIONAHA.118.038584. PMID: 30776252.

Meyer G, Boczek U, Bojunga J. Hormonal Gender Reassignment Treatment for Gender Dysphoria. *Dtsch Arztebl Int*. 2020 Oct 23; 117(43):725-732. doi: 10.3238/arztebl.2020.0725. PMID: 33559593; PMCID: PMC7871443.

Mayhew AC, Gomez-Lobo V. Fertility Options for the Transgender and Gender Nonbinary Patient. *J Clin Endocrinol Metab*. 2020 Oct 1;105(10):3335-45. doi: 10.1210/clinem/dgaa529. PMID: 32797184; PMCID: PMC7455280.

Cheng PJ, Pastuszak AW, Myers JB, Goodwin IA, Hotelling 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.

Nota NM, Wiepjes CM, de Blok CJM, Gooren LJG, Peerdeman SM, Kreukels BPC, den Heijer M. The occurrence of benign brain tumours in trans gender individuals during cross-sex hormone treatment. *Brain*. 2018 Jul 1;141(7):2047-2054. doi: 10.1093/brain/awy108. PMID: 29688280.

Stevenson MO, Tangpricha V. Osteoporosis and Bone Health in Transgender Persons. *Endocrinol Metab Clin North Am*. 2019 Jun;48(2):421-427. doi: 10.1016/j.ecl.2019.02.006. Epub 2019 Mar 23. PMID: 31027549; PMCID: PMC6487870.

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.

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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 themselves¹ 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 ($\pm$ 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 [$\pm$ 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 [$\pm$ 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 [$\pm$ 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 [$\pm$ SD] body image (BIS) scores were not statistically significantly different from baseline compared with follow-up for primary sexual characteristics (n=57, 4.10 [$\pm$ 0.56] versus 3.98 [$\pm$ 0.71], p=0.145), secondary sexual characteristics (n=57, 2.74 [$\pm$ 0.65] versus 2.82 [$\pm$ 0.68], p=0.569) or neutral body characteristics (n=57, 2.41 [$\pm$ 0.63] versus 2.47 [$\pm$ 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 [$\pm$ SD] CGAS score was statistically significantly higher (improved) from baseline compared with follow-up (n=41, 70.24 [$\pm$ 10.12] versus 73.90 [$\pm$ 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 [$\pm$ SD] CBCL scores were statistically significantly lower (improved) from baseline compared with follow-up for Total T score (n=54, 60.70 [$\pm$ 12.76] versus 54.46 [$\pm$ 11.23], p<0.001), internalising T score (n=54, 61.00 [$\pm$ 12.21] versus 52.17 [$\pm$ 9.81], p<0.001) and externalising T score (n=54, 58.04 [$\pm$ 12.99] versus 53.81 [$\pm$ 11.86], p=0.001). The mean [$\pm$ SD] YSR scores were statistically significantly lower (improved) from baseline compared with follow-up for Total T score (n=54, 55.46 [$\pm$ 11.56] versus 50.00 [$\pm$ 10.56], p<0.001), internalising T score (n=54, 56.04 [$\pm$ 12.49] versus 49.78 [$\pm$ 11.63], p<0.001) and externalising T score (n=54, 53.30 [$\pm$ 11.87] versus 49.98 [$\pm$ 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 [$\pm$ SD] CGAS score was statistically significantly higher (improved) after 6 months (n=60, 64.70 [$\pm$ 13.34]) and 12 months (n=35, 67.40 [$\pm$ 13.39]) compared with baseline (n=101, 58.72 [$\pm$ 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 [$\pm$ SD] CBCL scores for each group, but statistical analysis is unclear (transfemales receiving GnRH analogues 57.4 [$\pm$ 9.8], transfemales not receiving GnRH analogues 58.2 [$\pm$ 9.3], transmales receiving GnRH analogues 57.5 [$\pm$ 9.4], transmales not receiving GnRH analogues 63.9 [$\pm$ 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 [$\pm$ SD] for lumbar bone mineral apparent density (BMAD) was statistically significantly lower at 1 year compared with baseline in transfemales (baseline 0.859 [$\pm$ 0.154], 1 year -0.228 [$\pm$ 1.027], $p=0.000$) and transmales (baseline -0.186 [$\pm$ 1.230], 1 year -0.541 [$\pm$ 1.396], $p=0.006$).
- The mean z-score [$\pm$ SD] for lumbar BMAD was statistically significantly lower after receiving GnRH analogues for 2 years compared with baseline in transfemales (baseline 0.486 [$\pm$ 0.809], 2 years -0.279 [$\pm$ 0.930], $p=0.000$) and transmales (baseline -0.361 [$\pm$ 1.439], 2 years -0.913 [$\pm$ 1.318], $p=0.001$).
- The mean z-score [$\pm$ 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 [$\pm$ 0.781], 2 years -0.600 [$\pm$ 1.059], $p=0.002$) and transmales (baseline -1.075 [$\pm$ 1.145], 2 years -1.779 [$\pm$ 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 [$\pm$ 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 [$\pm$ 0.90], gender-affirming hormones -0.50 [$\pm$ 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], $p\leq 0.0001$).

- 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], $p \leq 0.1$) 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 ($\pm$ SD) IQ in transfemales receiving GnRH analogues was 94.0 ($\pm$ 10.3) and 109.4 ($\pm$ 21.2) in the control group. In transmales receiving GnRH analogues the mean ($\pm$ SD) IQ was 95.8 ($\pm$ 15.6) and 98.5 ($\pm$ 15.9) in the control group.
- The mean ($\pm$ SD) reaction time in transfemales receiving GnRH analogues was 10.9 ($\pm$ 4.1) and 9.9 ($\pm$ 3.1) in the control group. In transmales receiving GnRH analogue it was 9.9 ($\pm$ 3.1) and 10.0 ($\pm$ 2.0) in the control group.
- The mean ($\pm$ SD) accuracy score in transfemales receiving GnRH analogues was 73.9 ($\pm$ 9.1) and 83.4 ($\pm$ 9.5) in the control group. In transmales receiving GnRH analogues it was 85.7 ($\pm$ 10.5) and 88.8 ($\pm$ 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 [$\pm$ SD] UGDS score of 51.6 [$\pm$ 9.7] compared with sex assigned at birth females (56.1 [$\pm$ 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 [$\pm$ 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 [$\pm$ 9.70] versus 56.57 [$\pm$ 3.89]) and follow up (n=not reported, 49.67 [$\pm$ 9.47] versus 56.62 [$\pm$ 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 [$\pm$ 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 [$\pm$ SD]: 5.71 [$\pm$ 4.31] versus 10.34 [$\pm$ 8.24]) and follow-up (n=not reported, 3.50 [$\pm$ 4.58] versus 6.09 [$\pm$ 7.93]), between sex difference $p = 0.057$

- The mean [$\pm$ 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 [$\pm$ SD]: 5.22 [$\pm$ 2.76] versus 6.43 [$\pm$ 2.78]) and follow-up (n=not reported, 5.00 [$\pm$ 3.07] versus 6.39 [$\pm$ 2.59]), between sex difference $p=0.022$
- The mean [$\pm$ 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 [$\pm$ SD]: 4.33 [$\pm$ 2.68] versus 7.00 [$\pm$ 2.36]) and follow-up (n=not reported, 4.39 [$\pm$ 2.64] versus 6.17 [$\pm$ 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 [$\pm$ 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 [$\pm$ SD]: 4.02 [$\pm$ 0.61] versus 4.16 [$\pm$ 0.52]) and follow up (n=not reported, 3.74 [$\pm$ 0.78] versus 4.17 [$\pm$ 0.58]) between sex difference $p=0.047$.
- The mean [$\pm$ 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 [$\pm$ SD]: 2.66 [$\pm$ 0.50] versus 2.81 [$\pm$ 0.76]) and follow up (n=not reported, 2.39 [$\pm$ 0.69] versus 3.18 [$\pm$ 0.42]), between sex difference $p=0.001$.
- The mean [$\pm$ 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 [$\pm$ 0.58] versus 2.24 [$\pm$ 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 [$\pm$ SD] CGAS scores at baseline compared with sex assigned at birth females (n=201, 55.4 [$\pm$ 12.7] versus 59.2 [$\pm$ 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 [$\pm$ SD] CGAS scores compared with sex assigned at birth females at baseline (n=54, 73.10 [$\pm$ 8.44] versus 67.25 [$\pm$ 11.06]) and follow up (n=54, 77.33 [$\pm$ 8.69] versus 70.30 [$\pm$ 9.44]), between sex difference p=0.021.
- Sex assigned at birth males had statistically lower mean [$\pm$ SD] CBCL externalising T scores compared with sex assigned at birth females at baseline (n=54, 54.71 [$\pm$ 12.91] versus 60.70 [$\pm$ 12.64]) and follow up (n=54, 48.75 [$\pm$ 10.22] versus 57.87 [$\pm$ 11.66]), between sex difference p=0.015.
- Sex assigned at birth males had statistically lower mean [$\pm$ SD] YSR externalising T scores compared with sex assigned at birth females at both baseline (n=54, 48.72 [$\pm$ 11.38] versus 57.24 [$\pm$ 10.59]) and follow up (n=54, 46.52 [$\pm$ 9.23] versus 52.97 [$\pm$ 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 ($\pm$SD) age 15.1 ($\pm$2.4) years in transfemales and 15.8 ($\pm$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 $\pm$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 [$\pm$SD] age: 14.75 [$\pm$1.92] years), and - shortly before starting gender-affirming hormones (mean [$\pm$SD] age: 16.64 [$\pm$1.90] years). The mean ($\pm$SD) UGDS score was not statistically significantly different at baseline compared with follow-up (n=41, 53.20 [$\pm$7.91] versus 53.9 [$\pm$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 [$\pm$SD] age: 14.75 [$\pm$1.92] years), and • shortly before starting gender-affirming hormones (mean [$\pm$SD] age: 16.64 [$\pm$1.90] years). The mean ($\pm$SD) depression (BDI) score was statistically significantly lower (improved) from baseline compared with follow-up (n=41, 8.31 [$\pm$7.12] versus 4.95 [$\pm$6.72], p=0.004) (VERY LOW). This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, may reduce depression.
Impact on mental health: anger Certainty of evidence: very low	This is a critical outcome because self-harm and thoughts of suicide have the potential to result in significant physical harm and, for completed suicides, the death of the young person. One uncontrolled, prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on anger in children and adolescents with gender dysphoria. Anger was measured using the Trait Anger Scale of the State-Trait Personality Inventory (TPI). This is a validated 20-item inventory tool which measures the intensity of anger as the disposition to experience angry feelings as a personality trait. Higher scores indicate greater anger. The study provided evidence for anger measured at 2 time points: • before starting a GnRH analogue (mean [$\pm$SD] age: 14.75 [$\pm$1.92] years), and • shortly before starting gender-affirming hormones (mean [$\pm$SD] age: 16.64 [$\pm$1.90] years). The mean ($\pm$SD) anger (TPI) score was not statistically significantly different at baseline compared with follow-up (n=41, 18.29 [$\pm$5.54] versus 17.88 [$\pm$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 [$\pm$SD] age: 14.75 [$\pm$1.92] years), and • shortly before starting gender-affirming hormones (mean [$\pm$SD] age: 16.64 [$\pm$1.90] years). The mean ($\pm$SD) anxiety (STAI) score was not statistically significantly different at baseline compared with follow-up (n=41, 39.43 [$\pm$10.07] versus 37.95 [$\pm$9.38], p=0.276) (VERY LOW). This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, does not affect levels of anxiety.
Quality of life	This is a critical outcome because gender dysphoria in children and adolescents may be associated with a significant reduction in health-related quality of life. No evidence was identified.
Important outcomes	
Impact on body image Certainty of evidence: very low	This is an important outcome because some children and adolescents with gender dysphoria may want to take steps to suppress features of their physical appearance associated with their sex assigned at birth or accentuate physical features of their desired gender. One uncontrolled, prospective observational longitudinal study provided evidence relating to the impact on body image (de Vries et al. 2011). Body image was measured using the Body Image Scale (BIS) which is a validated 30-item scale covering 3 aspects: primary, secondary and neutral body characteristics. Higher scores represent a higher degree of body dissatisfaction. The study (de Vries et al. 2011) provided evidence for body image measured at 2 time points: • before starting a GnRH analogue (mean [$\pm$SD] age: 14.75 [$\pm$1.92] years), and • shortly before starting gender-affirming hormones (mean [$\pm$SD] age: 16.64 [$\pm$1.90] years). The mean ($\pm$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 [$\pm$0.56] versus 3.98 [$\pm$0.71], p=0.145) • secondary sexual characteristics (n=57, 2.74 [$\pm$0.65] versus 2.82 [$\pm$0.68], p=0.569) • neutral body characteristics (n=57, 2.41 [$\pm$0.63] versus 2.47 [$\pm$0.56], p=0.620) (VERY LOW). This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender affirming hormones, does not affect body image.
Psychosocial impact: global functioning Certainty of evidence: very low	This is an important outcome because gender dysphoria in children and adolescents is associated with internalising and externalising behaviours, and emotional and behavioural problems which may impact on social and occupational functioning. One uncontrolled, observational, prospective cohort study (de Vries et al 2011) and one prospective cross-sectional cohort study (Costa et al. 2015) provided evidence relating to psychosocial impact in terms of global functioning. Global functioning was measured using the Children's Global Assessment Scale (CGAS). The CGAS tool is a validated measure of global functioning on a single rating scale from 1 to 100. Lower scores indicate poorer functioning. One study (de Vries et al. 2011) provided evidence for global functioning (CGAS) at 2 time points: • before starting a GnRH analogue (mean [$\pm$SD] age: 14.75 [$\pm$1.92] years), and • shortly before starting gender-affirming hormones (mean [$\pm$SD] age: 16.64 [$\pm$1.90] years). The mean ($\pm$SD) CGAS score was statistically significantly higher (improved) from baseline compared with follow-up (n=41, 70.24 [$\pm$10.12] versus 73.90 [$\pm$9.63], p=0.005) (VERY LOW). One study (Costa et al. 2015) in adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support (the immediately eligible group) or continued psychological support only (the delayed eligible group who did not receive GnRH analogues) provided evidence for global functioning (CGAS) measured at 4 time points: • at baseline (T0) in both groups, • after 6 months of psychological support in both groups (T1), • after 6 months of GnRH analogues and 12 months of psychological support in the immediately eligible group and 12 months of psychological support only in the delayed eligible group (T2), and • after 18 months of psychological support and 12 months of GnRH analogues in the immediately eligible group and after 18 months of psychological support only in the delayed eligible group (T3). The mean [$\pm$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 ($\pm$SD) CGAS score was not statistically significantly different at: • T1 compared with T0 • T2 compared with T1 • T3 compared with T2. The mean ($\pm$SD) CGAS score was statistically significantly higher (improved) at: • T2 compared with T0 (n=60, 64.70 [$\pm$13.34] versus n=101, 58.72 [$\pm$11.38], p=0.003) • T3 compared with T0 (n=35, 67.40 [$\pm$13.39] versus n=101, 58.72 [$\pm$11.38], p<0.001) • T3 compared with T1 (n=35, 67.40 [$\pm$13.93] versus n=101, 60.89 [$\pm$12.17], p<0.001) (VERY LOW). These studies provide very low certainty evidence that during treatment with GnRH analogues, global functioning may improve over time. However, there was no statistically significant difference in global functioning between GnRH analogues plus psychological support compared with psychological support only at any time point.
Psychosocial impact: psychosocial functioning Certainty of evidence: very low	This is an important outcome because gender dysphoria in children and adolescents is associated with internalising and externalising behaviours, and emotional and behavioural problems which may impact on social and occupational functioning. Two studies provided evidence for this outcome. One uncontrolled, observational, prospective cohort study (de Vries et al. 2011) and 1 cross-sectional observational study (Staphorsius et al. 2015) assessed psychosocial functioning using the Child Behaviour Checklist (CBCL) and the self-administered Youth Self-Report (YSR). The CBCL is a checklist parents complete to detect emotional and behavioural problems in children and adolescents. YSR is similar but is self-completed by the child or adolescent. The scales consist of a Total problems score, which is the sum of the scores of all the problem items. An internalising problem scale sums the anxious/depressed, withdrawn-depressed, and somatic complaints scores while the externalising problem scale combines rule-breaking and aggressive behaviour. The standard scores are scaled so that 50 is average for the child or adolescent's age and gender, with a SD of 10 points. Higher scores indicate greater problems, with a T-score above 63 considered to be in the clinical range. One study (de Vries et al. 2011) provided evidence for psychosocial functioning (CBCL and YSR scores) at 2 time points: • before starting a GnRH analogue (mean [$\pm$SD] age: 14.75 [$\pm$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/cm³ 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/cm³ 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/cm³ 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/cm³ 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/m² 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 [$\pm$SD]: GnRH analogue 0.17 [$\pm$1.18], gender-affirming hormone -0.72 [$\pm$0.99], $p < 0.001$) (VERY LOW). Actual lumbar BMD in g/cm² 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 [$\pm$SD]: GnRH analogues 0.95 [$\pm$0.12], gender-affirming hormones 0.91 [$\pm$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], $p \leq 0.1$) 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/m² 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 [$\pm$SD] GnRH analogue 0.92 [$\pm$0.10], gender-affirming hormone 0.88 [$\pm$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 [$\pm$SD] GnRH analogue 94.0 [$\pm$10.3], control 109.4 [$\pm$21.2]). IQ transmales (GnRH analogue 95.8 [$\pm$15.6], control 98.5 [$\pm$15.9]). • Reaction time in transfemales (mean [$\pm$SD] GnRH analogue 10.9 [$\pm$4.1], control: 9.9 [$\pm$3.1]). Reaction time transmales (GnRH analogue 9.9 [$\pm$3.1], control 10.0 [$\pm$2.0]). • Accuracy score in transfemales (GnRH analogue 73.9 [$\pm$9.1], control 83.4 [$\pm$9.5]). Accuracy score in transmales (GnRH analogue 85.7 [$\pm$10.5], control 88.8 [$\pm$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 [$\pm$SD] baseline 70 [$\pm$12], 1 year 66 [$\pm$13], $p=0.20$). • There was a statistically significant decrease between baseline and 1 year for serum creatinine in transmales (baseline 73 [$\pm$8], 1 year 68 [$\pm$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)	Some studies reported data separately for sex assigned at birth males (transfemales). This included some direct comparisons with sex assigned at birth females (transmales).
Certainty of evidence: Very low	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 ($\pm$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 [$\pm$SD]: 47.95 [$\pm$9.70] versus 56.57 [$\pm$3.89]) and T1 (n=not reported, 49.67 [$\pm$9.47] versus 56.62 [$\pm$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 ($\pm$SD) UGDS score of 51.6 [$\pm$9.7] compared with sex assigned at birth females (56.1 [$\pm$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 ($\pm$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 [$\pm$SD]: 5.71 [$\pm$4.31] versus 10.34 [$\pm$8.24]) and T1 (n=not reported, 3.50 [$\pm$4.58] versus 6.09 [$\pm$7.93]), between sex difference $p = 0.057$ - The mean ($\pm$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 [$\pm$SD]: 5.22 [$\pm$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 ($\pm$ 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 [$\pm$ 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 ($\pm$ 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 [$\pm$ 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 ($\pm$ 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 [$\pm$ 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 ($\pm$ 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 [$\pm$ 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 ($\pm$ SD) CGAS scores compared with sex assigned at birth females at both baseline (T0) (n=54, 73.10 [$\pm$ 8.44] versus 67.25 [$\pm$ 11.06]) and T1 (n=54, 77.33 [$\pm$ 8.69] versus 70.30 [$\pm$ 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 ($\pm$ SD) CBCL externalising T scores compared with sex assigned at birth females at both T0 (n=54, 54.71 [$\pm$ 12.91] versus 60.70 [$\pm$ 12.64]) and T1 (n=54, 48.75 [$\pm$ 10.22] versus 57.87 [$\pm$ 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 ($\pm$ SD) YSR externalising T scores compared with sex assigned at birth females at both T0 (n=54, 48.72 [$\pm$ 11.38] versus 57.24 [$\pm$ 10.59]) and T1 (n=54, 46.52 [$\pm$ 9.23] versus 52.97 [$\pm$ 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 ($\pm$ SD CGAS scores at baseline) compared with sex assigned at birth females (n=201, 55.4 [$\pm$ 12.7] versus 59.2 [$\pm$ 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?**

Outcome	Evidence statement										
Diagnostic criteria	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.										
Age when GnRH analogues started	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 border="1"> <thead> <tr> <th>Study</th><th>Mean age (±SD)</th></tr> </thead> <tbody> <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> </tbody> </table>	Study	Mean age (±SD)	Costa et al. 2015	16.5 years (±1.3)	de Vries et al. 2011	13.6 years (±1.8)	Joseph et al. 2019	13.2 years (±1.4) in transfemales 12.6 years (±1.0) in transmales	Khatchadourian et al. 2014	14.7 years (±1.9)
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Costa et al. 2015	16.5 years (±1.3)										
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Khatchadourian et al. 2014	14.7 years (±1.9)										

	Klink et al. 2015	14.9 years (± 1.9) in transfemales 15.0 years (± 2.0) in transmales
	Study	Median age (range)
	Brik et al. 2020	15.5 years (11.1–18.6) in transfemales 16.1 years (10.1–17.9) in transmales
	Schagen et al. 2016	13.6 years (11.6–17.9) in transfemales 14.2 years (11.1–18.6) in transmales
	Vlot et al. 2017	13.5 years (11.5–18.3) in transfemales 15.1 years (11.7–18.6) in transmales
	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.	
Duration of treatment	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.	

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 ($\pm$ SD) BDI-II score decreasing from 8.31 ($\pm$ 7.12) at baseline to 4.95 ($\pm$ 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 ($\pm$ SD) CGAS score statistically significantly increased over time from 70.24 [$\pm$ 10.12] at baseline to 73.90 [$\pm$ 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 [$\pm$ SD] 58.72 [$\pm$ 11.38] compared with 67.40 [$\pm$ 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 ($\pm$ 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); leuporelin/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. <u>A: Clinical Effectiveness</u> <i>Critical to decision making</i> • 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. <i>Important to decision making</i> • 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. <u>B: Safety</u> - 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: - Impact of the drug use such as its impact on bone density, arterial hypertension, cognitive development/functioning - Impact of withdrawing the drug such as, slipped upper femoral epiphysis, reversibility on the reproductive system, and any others as reported. <u>C: Cost effectiveness</u> 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 cetorelix.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 cetorelix.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 cetorelix.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 cetorelix.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 cetorelix.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 cetorelix.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)

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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 cetorelix/ (2278)
 103 cetorelix.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 cetorelix.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.

#1 [mh ^"Gender Dysphoria"] 3
 #2 [mh ^"gender identity"] 227
 #3 [mh ^"sexual and gender disorders"] 2
 #4 [mh ^transsexualism] 27
 #5 [mh ^"transgender persons"] 36
 #6 [mh ^"health services for transgender persons"] 0
 #7 [mh "sex reassignment procedures"] 4
 #8 (gender* NEAR/3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus*
 or minorit* or queer*)):ti,ab 308
 #9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or
 transmen* or transperson* or transpeopl*):ti,ab 929
 #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
 #14 [mh infant] or [mh ^"infant health"] or [mh ^"infant welfare"] 27769
 #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
 #16 [mh child] or [mh "child behavior"] or [mh ^"child health"] or [mh ^"child welfare"] 42703
 #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
 #31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*):ti,ab 0
 #32 #30 or #31 2146
 #33 [mh ^"Gonadotropin-Releasing Hormone"] 1311
 #34 (pubert* NEAR/3 block*):ti,ab 1
 #35 ((gonadotrophin or gonadotropin) and releasing):ti,ab 2095
 #36 (GnRH NEAR/2 analog*):ti,ab 493
 #37 GnRH*:ti,ab 3764
 #38 "GnRH agonist*":ti,ab 1399
 #39 [mh ^"Triptorelin Pamoate"] 451
 #40 triptorelin:ti,ab 451
 #41 arvekap:ti,ab 4
 #42 ("AY 25650" or AY25650):ti,ab 0
 #43 ("BIM 21003" or BIM21003):ti,ab 0
 #44 ("BN 52014" or BN52014):ti,ab 0
 #45 ("CL 118532" or CL118532):ti,ab 0
 #46 Debio:ti,ab 301
 #47 diphereline:ti,ab 25
 #48 moapar:ti,ab 0
 #49 pamorelin:ti,ab 5
 #50 trelstar:ti,ab 3

#51	triptodur:ti,ab	0	
#52	("WY 42422" or WY42422):ti,ab	0	
#53	("WY 42462" or WY42462):ti,ab	0	
#54	gonapeptyl:ti,ab	11	
#55	decapeptyl:ti,ab	135	
#56	salvacyl:ti,ab	0	
#57	[mh ^Buserelin]	290	
#58	Buserelin:ti,ab	339	
#59	bigonist:ti,ab	0	
#60	("hoe 766" or hoe-766 or hoe766):ti,ab	11	
#61	profact:ti,ab	1	
#62	receptal:ti,ab	4	
#63	suprecur:ti,ab	0	
#64	suprefact:ti,ab	28	
#65	tiloryth:ti,ab	0	
#66	histrelin:ti,ab	5	
#67	"LHRH-hydrogel implant":ti,ab	0	
#68	("RL 0903" or RL0903):ti,ab	0	
#69	("SPD 424" or SPD424):ti,ab	0	
#70	goserelin:ti,ab	761	
#71	[mh ^goserelin]	568	
#72	("ici 118630" or ici118630):ti,ab	7	
#73	("ZD-9393" or ZD9393):ti,ab	1	
#74	zoladex:ti,ab	318	
#75	leuprorelin:ti,ab	248	
#76	carcinil:ti,ab	0	
#77	enanton*:ti,ab	21	
#78	ginecrin:ti,ab	1	
#79	leuplin:ti,ab	7	
#80	[mh ^Leuprolide]	686	
#81	leuprolide:ti,ab	696	
#82	lucrin:ti,ab	21	
#83	lupron:ti,ab	77	
#84	provren:ti,ab	0	
#85	procrin:ti,ab	2	
#86	("tap 144" or tap144):ti,ab	24	
#87	(a-43818 or a43818):ti,ab	0	
#88	Trenantone:ti,ab	3	
#89	staladex:ti,ab	0	
#90	prostag:ti,ab	9	
#91	[mh ^Nafarelin]	77	
#92	nafarelin:ti,ab	114	
#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 cetorelix:ti,ab 221
 #104 cetrotide:ti,ab 111
 #105 ("NS 75A" or NS75A):ti,ab 0
 #106 ("NS 75B" or NS75B):ti,ab 0
 #107 ("SB 075" or SB075):ti,ab 0
 #108 ("SB 75" or SB75):ti,ab 10
 #109 gonadoliberin:ti,ab 5
 #110 kryptocur:ti,ab 0
 #111 cetorelix:ti,ab 221
 #112 cetrotide:ti,ab 111
 #113 antagon:ti,ab 12
 #114 ganirelix:ti,ab 142
 #115 ("ORG 37462" or ORG37462):ti,ab 4
 #116 orgalutran:ti,ab 45
 #117 ("RS 26306" or RS26306):ti,ab 0
 #118 ("AY 24031" or AY24031):ti,ab 0
 #119 factrel:ti,ab 1
 #120 fertagyl:ti,ab 0
 #121 lutrelef:ti,ab 0
 #122 lutrepulse:ti,ab 1
 #123 relefact:ti,ab 1
 #124 fertiral:ti,ab 0
 #125 (hoe471 or "hoe 471"):ti,ab 3
 #126 relisorm:ti,ab 0
 #127 cystorelin:ti,ab 0
 #128 dirigestran:ti,ab 0
 #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:

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)

47 ("WY 42422" or WY42422).ti,ab. (0)

48 ("WY 42462" or WY42462).ti,ab. (0)

49 gonapeptyl.ti,ab. (0)

50 decapeptyl.ti,ab. (3)

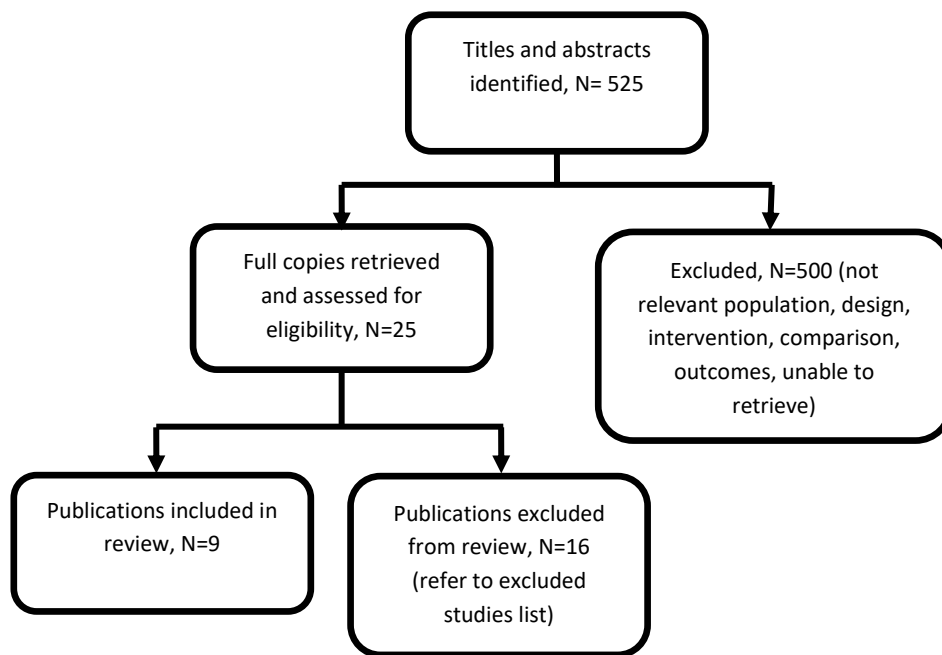
51 salvacyl.ti,ab. (1)

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)
 65 ("ici 118630" or ici118630).ti,ab. (0)
 66 ("ZD-9393" or ZD9393).ti,ab. (0)
 67 zoladex.ti,ab. (3)
 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)
 84 ("76932-56-4" or "76932564").ti,ab. (0)
 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 cetrotorelix.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 cetorelix.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. <i>International Journal of Pediatric Endocrinology</i> 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. <i>Journal of sex & marital therapy</i> 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. <i>Pediatrics</i> 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. <i>Pediatrics</i> 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. <i>Journal of pediatric endocrinology & metabolism: JPEM</i> 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 <i>Psychosocial impact</i> 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 - somewhat representative - no-non exposed cohort - secure record - yes Domain 2: Comparability - no comparator Domain 3: Outcome - record linkage - yes - 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 years³ • 1 transmale stopped GnRH analogues as his parents were unable to regularly collect medication from the pharmacy and take him to appointments for the injections⁴ 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 ($\pm$ SD) UGDS score of 51.6 [$\pm$ 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 ($\pm$SD) age 15.52$\pm$1.41 years) from a sampling frame of 436 consecutive adolescents referred to the service between 2010 and 2014. The mean ($\pm$SD) age (n=201) at the start of GnRH analogues was 16.48 [$\pm$1.26], range 13 to 17 years. The interval from the start of the diagnostic procedure to the start of puberty suppression took approximately 1.5 years [$\pm$0.63] from baseline. None of the delayed eligible individuals received puberty suppression at the time of this study. Tanner stage was not reported.	and delayed eligible (n=100) adolescents, Baseline assessment (following diagnostic procedure) was followed by follow-up at 6 months from baseline (T1), 12 months from baseline (T2) and 18 months from baseline (T3).	females score of 56.1 [$\pm$4.3], <i>t</i>-test 4.07; <i>p</i><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 $\leq$ Cronbach's α $\leq$0.94). At baseline, CGAS scores were not associated with any demographic variable, in both sex assigned at birth males and sex assigned at birth females (all <i>p</i>>0.1). In comparison with sex assigned at birth females, sex assigned at birth males had statistically significantly lower mean ($\pm$SD) baseline CGAS scores (55.4 [$\pm$12.7] versus 59.2 [11.8]; <i>t</i>-test 2.15; <i>p</i>=0.03). There was no statistically significant difference in mean ($\pm$SD) CGAS scores at baseline (T0) between immediately eligible adolescents and delayed eligible adolescents (n=201, 58.72 [$\pm$11.38] versus 56.63 [$\pm$13.14]; <i>t</i>-test 1.21; <i>p</i>=0.23). Immediately eligible compared with delayed eligible participants At follow-up, there was no statistically significant difference in mean ($\pm$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]; <i>t</i>-test 0.34; p=0.73 • T2, n=121, 64.70 [±13.34] versus 62.97 [±14.10]; <i>t</i>-test 0.69; p=0.49 • T3, n=71, 67.40 [±13.93] versus 62.53 [±13.54]; <i>t</i>-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]; <i>t</i>-test 4.87; p<0.001 • T0 (n=201) versus T2 (n=121), 57.73 [±12.27] versus 63.31 [±14.41]; <i>t</i>-test 3.70; p<0.001 • T0 (n=201) versus T3 (n=71), 57.73 [±12.27] versus 64.93 [±13.85]; <i>t</i>-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]; <i>t</i>-test 1.73; p<0.08 • T1 (n=201) versus T3 (n=71), 60.68 [±12.47] versus 64.93 [±13.85], <i>t</i>-test 2.40; p<0.02 • T2 (n=121) versus T3 (n=71), 63.31 [±14.41] versus 64.93 [±13.85], <i>t</i>-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 ($\pm$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 [$\pm$11.38] versus 60.89 [$\pm$12.17]; <i>t</i>-test 1.31; $p=0.19$ • T0 (n=101) versus T2 (n=60), 58.72 [$\pm$11.38] versus 64.70 [$\pm$13.34]; <i>t</i>-test 3.02; $p=0.003$ • T0 (n=101) versus T3 (n=35), 58.72 [$\pm$11.38] versus 67.40 [$\pm$13.93]; <i>t</i>-test 3.66; $p<0.001$ There was a statistically significant increase in mean ($\pm$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 [$\pm$12.17] versus 64.70 [$\pm$13.34]; <i>t</i>-test 1.85; $p=0.07$ • T1 (n=101) versus T3 (n=35), 60.89 [$\pm$12.17] versus 67.40 [$\pm$13.93], <i>t</i>-test 2.63; $p<0.001$	

			T2 (n=60) versus T3 (n=35), 64.70 [± 13.34] versus 67.40 [± 13.93], <i>t</i>-test 0.94; <i>p</i>=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, <i>t</i>=0.01, <i>p</i>=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 [$\pm$SD] at assessment 13.6$\pm$1.8 years) from a sampling frame of 196 consecutive adolescents referred to the service between 2000 and 2008. Inclusion criteria were if they subsequently started gender-affirming hormones between 2003 and 2009 (mean [$\pm$SD] age at start of GnRH analogues was 14.75 [$\pm$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 items².	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, <i>F</i> (<i>df</i>, <i>errdf</i>), <i>P</i>: 15.98 (1,39), <i>p</i><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], <i>F</i> (<i>df</i>, <i>errdf</i>), <i>P</i>: 9.28 (1,39), <i>p</i>=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 - somewhat representative of children and adolescents who have gender dysphoria - no non-exposed cohort - no description - no Domain 2: Comparability - study controls for age, age at start of treatment, IQ, and parental factors Domain 3: Outcome - no description - no/unclear - 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 ($\pm$SD) total, internalising, and externalising³ parental	

			CBCL scores between T0 and T1⁴ 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 ($\pm SD$) total, internalising, and externalising³ 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 ($\pm SD$) score between T0 and T1 ($n=41$), $70.24[\pm 10.12]$ versus $73.90[\pm 9.63]$, $F(df, errdf), P: 8.76(1,39), p=0.005$. 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 ($\pm SD$) differences between sex assigned at birth males and sex assigned at birth females for age at assessment ($13.14[\pm 1.55]$ versus $14.10[\pm 1.99]$ years, $p=0.028$), age at start of GnRH analogues ($14.25[\pm 1.79]$ versus $15.21[\pm 1.95]$ years, $p=0.036$) and age at the start of gender-affirming hormones ($16.24[\pm 1.21]$ versus $16.99[\pm 1.09]$ 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: lumbar¹ Lumbar spine bone mineral apparent density (BMAD)² 0 to 1 year Transfemales (mean [$\pm SD$]):	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 <i>Stopping treatment</i>	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 $\pm$SD 14.9$\pm$1.9 for transfemales and 15.0$\pm$2.0 for transmales at start of GnRH analogues). Participants were included if they met DSM-IV-TR criteria for gender identity disorder of adolescence and had been treated with GnRH analogues and gender-affirming hormones during their pubertal years. No concomitant treatments were reported.	The intervention was GnRH analogue monotherapy (triptorelin pamoate 3.75 mg subcutaneously every 4 weeks) followed by gender-affirming hormones from 16 years with discontinuation of GnRH analogue after gonadectomy. Median duration of GnRH analogue monotherapy in transfemales was 1.3 years (range, 0.5 to 3.8 years), and in transmales was 1.5 years	Critical outcomes No critical outcomes assessed. Important outcomes Bone density: lumbar Lumbar spine bone mineral apparent density (BMAD)¹ Change from starting GnRH analogue (mean age 14.9$\pm$1.9) to starting gender-affirming hormones (mean age 16.6$\pm$1.4) in transfemales (mean [$\pm$SD]): GnRH analogue: 0.22 (0.03) g/cm³, gender-affirming hormones: 0.22 (0.02) g/cm³ (NS); z-score GnRH analogue: -0.44 (1.10), gender-affirming hormones: -0.90 (0.80) (p=NS) Change from starting GnRH analogue (mean age 15.0$\pm$2.0) to starting gender-affirming hormones (mean age 16.4$\pm$2.3) in transmales (mean [$\pm$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 BMAD¹ 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 BMD¹ 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 [$\pm$SD]): 70 (12) micromol/l at baseline, 66 (13) micromol/l at 1 year (p=0.20) Transmales (mean [$\pm$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 ($\pm$SD) Tanner stage for each group was reported: • Transfemales 3.9 [$\pm$1.1] • Transfemales on GnRH analogues 4.1 [$\pm$1.0]	subcutaneously or intramuscularly). Comparison The comparison was between adolescents with gender dysphoria receiving GnRH analogues and those without GnRH analogues.	The Child Behaviour Checklist (CBCL) was used to assess psychosocial impact. The CBCL was administered once during the study. The reported outcomes for each group were (n, mean [$\pm$SD]): • Transfemales (all, n=18) 57.8 [$\pm$9.2] • Transfemales on GnRH analogues (n=8) 57.4 [$\pm$9.8] • Transfemales without GnRH analogues (n=10) 58.2 [$\pm$9.3] • Transmales (all, n=22) 60.4 [$\pm$10.2] • Transmales on GnRH analogues (n=12) 57.5 [$\pm$9.4] • Transmales without GnRH analogues (n=10) 63.9 [$\pm$10.5] The analysis of the CBCL data is not discussed, and statistical analysis is unclear. Cognitive development or functioning IQ¹ • Transfemales (mean [$\pm$SD]) on GnRH analogues: 94.0 (10.3) • Transfemales (mean [$\pm$SD]) without GnRH analogues: 109.4 (21.2) • Transmales (mean [$\pm$SD]) on GnRH analogues: 95.8 (15.6) • Transmales (mean [$\pm$SD]) without GnRH analogues: 98.5 (15.9) Reaction time² • Transfemales (mean [$\pm$SD]) on GnRH analogues: 10.9 (4.1) • Transfemales (mean [$\pm$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 [$\pm$1.1] • Transmales 4.5 [$\pm$0.9] • Transmales on GnRH analogues 4.1 [$\pm$1.1] Transmales without GnRH analogues 4.9 [$\pm$0.3]		• Transmales (mean [$\pm$SD]) on GnRH analogues: 9.9 (3.1) • Transmales (mean [$\pm$SD]) without GnRH analogues: 10.0 (2.0) Accuracy³ • Transfemales (mean [$\pm$SD]) on GnRH analogues: 73.9 (9.1) • Transfemales (mean [$\pm$SD]) without GnRH analogues: 83.4 (9.5) • Transmales (mean [$\pm$SD]) on GnRH analogues: 85.7 (10.5) • Transmales (mean [$\pm$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 months² (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 months³ (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 months⁴ (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 months² 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 months³ 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 <i>P</i> <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 months⁴ 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 <i>P</i> <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 <i>P</i> <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 <i>P</i> <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 <i>P</i> <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 Khatchadorian 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/m ² 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/m ² 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/m ² 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/m ² 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/m ² 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/cm ³ 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/cm ³ 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/cm ³ 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/cm ³ 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	
<i>Cognitive development or functioning (1 cross-sectional study)</i>								
<i>IQ (4 subscales: arithmetic, vocabulary, picture arrangement, and block design) at a single time point between GnRH analogue treated and untreated transfemales</i>								
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
<i>IQ (4 subscales: arithmetic, vocabulary, picture arrangement, and block design) at a single time point between GnRH analogue treated and untreated transmales</i>								
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
<i>Reaction time at a single time point between GnRH analogue treated and untreated transfemales</i>								
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
<i>Reaction time at a single time point between GnRH analogue treated and untreated transmales</i>								
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 ($\mu\text{mol/l}$) 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]	<i>F</i> -ratio 3.85 (<i>df</i> , <i>errdf</i> : 1,39), <i>P</i> =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]	<i>F</i> -ratio 5.70 (<i>df</i> , <i>errdf</i> : 1,39), <i>P</i> =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]	<i>F</i> -ratio 16.07 (<i>df</i> , <i>errdf</i> : 1,39), <i>P</i> <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 GnRHα) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	n-NR ⁷ score at T0 48.72 [±11.83] score at T1 46.52 [±9.23]	n-NR ⁷ score at T0 57.24 [±10.59] score at T1 52.97 [±8.51]	F-ratio 9.14 (df, errdf: 1,52), P=0.004	Important	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; NR, not reported; P, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

2 The overall sample size completing the outcome at both time points was 57.

3 There was a significant interaction effect between sex assigned at birth and BDI between T0 and T1; sex assigned at birth females became more dissatisfied with their secondary F (df, errdf), P: 14.59 (1,55), P<0.001) and neutral F (df, errdf), P: 15.26 (1,55), P<0.001) sex characteristics compared with sex assigned at birth males.

4 Serious limitations – the cohort study by Costa et al. 2015 was assessed as at high risk of bias (poor quality).

5 At baseline, CGAS scores were not associated with any demographic variable, in both sex assigned at birth males and females. There were no statistically significant differences in CGAS scores between gender dysphoric sex assigned at birth males and females in all follow-up evaluations (P>0.1; full data not reported).

6 The overall sample size completing the outcome at both time points was 41

7 The overall sample size completing the outcome at both time points was 54.

Glossary

Beck Depression Inventory-II (BDI-II)	The BDI-II is a tool for assessing depressive symptoms. There are no specific scores to categorise depression severity, but it is suggested that 0 to 13 is minimal symptoms, 14 to 19 is mild depression, 20 to 28 is moderate depression, and severe depression is 29 to 63.
Body Image Scale (BIS)	The BIS is used to measure body satisfaction. The scale consists of 30 body features, which the person rates on a 5-point scale. Each of the 30 items falls into one of 3 basic groups based on its relative importance as a gender-defining body feature: primary sex characteristics, secondary sex characteristics, and neutral body characteristics. A higher score indicates more dissatisfaction.
Bone mineral apparent density (BMAD)	BMAD is a size adjusted value of bone mineral density (BMD) incorporating body size measurements using UK norms in growing adolescents.
Child Behaviour Checklist (CBCL)	CBCL is a checklist parents complete to detect emotional and behavioural problems in children and adolescents.
Children's Global Assessment Scale (CGAS)	The CGAS tool is a validated measure of global functioning on a single rating scale from 1 to 100. Lower scores indicate poorer functioning.
Gender	The roles, behaviours, activities, attributes, and opportunities that any society considers appropriate for girls and boys, and women and men.
Gender dysphoria	Discomfort or distress that is caused by a discrepancy between a person's gender identity (how they see themselves regarding their gender) and that person's sex assigned at birth (and the associated gender role, and/or primary and secondary sex characteristics).
Gonadotrophin releasing hormone (GnRH) analogues	GnRH analogues competitively block GnRH receptors to prevent the spontaneous release of 2 gonadotropin hormones, Follicular Stimulating Hormone (FSH) and Luteinising Hormone (LH) from the pituitary gland. The reduction in FSH and LH secretion reduces oestradiol secretion from the ovaries in those whose sex assigned at birth was female and testosterone secretion from the testes in those whose sex assigned at birth was male.
Sex assigned at birth	Sex assigned at birth (male or female) is a biological term and is based on genes and how external and internal sex and reproductive organs work and respond to hormones. Sex is the label that is recorded when a baby's birth is registered.
Tanner stage	Tanner staging is a scale of physical development.
Trait Anger Spielberger scales of the State-Trait Personality Inventory (TPI)	The TPI is a validated 20-item inventory tool which measures the intensity of anger as the disposition to experience angry feelings as a personality trait. Higher scores indicate greater anger.
Transgender (including transmale and transfemale)	Transgender is a term for someone whose gender identity is not congruent with their birth-registered sex. A transmale is a person who identifies as male and a transfemale is a person who identifies as female.

Utrecht Gender Dysphoria Scale (UGDS)	The UGDS is a validated screening tool for both adolescents and adults to assess gender dysphoria. It consists of 12 items, to be answered on a 1- to 5-point scale, resulting in a sum score between 12 and 60. The higher the UGDS score the greater the impact on gender dysphoria.
Youth Self-Report (YSR)	The self-administered YSR is a checklist to detect emotional and behavioural problems in children and adolescents. It is self-completed by the child or adolescent. The scales consist of a Total problems score, which is the sum of the scores of all the problem items. An internalising problem scale sums the anxious/depressed, withdrawn-depressed, and somatic complaints scores while the externalising problem scale combines rule-breaking and aggressive behaviour.

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Evidence review: Gender-affirming hormones for children and adolescents with gender dysphoria

This document will help inform Dr Hilary Cass' independent review into gender identity services for children and young people. It was commissioned by NHS England and Improvement who commissioned the Cass review. It aims to assess the evidence for the clinical effectiveness, safety and cost-effectiveness of gender-affirming hormones for children and adolescents aged 18 years or under with gender dysphoria.

The document was prepared by NICE in October 2020.

The content of this evidence review was up to date on 21 October 2020. See [summaries of product characteristics](#) (SPCs), [British National Formulary](#) (BNF) or the [Medicines and Healthcare products Regulatory Agency](#) (MHRA) or [NICE](#) websites for up-to-date information.



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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 themselves¹ regarding their gender) and that person's sex assigned at birth and the associated gender role, and/or primary and secondary sex characteristics ([Diagnostic and Statistical Manual of Mental Disorders 2013](#)).

Gender-affirming hormones are oestradiol for sex assigned at birth males (transfemales) and testosterone for sex assigned at birth females (transmales). The aim of gender-affirming hormones is to induce the development of the physical sex characteristics congruent with the individual's gender expression while aiming to improve mental health and quality of life outcomes.

No oestradiol-containing products are licensed for gender dysphoria and therefore any use for children and adolescents with gender dysphoria is off-label.

The only testosterone-containing product licensed for gender dysphoria is Sustanon 250 mg/ml solution for injection, which is indicated as supportive therapy for transmales, use of all other testosterone-containing products for children and adolescents with gender dysphoria is off-label.

For children and adolescents with gender dysphoria it is recommended that management plans are tailored to the needs of the individual and aim to ameliorate the potentially negative impact of gender dysphoria on general developmental processes, to support young people and their families in managing the uncertainties inherent in gender identity development and to provide ongoing opportunities for exploration of gender identity. The plans may also include psychological support and exploration and, for some individuals, the use of gonadotrophin releasing hormone (GnRH) analogues in adolescence to suppress puberty; this may be followed later with gender-affirming hormones of the desired sex ([NHS England 2013](#)).

Currently NHS England, as part of the Gender Identity Development Service for Children and Adolescents, routinely commissions gender-affirming hormones for young people with continuing gender dysphoria from around their 16th birthday subject to individuals meeting the eligibility and readiness criteria ([Clinical Commissioning Policy 2016](#)).

¹ Gender refers to the roles, behaviours, activities, attributes and opportunities that any society considers appropriate for girls and boys, and women and men ([World Health Organisation, Health Topics: Gender](#)).

2. Executive summary of the review

Ten observational studies were included in the evidence review. Seven studies were retrospective observational studies ([Allen et al. 2019](#), [Kaltiala et al. 2020](#), [Khatchadourian et al. 2014](#), [Klaver et al. 2020](#), [Klink et al. 2015](#), [Stoffers et al. 2019](#), [Vlot et al. 2017](#)) and 3 studies were prospective longitudinal observational studies ([Achille et al. 2020](#), [Kuper et al. 2020](#), [Lopez de Lara et al. 2020](#)). No studies directly compared gender-affirming hormones to a control group (either placebo or active comparator). Follow-up was relatively short across all studies, with an average duration of treatment with gender-affirming hormones between around 1 year and 5.8 years.

The terminology used in this topic area is continually evolving and is different depending on stakeholder perspectives. In this evidence review we have used the phrase 'people's assigned sex at birth' rather than saying natal or biological sex and 'cross sex hormones' are now referred to as 'gender-affirming hormones'. The research studies may use historical terms which are no longer considered appropriate.

In children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Critical outcomes

The critical outcomes for decision making are impact on gender dysphoria, impact on mental health and quality of life. The quality of evidence for all these outcomes was assessed as very low certainty using modified GRADE.

Impact on gender dysphoria

The study by [Lopez de Lara et al. 2020](#) in 23 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, gender dysphoria (measured using the Utrecht Gender Dysphoria Scale [UGDS]) was statistically significantly reduced (improved) from a mean [$\pm$ SD] score of 57.1 ($\pm$ 4.1) points at baseline to 14.7 ($\pm$ 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 [$\pm$ SD] score of 19.3 ($\pm$ 5.5) points at baseline to 9.7 ($\pm$ 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 ($\pm$ SD) self-reported score was 9.6 points ($\pm$ 5.0) at baseline and 7.4 ($\pm$ 4.5) at follow-up. The mean ($\pm$ SD) clinician-reported score was 5.9 points ($\pm$ 4.1) at baseline and 6.0 ($\pm$ 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 ($\pm$ SD) score of 33.3 points ($\pm$ 9.1) at baseline to 16.8 points ($\pm$ 8.1) at 12 months ($p < 0.001$). Trait anxiety (measured using STAI – Trait subscale) was also statistically significantly reduced from a mean ($\pm$ SD) score of 33.0 ($\pm$ 7.2) points at baseline to 18.5 ($\pm$ 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 ($\pm$ SE) score of 1.11 points ($\pm$ 0.22) at baseline to 0.27 points ($\pm$ 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 ($\pm$ 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 ($\pm$ SD) BIS score was 70.7 points ($\pm$ 15.2) at baseline and 51.4 points ($\pm$ 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 ($\pm$ SD) of 14.7 ($\pm$ 3.3) points at baseline to 10.3 points ($\pm$ 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 [$\pm$ SD]: start of hormones -0.50 [$\pm$ 0.81], age 22 years -0.033 [$\pm$ 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], $p\leq 0.05$) 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], $p\leq 0.05$).
- 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], $p\leq 0.01$) 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], $p\leq 0.01$).
- 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], $p \leq 0.01$) 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], $p \leq 0.05$).
- 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 'transsexualism'. 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 to 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 <i>Impact on mental health</i> - Depression- The Center for Epidemiologic Studies Depression Scale (CESD-R) - Depression- The Patient Health Questionnaire Modified for Teens (PHQ 9_Modified for Teens) <i>Impact on quality of life</i> - Quality of Life Enjoyment and Satisfaction Questionnaire (QLES-Q-SF) Important Outcomes <i>None reported</i>

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 <i>Impact on mental health</i> - Suicidality- Ask Suicide-Screening Questions (ASQ) instrument <i>Impact on quality of life</i> - General Well-Being Scale (GWBS) of the Pediatric Quality of Life Inventory Important Outcomes <i>None reported</i>
Kaltiala et al. 2020	52 adolescents with gender dysphoria: 11 transfemales and 41 transmales.	Intervention Hormonal sex assignment treatment – details of	Critical Outcomes <i>Impact on mental health</i>

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 <i>Psychosocial Impact</i> 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 <i>None reported</i> Important Outcomes <i>Safety:</i> - 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 <i>None reported</i> Important Outcomes <i>Safety</i> 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 <i>Safety</i> - 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 to 18 years), n=148, of whom: 25 received puberty suppression only	Intervention Gender-affirming hormones, guided by Endocrine Society Clinical Practice Guidelines	Critical Outcomes <i>Impact on mental health</i> 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 <i>Impact on body image</i> - 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 <i>Impact on gender dysphoria</i> - Utrecht Gender Dysphoria Scale (UGDS) <i>Impact on mental health</i> - Depression- Beck Depression Inventory II (BDI-II) - Anxiety- State-Trait Anxiety Inventory Important Outcomes <i>Psychosocial Impact</i> - 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 ($\pm$SD) UGDS score was statistically significantly reduced (improved) from 57.1 ($\pm$4.1) points at baseline to 14.7 points ($\pm$3.2) at 12 months ($p < 0.001$). A UGDS score below 40 suggests an absence of gender dysphoria (VERY LOW). This study provides very low certainty evidence that gender-affirming hormones statistically significantly improve gender dysphoria from baseline to 12 months follow-up. The mean UGDS score was below the threshold for gender dysphoria at follow-up.
Impact on mental health: depression Certainty of evidence: very low	This is a critical outcome because depression may impact on social, occupational, or other areas of functioning in children and adolescents. Four observational studies (Achille et al. 2020; Kaltiala et al. 2020; Kuper et al. 2020; Lopez de Lara et al. 2020) provided evidence relating to the impact on depression in children and adolescents with gender dysphoria, with follow-up of around 12 months. Five different outcome measures for depression were reported. Beck Depression Inventory (BDI-II) One uncontrolled, prospective, analytical study (Lopez de Lara et al. 2020) reported the change in BDI-II. The BDI-II is a valid, reliable, and widely used tool for assessing depressive symptoms. There are no specific scores to categorise depression severity, but it is suggested that 0 to 13 is minimal symptoms, 14 to 19 is mild depression, 20 to 28 is moderate depression, and severe depression is 29 to 63. In Lopez de Lara et al. 2020 (n=23) the mean ($\pm$SD) BDI-II score was statistically significantly reduced (improved) from 19.3 ($\pm$5.5) points at baseline to 9.7 ($\pm$3.9) points at 12 months ($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 ($\pm$ 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 ($\pm$ 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 ($\pm$SD) STAI-State subscale was statistically significantly reduced (improved) with gender-affirming hormones from 33.3 points ($\pm$9.1) at baseline to 16.8 points ($\pm$8.1) at 12 months ($p < 0.001$). The mean STAI-Trait subscale scores also statistically significantly reduced (improved) from 33.0 points ($\pm$7.2) at baseline to 18.5 points ($\pm$8.4) at 12 months ($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 ("<i>Have you ever tried to kill yourself?</i>") by prefacing it with "<i>In the past few weeks . . .</i>" 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 ($\pm$SE) ASQ score statistically significantly reduced from 1.11 points ($\pm$0.22) at baseline to 0.27 points ($\pm$0.12) after a mean duration of treatment of about 12 months ($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 ($\pm$SE) GWBS of the Paediatric Quality of Life Inventory score was statistically significantly increased (improved) from 61.70 ($\pm$2.43) points at baseline to 70.23 ($\pm$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 ($\pm$SD) BIS score was 70.7 points ($\pm$15.2) at baseline and 51.4 points ($\pm$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 ($\pm$SD) SDQ score was statistically significantly reduced (improved) from 14.7 points ($\pm$3.3) at baseline to 10.3 points ($\pm$2.9) at 12-month follow-up ($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/cm³ 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], $p \leq 0.05$). 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], $p \leq 0.05$).
- 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], $p \leq 0.01$). 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], $p \leq 0.01$).
- 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 lumbar 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/cm³ at age 22 years compared with start of gender-affirming hormones. In transmales actual lumbar spine BMAD values in g/cm³ 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], $p \leq 0.05$). - 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 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 ($\pm$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 lumbar 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 ($\pm$SD) BIS score was 71.1 points ($\pm$13.4) at baseline and 52.9 points ($\pm$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 lumbar spine bone density in transmales ([Klink et al. 2015](#), [Stoffers et al. 2019](#) and [Vlot et al. 2017](#)). See the safety results table above for a full details of the results.

These studies provide very low certainty evidence that lumbar spine bone density (measured by BMAD) increases during 2 to 5 years treatment with gender-affirming hormones in sex assigned at birth females (transmales). Z-scores at the end of follow-up suggest the average lumbar spine bone density was generally lower than in the equivalent cisgender population. The results for lumbar spine bone density (measured by BMD) were inconsistent.

Change in bone density: femoral neck

Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of gender-affirming hormones on femoral neck bone density in transmales ([Klink et al. 2015](#), [Stoffers et al. 2019](#) and [Vlot et al. 2017](#)). See the safety results table above for a full details of the results.

These studies provide very low certainty evidence that femoral neck bone density (measured by BMAD) statistically significantly increased in sex assigned at birth females (transmales) during 2 to 5 years treatment with gender-affirming hormones. Z-scores at the end of follow-up suggest the average femoral neck bone density was generally lower than in the equivalent cisgender population. The results for femoral neck bone density (measured by BMD) were inconsistent.

Change in clinical parameters: glucose, insulin and HbA1c

Two uncontrolled, retrospective chart reviews ([Klaver et al. 2020](#); [Stoffers et al. 2019](#)) provided evidence on glucose, insulin and HbA1c in transmales. See the safety results table above for full details of the results.

This study provided very low certainty evidence that gender-affirming hormones do not affect HbA1c, glucose levels, insulin levels and insulin resistance in sex assigned at birth females (transmales). Reported from start of treatment to age 22 years.

Change in clinical parameters: lipids

One retrospective chart review ([Klaver et al. 2020](#)) provided evidence on the change in lipids (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides) in transmales. See the safety results table above for full details of the results.

This study provides very low certainty evidence that treatment with gender-affirming hormones is associated with a small but statistically significant worsening of cholesterol levels in sex assigned at birth females (transmales), but mean cholesterol and triglyceride levels were within the UK reference range at end of treatment, from start of treatment to age 22 years.

	Change in clinical parameters: blood pressure One retrospective chart review (Klaver et al. 2020) provided evidence on the change in blood pressure in transmales. See the safety results table above for full details of the results. This study provides very low certainty evidence that gender-affirming hormones statistically significantly increase blood pressure in sex assigned at birth females (transmales), although the absolute increase was small, from start of treatment to age 22 years. Change in clinical parameters: body mass index (BMI) One retrospective chart review (Klaver et al. 2020) provided evidence on the change in body mass index (BMI) in transmales. See the safety results table above for full details of the results. This study provides very low certainty evidence that gender-affirming hormones statistically significantly increase BMI in sex assigned at birth females (transmales), although most participants were within the healthy weight range, from start of treatment to age 22 years. Change in clinical parameters: liver function One retrospective chart review (Stoffers et al. 2019) provided non-comparative evidence on the change in liver enzymes in transmales between starting gender-affirming hormones and up to 24-months follow-up. See the safety results table above for full details of the results. This study provides very low certainty evidence that gender-affirming hormones for about 12 months do not affect liver function in sex assigned at birth females (transmales). Change in clinical parameters: kidney function One retrospective chart review (Stoffers et al. 2019) provided non-comparative evidence on the change in serum creatinine and serum urea levels in transmales between starting gender-affirming hormones and up to 24-months follow-up. See the safety results table above for full details of the results. This study provides very low certainty evidence on the effects of gender-affirming hormones on kidney function in sex assigned at birth females (transmales). A statistically significant increase in creatinine levels was seen at about 12 months follow-up, but these were within the UK reference range. Urea levels were unchanged. Treatment discontinuation One uncontrolled, retrospective chart review provided evidence relating to permanent or temporary discontinuation of gender-affirming hormones in transmales (Khatchadourian et al. 2014). See the safety results table above for full details of the results. This study provides very low certainty evidence that the rates of treatment discontinuation with gender-affirming hormones in sex

	assigned at birth females (transmales) is low. Duration of gender-affirming hormones not reported. Adverse effects One uncontrolled, retrospective chart review provided evidence for adverse effects from gender-affirming hormones in transmales (Khatchadourian et al. 2014). See the safety results table above for full details of the results. This study provides very low certainty evidence about the potential adverse effects of gender-affirming hormones in sex assigned at birth females (transmales). No conclusions could be drawn. Duration of gender-affirming hormones not reported.
Duration of gender dysphoria	No evidence was identified.
Age at onset of gender dysphoria	No evidence was identified.
Age at onset of puberty	No evidence was identified.
Tanner stage at which GnRH analogue or gender-affirming hormones started	One uncontrolled, prospective, longitudinal study (Kuper et al. 2020) reported the impact of Tanner stage on outcomes, although it is not clear whether this is referring to Tanner stage at initial assessment, at the start of GnRH analogues or at another timepoint.
Diagnosis of autistic spectrum disorder	No evidence was identified.
Diagnosis of a mental health condition	One uncontrolled, prospective, longitudinal study (Achille et al. 2020) reported outcomes that were adjusted for engagement in counselling and medicines for mental health problems. Information about diagnoses and treatment were not provided. Rates of mental health issues appear to be high in the cohort. Impact on mental health Achille et al. 2020 reported the change in depression scores, controlled for engagement in counselling and medicines for mental health problems (measured using the Center for Epidemiologic Studies Depression [CESD-R] scale and Patient Health Questionnaire Modified for Teens [PHQ 9_Modified for Teens] score: • There was no statistically significant change in CESD-R from baseline to about 12-months follow-up. • There was no statistically significant change in PHQ 9_Modified for Teens score from baseline to about 12-months follow-up (VERY LOW). Impact on quality of life Achille et al. 2020 reported the change in quality of life scores, controlled for engagement in counselling and medicines for mental health problems (measured using the Quality of Life Enjoyment and Satisfaction Questionnaire [QLES-Q-SF] score: • There was no statistically significant change in QLES-Q-SF score from baseline to about 12-months follow-up (VERY LOW).

	This study provides very low certainty evidence about outcomes that were adjusted for engagement in counselling and medicines for mental health problems. No conclusions could be drawn.

Abbreviations: ASQ: Ask Suicide-Screening Questions; CESD-R: Center for Epidemiologic Studies Depression; GnRH: Gonadotrophin releasing hormone; GWBS: General Well-Being Scale; HDL: high-density lipoproteins; LDL: low-density lipoproteins; p: p-value; PHQ 9_Modified for Teens: Patient Health Questionnaire Modified for Teens; QLES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire.

From the evidence selected,

- (a) **what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?**
- (b) **what were the ages at which participants commenced treatment with gender-affirming hormones?**
- (c) **what was the duration of treatment with GnRH analogues?**

Outcome	Evidence statement												
Diagnostic criteria	The DSM-IV-TR criteria was used in 3 studies (Klaver et al. 2020, Klink et al. 2015 and Vlot et al. 2017). The DSM-V criteria was used in 2 studies (Kuper et al. 2020 and Stoffers et al. 2019). The DSM-V has one overarching definition of gender dysphoria with separate specific criteria for children and for adolescents and adults. The general definition describes a conflict associated with significant distress and/or problems functioning associated with this conflict between the way they feel and think of themselves which must have lasted at least 6 months. The ICD-10 diagnosis of 'transsexualism' was used in 1 study (Kaltiala et al. 2020). The authors state that this is the corresponding diagnosis to 'gender dysphoria' in the DSM-V, and that diagnostic assessments in the study location (Finland) take place according to ICD-10. It was not reported how gender dysphoria was defined in the remaining 4 studies (VERY LOW). From the evidence selected, the most commonly reported diagnostic criteria for gender dysphoria (5/10 studies) was the DSM criteria in use at the time the study was conducted.												
Age when gender-affirming hormones started	8/10 studies reported the age at which participants started treatment with gender-affirming hormones, either as the mean age (with SD) or median age (with the range): <table border="1"> <thead> <tr> <th>Study</th><th>Mean age ($\pm$ SD)</th></tr> </thead> <tbody> <tr> <td>Allen et al. 2019</td><td>16.7 years (not reported)</td></tr> <tr> <td>Khatchadourian et al. 2014</td><td>17.4 years (1.9)</td></tr> <tr> <td>Klaver et al. 2020</td><td>16.4 years (1.1) in transfemales 16.9 years (0.9) in transmales</td></tr> <tr> <td>Kuper et al. 2020</td><td>16.2 (1.2)</td></tr> <tr> <td>Klink et al. 2015</td><td>16.6 years (1.4) in transfemales 16.4 years (2.3) in transmales</td></tr> </tbody> </table>	Study	Mean age ($\pm$ SD)	Allen et al. 2019	16.7 years (not reported)	Khatchadourian et al. 2014	17.4 years (1.9)	Klaver et al. 2020	16.4 years (1.1) in transfemales 16.9 years (0.9) in transmales	Kuper et al. 2020	16.2 (1.2)	Klink et al. 2015	16.6 years (1.4) in transfemales 16.4 years (2.3) in transmales
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	<table><tr><th>Study</th><th>Median age (range)</th></tr><tr><td>Stoffers et al. 2019</td><td>17.2 years (15 to 19.5)</td></tr><tr><td>Vlot et al. 2017</td><td>16.3 years (15.9 to 19.5) in transfemales 16.0 years (14.0 to 18.9) in transmales</td></tr></table> Age at the start of treatment was not reported in 3 studies: • In Achille et al. 2020 the mean age at initial assessment (baseline) was 16.2 years (SD ±2.2) • In Kaltiala et al. 2020 the mean age at diagnosis was 18.1 years (range 15.2 to 19.9) • In Lopez de Lara et al. 2020 the mean age of participants was 16 years (range 14 to 18), although it is not clear if this is at the initial assessment or at the start of gender-affirming hormones. The evidence included showed that most children and adolescents started treatment with gender-affirming hormones at about 16 to 17 years, with a range of about 14 to 19 years.	Study	Median age (range)	Stoffers et al. 2019	17.2 years (15 to 19.5)	Vlot et al. 2017	16.3 years (15.9 to 19.5) in transfemales 16.0 years (14.0 to 18.9) in transmales		
Study	Median age (range)								
Stoffers et al. 2019	17.2 years (15 to 19.5)								
Vlot et al. 2017	16.3 years (15.9 to 19.5) in transfemales 16.0 years (14.0 to 18.9) in transmales								
Duration of treatment with GnRH analogues	The duration of treatment with GnRH analogues was reported in 3/10 studies: <table><tr><th>Study</th><th>Median duration</th></tr><tr><td>Klaver et al. 2020</td><td>2.1 years (IQR 1.0 to 2.7) in transfemales 1.0 years (IQR 0.5 to 2.9) in transmales</td></tr><tr><td>Klink et al. 2015</td><td>1.3 years (range 0.5 to 3.8) in transfemales 1.5 years (range 0.25 to 5.2) in transmales (GnRH analogue monotherapy)</td></tr><tr><td>Stoffers et al. 2019</td><td>8 months (range 3 to 39)</td></tr></table> The evidence included showed wide variation in the duration of treatment with gender-affirming hormones, but most studies did not report this information. Treatment duration ranged from a few months up to about 5 years.	Study	Median duration	Klaver et al. 2020	2.1 years (IQR 1.0 to 2.7) in transfemales 1.0 years (IQR 0.5 to 2.9) in transmales	Klink et al. 2015	1.3 years (range 0.5 to 3.8) in transfemales 1.5 years (range 0.25 to 5.2) in transmales (GnRH analogue monotherapy)	Stoffers et al. 2019	8 months (range 3 to 39)
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Stoffers et al. 2019	8 months (range 3 to 39)								

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders criteria; GnRH, Gonadotrophin-releasing hormone; ICD, International Statistical Classification of Diseases and Related Health Problems; IQR, interquartile range; SD, standard deviation.

6. Discussion

A key limitation to identifying the effectiveness and safety of gender-affirming hormones for children and adolescents with gender dysphoria is the lack of reliable comparative studies. All the studies included in this evidence review are uncontrolled observational studies, which are subject to bias and confounding and were of very low certainty using modified GRADE. The size of the population with gender dysphoria means conducting a prospective trial may be unrealistic, at least on a single centre basis. There may also be ethical issues with a 'no treatment arm' in comparative trials of gender-affirming hormones, where there may be poor mental health outcomes if treatment is withheld. However, the use of an active comparator such as close psychological support may reduce ethical concerns in future trials. A fundamental limitation of all the uncontrolled studies included in this review is that any changes in scores from baseline to follow-up could be attributed to a regression-to-the-mean.

The included studies have relatively short follow-up, with an average duration of treatment with gender-affirming hormones between around 1 year and 5.8 years. Further studies with a longer follow-up are needed to determine the long-term effect of gender-affirming hormones for children and adolescents with gender dysphoria.

Most studies included in this review did not report comorbidities (physical or mental health) and no study reported concomitant treatments in detail. Because of this it is not clear whether any changes observed were due to gender-affirming hormones or other treatments the participants may have received. For example, we do not know if any improvement in depression symptom score over time was the result of gender-affirming hormones or the mental health support the person may be receiving (including medicines or counselling). This may be of particular importance for the mental health outcomes discussed in this review, since depression, anxiety and other related symptoms are common in children and adolescents with gender dysphoria. In [Achille et al. 2020](#), at baseline around one-third of participants were taking medicines for mental health problems and around two-thirds reported being depressed in the past year. In [Kaltiala et al. 2020](#), half the participants needed mental health treatment during and before gender identity assessment, with the most common reasons for treatment being depression, anxiety and suicidality. Only 1 study reported outcomes adjusted for engagement in counselling and medicines for mental health problems (Achille et al. 2020). This study found that gender-affirming hormones had no significant impact on depression and quality of life when adjusted for mental health care, despite significant improvements reported for the unadjusted results. However, it is not possible to draw conclusions on the impact of concurrent mental health treatment on the effect of gender-affirming hormones based on this study alone. Details of the mental health care provided are not reported in the study and results are presented for transfemales and transmales separately, resulting in small patient numbers and possible underpowering.

In most of the included studies, details of the gender-affirming hormone treatment regimens are poorly reported, with limited information provided about the medicines, doses and routes of administration used. It is not clear whether the interventions used in the studies are reflective of current UK practice for children and adolescents with gender dysphoria. There is also the suggestion that the hormone dose used in 1 study may have been too low; the authors of [Klink et al. 2015](#) suggest that the relatively low initial dose of oestrogen for transfemales may be the reason for the observed lack of effect on lumbar spine bone density. Duration of treatment with a GnRH analogue is also poorly reported and is only stated in 3/10 studies.

There is a degree of indirectness in some studies, with some participants included that fall outside of the population of this evidence review. For example, in [Kuper et al. 2020](#) 17% of participants received puberty suppression alone, and in Achille et al. 2020, 30% of participants received no treatment or puberty suppression alone. Some results and statistical analyses are only reported for the whole cohort in these studies and not the subgroup of participants who received gender-affirming hormones.

Participant numbers are poorly reported in some of the included studies. In [Achille et al. 2020](#), 47% (45/95) of the people who entered the study did not have follow-up data and were excluded from the analyses, with no explanation or description of those people lost to follow-up. In Kuper et al. 2020, the number of participants varied by outcome, with less than

two-thirds of participants providing data for some outcomes. The authors provide no explanation for this incomplete reporting.

It is not clear whether some outcome measures, specifically those related to psychosocial functioning, are relevant to the UK population. In Kaltiala et al. 2020, an observational study conducted in Finland, the proportion of participants living with parents or guardians is reported as marker of appropriate functioning. The authors state that in Finnish culture young people tend to leave the parental home early, with only around one-quarter of 20 to 24 year olds still living at home. This is lower than in the UK, where around half of 20 to 24 year olds live with their parents or guardians ([ONS: Why are more young people living with their parents?](#)).

It is difficult to draw firm conclusions for many of the effectiveness and safety outcomes reported in the included studies because many different scoring tools and methods were used to assess the same outcome, often with conflicting results. For example, bone density is reported as bone mineral density (BMD) and bone mineral apparent density (BMAD) in the same study, the latter being a size-adjusted measure often useful for people whose bones are still growing. For some populations (transfemale versus transmale) and bone regions (lumber spine versus femoral neck), statistically significant differences in BMD are reported but not for BMAD, and vice versa.

In addition to this, most outcomes reported across the included studies do not have an accepted minimal clinically important difference (MCID), making it difficult to determine whether any observed statistically significant changes are clinically meaningful. However, the authors of some studies report thresholds to interpret the results of the scoring tools, so some conclusions can be made. For example, the mean Utrecht Gender Dysphoria Scale (UGDS) score (a measure of gender dysphoria symptoms) reduced to about 15 points after treatment with gender-affirming hormones ([Lopez de Lara et al. 2020](#)). The authors state that scores of 40 points or above signify gender dysphoria, suggesting that after about 12 months of treatment with gender-affirming hormones, the majority of participants did not have symptoms of gender dysphoria.

The impact of gender-affirming hormones on bone density was reported in 3 studies (Klink et al. 2015, [Stoffers et al. 2019](#) and [Vlot et al. 2017](#)). Although these studies did not include a control group, comparisons to a reference population are reported using z-scores. Comparisons were made to a cisgender population, meaning for example that bone density in transfemales was compared with bone density in cisgender males. The authors of Klink et al. 2015 note that this may not be the ideal comparison, because androgens and oestrogens affect bone differently, and that bone properties in a trans population differ from their age- and sex assigned at birth-matched controls. Beyond this, a major limitation when trying to determine the impact of gender-affirming hormones on the short- and long-term bone health of children and adolescents is the lack of data on fracture rates and other patient-orientated outcomes, including rates of osteoporosis. Studies of GnRH analogues in children and adolescents with gender dysphoria suggest that GnRH analogue treatment may reduce the expected increase in bone density (which is expected during puberty). Although improvements in bone density were reported following treatment with gender-affirming hormones, Z-scores suggest that bone density remained lower in transfemales and transmales compared with an equivalent cisgender population.

One study reported on cardiovascular risk factors at age 22 years in people who started gender-affirming hormones for gender dysphoria as adolescents. While glucose levels, insulin levels and insulin resistance were broadly unchanged at 22 years, statistically significant increases in blood pressure and body mass index were seen. A small but statistically significant worsening of the lipid profile in transmales who received testosterone was also seen at age 22 years. However, further studies with a considerably longer follow-up and a focus on patient-oriented outcomes, including cardiovascular events and mortality are needed to determine the long-term impact on cardiovascular health of starting gender-affirming hormones during childhood and adolescence.

Only 1 study reported adverse events and discontinuation rates with gender-affirming hormones in children and adolescents. Conclusions on these outcomes cannot be made based on this study alone.

This review did not identify sub-groups of people who may benefit more from gender-affirming hormones. Limited evidence from 2 studies suggests there was no difference in response to treatment between transfemales and transmales for mental health and quality of life (Achille et al. 2020 and [Allen et al. 2019](#)).

7. Conclusion

This evidence review found limited evidence for the effectiveness and safety of gender-affirming hormones in children and adolescents with gender dysphoria, with all studies being uncontrolled, observational studies, and all outcomes of very low certainty. Any potential benefits of treatment must be weighed against the largely unknown long-term safety profile of these treatments.

The results from 5 uncontrolled, observational studies ([Achille et al. 2020](#), [Allen et al. 2019](#), [Kaltiala et al. 2020](#), [Kuper et al. 2020](#), [Lopez de Lara et al. 2020](#)) suggest that, in children and adolescents with gender dysphoria, gender-affirming hormones are likely to improve symptoms of gender dysphoria, and may also improve depression, anxiety, quality of life, suicidality, and psychosocial functioning. The impact of treatment on body image is unclear. All results were of very low certainty. The clinical relevance of any improvements to the person is difficult to determine because most outcomes do not have a recognised minimal clinically important difference, and the authors do not present statistical analysis for some outcomes.

A further 5 uncontrolled, observational studies ([Khatchadourian et al. 2014](#), [Klaver et al. 2020](#), [Klink et al. 2015](#), [Stoffers et al. 2019](#) and [Vlot et al. 2017](#)) reported on safety outcomes, all of which provided very low certainty evidence. Statistically significant increases in some measures of bone density were seen following treatment with gender-affirming hormones, although results varied by bone region (lumber spine versus femoral neck) and by population (transfemales versus transmales). However, z-scores suggest that bone density remained lower in transfemales and transmales compared with an equivalent cisgender population. Results from 1 study of gender-affirming hormones started during adolescence reported statistically significant increases in blood pressure and body mass index, and worsening of the lipid profile (in transmales) at age 22 years, although longer term studies that report on cardiovascular event rates are needed. Adverse events and discontinuation rates associated with gender-affirming hormones were only reported in 1 study, and no conclusions can be made on these outcomes.

This review did not identify sub-groups of people who may benefit more from gender-affirming hormones. Limited evidence from 2 studies suggests there was no difference in response to treatment between transfemales and transmales for mental health and quality of life (Achille et al. 2020 and Allen et al. 2019).

No cost-effectiveness evidence was found to determine whether gender-affirming hormones are a cost-effective treatment for children and adolescents with gender dysphoria.

Appendix A PICO

The review questions for this evidence review are:

1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
2. For children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
3. For children and adolescents with gender dysphoria, what is the cost-effectiveness of gender-affirming hormones compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?
4. From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria?
5. From the evidence selected,
 - (a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?
 - (b) what were the ages at which participants commenced treatment with gender-affirming hormones?
 - (c) what was the duration of GnRH analogues treatment?

PICO table

P –Population and Indication	Children and adolescents aged 18 years or less who have gender dysphoria, gender identity disorder or gender incongruence of childhood as defined by the study. The following subgroups of children and adolescents with gender dysphoria, gender identity disorder or gender incongruence of childhood need to be considered:

	• Sex assigned at birth males • Sex assigned at birth females • The duration of gender dysphoria: less than 6 months, 6-24 months, and more than 24 months) • The age at which treatment was initiated with GnRH analogues and with gender-affirming hormones. • The age of onset of gender dysphoria • The age of onset of puberty • Adolescents with gender dysphoria who have a pre-existing diagnosis of autistic spectrum disorder. • Adolescents with gender dysphoria who had a significant mental health symptom load at diagnosis including anxiety, depression (with or without a history of self-harm and suicidality), psychosis, personality disorder, Attention Deficit Hyperactivity Disorder and eating disorders.
I – Intervention	Gender-affirming hormone treatments: • A testosterone preparation for sex assigned at birth female patients which may include testosterone in the form of Sustanon injections*; testosterone enantate injections; Tostran gel*; Testogel; Testim gel; oral testosterone capsules in the form of testosterone undecanoate (Restandol); Andriol testocaps; Nebido • An oestradiol preparation** for sex assigned at birth male patients which may include: oral estradiol valerate*; oestrogen patches (7β-oestradiol patches e.g. Evorel or Estradem); Estradot patches; ethinyloestradiol *** *These are the used by Leeds Hospital, England. ** Be aware that the American spelling is oestrogen without the 'o'. ***Ethinyloestradiol is rarely used.
C – Comparator(s)	One or a combination of: • Psychological support • Social transitioning to the gender with which the individual identifies. No intervention
O – Outcomes	There are no known minimal clinically important differences and there are no preferred timepoints for the outcome measures selected. All outcomes should be stratified by: • The age at which treatment with gender-affirming hormones was initiated • The length of treatment with GnRH analogues where possible. <u>A: Clinical Effectiveness</u> <i>Critical to decision making</i> • Impact on gender dysphoria This outcome is critical because gender dysphoria in adolescents and children is associated with significant distress and problems functioning. Impact on gender

	dysphoria may be measured by the Utrecht Gender Dysphoria Scale. Other measures as reported in studies may be used as an alternative to the stated measure. Impact on mental health Examples of mental health problems include self-harm, thoughts of suicide, suicide attempts, suicide, eating disorders, depression/low mood and anxiety. These outcomes are critical because self-harm and thoughts of suicide have the potential to result in significant physical harm and for completed suicides the death of the young person. Disordered eating habits may cause significant morbidity in young people. Depression and anxiety are also critical outcomes because they may impact on social, occupational, or other areas of functioning of children and adolescents. The Child and Adolescent Psychiatric Assessment (CAPA) may be used to measure depression and anxiety. The impact on self-harm and suicidality (ideation and behaviour) may be measured using the Suicide Ideation Questionnaire Junior. Other measures may be used as an alternative to the stated measure. Impact on Quality of Life This outcome is critical because gender dysphoria in children and adolescents may be associated with a significant reduction in health-related quality of life. Quality of Life may be measured by the KINDL questionnaire, Kidscreen 52. Other measures as reported in studies may be used as an alternative to the stated measures. <i>Important to decision making</i> Impact on body image This outcome is important because some young people with gender dysphoria may desire to take steps to suppress features of their physical appearance associated with their sex assigned at birth or accentuate physical features of their experienced gender. The Body Image Scale could be used as a measure. Other measures as reported in studies may also be used as an alternative to the stated measure. Psychosocial Impact Examples of psychosocial impact are: coping mechanisms which may impact on substance misuse; family relationships; peer relationships. This outcome is important because gender dysphoria in adolescents and children is associated with internalising and externalising behaviours and emotional and behavioural problems which may impact on social and occupational functioning. The child behavioural check list (CBCL) may be used to measure the impact on psychosocial functioning. Other measures as reported in studies may be used as an alternative to the stated measure. Engagement with health care services This outcome is important because patient engagement with healthcare services will impact on their clinical outcomes. Engagement with health care services may be measured using the Youth Health Care measure-satisfaction, utilization, and needs (YHC-SUN) questionnaire. Loss to follow up and

	should also be ascertained as part of this outcome. Alternative measures to the YHC-SUN questionnaire may be used as reported in studies. • Transitioning surgery - Impact on extent of and satisfaction with surgery This outcome is important because some children and adolescents with gender dysphoria may in adulthood proceed to transitioning surgery. Stated measures of the extent of surgery and satisfaction with surgery in studies may be reported. • De-transition The proportion of patients who de-transition following the commencement of gender-affirming hormone treatment and the reasons why. This outcome is important to patients because there is uncertainty about the short and long term safety and adverse effects of gender-affirming hormones in children and adolescents with gender dysphoria. <u>B: Safety</u> • Short and long -term safety and adverse effects of taking gender-affirming hormones is important to assess whether treatment causes acute side effects that may lead to withdrawing the treatment or long term effects that may impact on decisions for transitioning or de-transitioning. Aspects to be reported on should include Impact of the drug use such as clinically relevant derangement in renal and liver function tests, lipids, glucose, insulin and glycosylated haemoglobin, cognitive development and functioning. The clinical and physical impact of temporary and permanent withdrawal the drug such as when patients decide to de-transition – e.g. delay in the attainment of peak bone mass, attenuation of peak bone mass, permanent physical effects. <u>C: Cost effectiveness</u> Cost effectiveness studies should be reported.
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	18 years or less
Date limits	2000-2020

Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines and pre-publication prints
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, the Cochrane Library, HTA and APA PsycInfo were searched on 21 July 2020, limiting the search to papers published in English language in the last 20 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines, pre-publication prints, case reports and resource utilisation studies were excluded.

Database: Medline

Platform: Ovid

Version: Ovid MEDLINE(R) <1946 to July 17, 2020>

Search date: 21 Jul 2020

Number of results retrieved: 650

Search strategy:

Database: Ovid MEDLINE(R) <1946 to July 17, 2020>

Search Strategy:

-
- 1 Gender Dysphoria/ (485)
 - 2 Gender Identity/ (18431)
 - 3 "Sexual and Gender Disorders"/ (75)
 - 4 Transsexualism/ (3758)
 - 5 Transgender Persons/ (3134)
 - 6 Health Services for Transgender Persons/ (136)
 - 7 exp Sex Reassignment Procedures/ (835)
 - 8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (7223)
 - 9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (12665)
 - 10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (102312)
 - 11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (6969)
 - 12 (male-to-female or m2f or female-to-male or f2m).tw. (114785)
 - 13 or/1-12 (252562)
 - 14 exp Infant/ or Infant Health/ or Infant Welfare/ (1137237)
 - 15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (852126)
 - 16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1912796)
 - 17 Minors/ (2572)
 - 18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (2360626)
 - 19 exp pediatrics/ (58102)
 - 20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (835833)
 - 21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (2023650)
 - 22 Puberty/ (13277)

23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (424041)

24 Schools/ (38087)

25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (7199)

26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (468784)

27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (89314)

28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (887443)

29 or/14-28 (5532185)

30 13 and 29 (79220)

31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (7)

32 30 or 31 (79220)

33 Hormones/ad, tu, th (4514)

34 exp Progesterone/ad, tu, th (10899)

35 exp Estrogens/ad, tu, th (28936)

36 exp Gonadal Steroid Hormones/ad, tu, th (34137)

37 (progesteron* or oestrogen* or estrogen*).tw. (196074)

38 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (544)

39 exp Estradiol/ad, tu, th (10823)

40 exp Testosterone/ad, tu, th (8318)

41 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (74936)

42 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (90464)

43 or/33-42 (304239)

44 32 and 43 (3183)

45 limit 44 to yr="2000 -Current" (2019)

46 animals/ not humans/ (4685420)

47 45 not 46 (1194)

48 limit 47 to english language (1155)

49 (MEDLINE or pubmed).tw. (163678)

50 systematic review.tw. (121198)

51 systematic review.pt. (130231)

52 meta-analysis.pt. (117148)

53 intervention\$.ti. (123904)

54 or/49-53 (380217)

55 randomized controlled trial.pt. (509468)

56 randomi?ed.mp. (796957)

57 placebo.mp. (194937)

58 or/55-57 (848627)

59 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ (5562241)

60 ((control and (group* or study)) or (time and factors)).mp. (3274107)

61 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (4624419)

62 or/59-61 (9030680)

63 Observational Studies as Topic/ (5177)

64 Observational Study/ (81866)

65 Epidemiologic Studies/ (8358)

66 exp Case-Control Studies/ (1090891)
 67 exp Cohort Studies/ (2011414)
 68 Cross-Sectional Studies/ (332273)
 69 Controlled Before-After Studies/ (526)
 70 Historically Controlled Study/ (185)
 71 Interrupted Time Series Analysis/ (913)
 72 Comparative Study.pt. (1866044)
 73 case control\$.tw. (112152)
 74 case series.tw. (59119)
 75 (cohort adj (study or studies)).tw. (170281)
 76 cohort analy\$.tw. (6758)
 77 (follow up adj (study or studies)).tw. (45131)
 78 (observational adj (study or studies)).tw. (86247)
 79 longitudinal.tw. (204239)
 80 prospective.tw. (495367)
 81 retrospective.tw. (442876)
 82 cross sectional.tw. (284856)
 83 or/63-82 (4368140)
 84 54 or 58 or 62 or 83 (9402123)
 85 48 and 84 (683)
 86 limit 85 to (letter or historical article or comment or editorial or news or case reports)
 (33)
 87 85 not 86 (650)

Database: Medline in-process

Platform: Ovid

Version: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to July 17, 2020>

Search date: 21 July 2020

Number of results retrieved: 122

Search strategy:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to July 17, 2020>

Search Strategy:

1 Gender Dysphoria/ (0)
 2 Gender Identity/ (0)
 3 "Sexual and Gender Disorders"/ (0)
 4 Transsexualism/ (0)
 5 Transgender Persons/ (0)
 6 Health Services for Transgender Persons/ (0)
 7 exp Sex Reassignment Procedures/ (0)
 8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (1473)
 9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (2315)
 10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (20821)
 11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (963)
 12 (male-to-female or m2f or female-to-male or f2m).tw. (15453)
 13 or/1-12 (39735)
 14 exp Infant/ or Infant Health/ or Infant Welfare/ (0)
 15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (80295)

16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)
 17 Minors/ (0)
 18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (320315)
 19 exp pediatrics/ (0)
 20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (119124)
 21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)
 22 Puberty/ (0)
 23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert*
 or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn.
 (59969)
 24 Schools/ (0)
 25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)
 26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or
 pupil* or student*).ti,ab,jn. (68979)
 27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen"
 or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or
 aged)).ti,ab. (10287)
 28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19")
 adj2 (year or years or age or ages or aged)).ti,ab. (112220)
 29 or/14-28 (523053)
 30 13 and 29 (9143)
 31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw.
 (3)
 32 30 or 31 (9144)
 33 Hormones/ad, tu, th (0)
 34 exp Progesterone/ad, tu, th (0)
 35 exp Estrogens/ad, tu, th (0)
 36 exp Gonadal Steroid Hormones/ad, tu, th (0)
 37 (progesteron* or oestrogen* or estrogen*).tw. (13291)
 38 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or
 treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (241)
 39 exp Estradiol/ad, tu, th (0)
 40 exp Testosterone/ad, tu, th (0)
 41 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or
 testocaps* or nebido or testavan).tw. (5458)
 42 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or
 progynova or zumenon or bedol or femseven or nuvelle).tw. (4772)
 43 or/33-42 (19706)
 44 32 and 43 (316)
 45 limit 44 to yr="2000 -Current" (303)
 46 animals/ not humans/ (1)
 47 45 not 46 (303)
 48 limit 47 to english language (303)
 49 (MEDLINE or pubmed).tw. (36030)
 50 systematic review.tw. (29830)
 51 systematic review.pt. (1007)
 52 meta-analysis.pt. (49)
 53 intervention\$.ti. (21354)
 54 or/49-53 (68976)
 55 randomized controlled trial.pt. (277)
 56 randomi?ed.mp. (74978)
 57 placebo.mp. (18290)
 58 or/55-57 (81427)
 59 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation
 studies as topic/ or exp statistics as topic/ (455)

60 ((control and (group* or study)) or (time and factors)).mp. (214372)
 61 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-
 up*).mp. (339764)
 62 or/59-61 (507046)
 63 Observational Studies as Topic/ (0)
 64 Observational Study/ (91)
 65 Epidemiologic Studies/ (0)
 66 exp Case-Control Studies/ (1)
 67 exp Cohort Studies/ (1)
 68 Cross-Sectional Studies/ (0)
 69 Controlled Before-After Studies/ (0)
 70 Historically Controlled Study/ (0)
 71 Interrupted Time Series Analysis/ (0)
 72 Comparative Study.pt. (46)
 73 case control\$.tw. (14451)
 74 case series.tw. (13070)
 75 (cohort adj (study or studies)).tw. (29119)
 76 cohort analy\$.tw. (1039)
 77 (follow up adj (study or studies)).tw. (3540)
 78 (observational adj (study or studies)).tw. (17421)
 79 longitudinal.tw. (34485)
 80 prospective.tw. (63689)
 81 retrospective.tw. (73761)
 82 cross sectional.tw. (60195)
 83 or/63-82 (250805)
 84 54 or 58 or 62 or 83 (687622)
 85 48 and 84 (126)
 86 limit 85 to (letter or historical article or comment or editorial or news or case reports) (4)
 87 85 not 86 (122)

Database: Medline epubs ahead of print

Platform: Ovid

Version: Ovid MEDLINE(R) Epub Ahead of Print <July 17, 2020>

Search date: 21 July 2020

Number of results retrieved: 32

Search strategy:

Database: Ovid MEDLINE(R) Epub Ahead of Print <July 17, 2020>

Search Strategy:

1 Gender Dysphoria/ (0)
 2 Gender Identity/ (0)
 3 "Sexual and Gender Disorders"/ (0)
 4 Transsexualism/ (0)
 5 Transgender Persons/ (0)
 6 Health Services for Transgender Persons/ (0)
 7 exp Sex Reassignment Procedures/ (0)
 8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or
 queer*)).tw. (430)
 9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or
 transmen* or transperson* or transpeopl*).tw. (637)
 10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw.
 (1499)
 11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (179)
 12 (male-to-female or m2f or female-to-male or f2m).tw. (2460)

13 or/1-12 (4883)
 14 exp Infant/ or Infant Health/ or Infant Welfare/ (0)
 15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born*
 or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn.
 (15416)
 16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)
 17 Minors/ (0)
 18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (53285)
 19 exp pediatrics/ (0)
 20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (22649)
 21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)
 22 Puberty/ (0)
 23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert*
 or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn.
 (13005)
 24 Schools/ (0)
 25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)
 26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or
 pupil* or student*).ti,ab,jn. (12420)
 27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen"
 or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or
 aged)).ti,ab. (1407)
 28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19")
 adj2 (year or years or age or ages or aged)).ti,ab. (20083)
 29 or/14-28 (87968)
 30 13 and 29 (1618)
 31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw.
 (1)
 32 30 or 31 (1618)
 33 Hormones/ad, tu, th (0)
 34 exp Progesterone/ad, tu, th (0)
 35 exp Estrogens/ad, tu, th (0)
 36 exp Gonadal Steroid Hormones/ad, tu, th (0)
 37 (progesteron* or oestrogen* or estrogen*).tw. (1876)
 38 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or
 treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (63)
 39 exp Estradiol/ad, tu, th (0)
 40 exp Testosterone/ad, tu, th (0)
 41 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or
 testocaps* or nebido or testavan).tw. (846)
 42 (oestrad* or estrad* or evorel or ethinyloestrاد* or ethinylestrad* or elleste or
 progynova or zumenon or bedol or femseven or nuvelle).tw. (665)
 43 or/33-42 (2850)
 44 32 and 43 (64)
 45 limit 44 to yr="2000 -Current" (61)
 46 animals/ not humans/ (0)
 47 45 not 46 (61)
 48 limit 47 to english language (61)
 49 (MEDLINE or pubmed).tw. (7948)
 50 systematic review.tw. (7508)
 51 systematic review.pt. (28)
 52 meta-analysis.pt. (37)
 53 intervention\$.ti. (4267)
 54 or/49-53 (15048)
 55 randomized controlled trial.pt. (1)

56 randomi?ed.mp. (14113)
 57 placebo.mp. (3097)
 58 or/55-57 (15128)
 59 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation
 studies as topic/ or exp statistics as topic/ (34)
 60 ((control and (group* or study)) or (time and factors)).mp. (31615)
 61 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-
 up*).mp. (65735)
 62 or/59-61 (88222)
 63 Observational Studies as Topic/ (0)
 64 Observational Study/ (4)
 65 Epidemiologic Studies/ (0)
 66 exp Case-Control Studies/ (0)
 67 exp Cohort Studies/ (0)
 68 Cross-Sectional Studies/ (0)
 69 Controlled Before-After Studies/ (0)
 70 Historically Controlled Study/ (0)
 71 Interrupted Time Series Analysis/ (0)
 72 Comparative Study.pt. (0)
 73 case control\$.tw. (2577)
 74 case series.tw. (2480)
 75 (cohort adj (study or studies)).tw. (7959)
 76 cohort analy\$.tw. (287)
 77 (follow up adj (study or studies)).tw. (632)
 78 (observational adj (study or studies)).tw. (3763)
 79 longitudinal.tw. (7079)
 80 prospective.tw. (12148)
 81 retrospective.tw. (16600)
 82 cross sectional.tw. (9459)
 83 or/63-82 (48534)
 84 54 or 58 or 62 or 83 (119752)
 85 48 and 84 (32)
 86 limit 85 to (letter or historical article or comment or editorial or news or case reports) (0)
 87 85 not 86 (32)

Database: Medline daily update

Platform: Ovid

Version: Ovid MEDLINE(R) Daily Update <July 21, 2020>

Search date: 22 July 2020

Number of results retrieved: 3

Search strategy

Database: Ovid MEDLINE(R) Daily Update <July 21, 2020>

Search Strategy:

1 Gender Dysphoria/ (4)
 2 Gender Identity/ (38)
 3 "Sexual and Gender Disorders"/ (0)
 4 Transsexualism/ (2)
 5 Transgender Persons/ (26)
 6 Health Services for Transgender Persons/ (1)
 7 exp Sex Reassignment Procedures/ (3)
 8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or
 queer*)).tw. (22)

9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or
 transmen* or transperson* or transpeopl*).tw. (39)
 10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw.
 (87)
 11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (15)
 12 (male-to-female or m2f or female-to-male or f2m).tw. (181)
 13 or/1-12 (358)
 14 exp Infant/ or Infant Health/ or Infant Welfare/ (932)
 15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born*
 or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (981)
 16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1756)
 17 Minors/ (3)
 18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (3672)
 19 exp pediatrics/ (75)
 20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (1658)
 21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (2006)
 22 Puberty/ (8)
 23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert*
 or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn.
 (732)
 24 Schools/ (56)
 25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (5)
 26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or
 pupil* or student*).ti,ab,jn. (622)
 27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen"
 or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or
 aged)).ti,ab. (98)
 28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19")
 adj2 (year or years or age or ages or aged)).ti,ab. (1301)
 29 or/14-28 (6705)
 30 13 and 29 (130)
 31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw.
 (0)
 32 30 or 31 (130)
 33 Hormones/ad, tu, th (3)
 34 exp Progesterone/ad, tu, th (3)
 35 exp Estrogens/ad, tu, th (8)
 36 exp Gonadal Steroid Hormones/ad, tu, th (22)
 37 (progesteron* or oestrogen* or estrogen*).tw. (161)
 38 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or
 treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (3)
 39 exp Estradiol/ad, tu, th (8)
 40 exp Testosterone/ad, tu, th (8)
 41 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or
 testocaps* or nebido or testavan).tw. (79)
 42 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylesttrad* or elleste or
 progynova or zumenon or bedol or femseven or nuvelle).tw. (61)
 43 or/33-42 (261)
 44 32 and 43 (7)
 45 limit 44 to yr="2000 -Current" (7)
 46 animals/ not humans/ (3647)
 47 45 not 46 (6)
 48 limit 47 to english language (6)
 49 (MEDLINE or pubmed).tw. (529)
 50 systematic review.tw. (512)

51 systematic review.pt. (522)
 52 meta-analysis.pt. (370)
 53 intervention\$.ti. (247)
 54 or/49-53 (1065)
 55 randomized controlled trial.pt. (595)
 56 randomi?ed.mp. (1203)
 57 placebo.mp. (219)
 58 or/55-57 (1234)
 59 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation
 studies as topic/ or exp statistics as topic/ (7958)
 60 ((control and (group* or study)) or (time and factors)).mp. (4307)
 61 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-
 up*).mp. (5828)
 62 or/59-61 (11814)
 63 Observational Studies as Topic/ (27)
 64 Observational Study/ (449)
 65 Epidemiologic Studies/ (7)
 66 exp Case-Control Studies/ (2173)
 67 exp Cohort Studies/ (3287)
 68 Cross-Sectional Studies/ (837)
 69 Controlled Before-After Studies/ (1)
 70 Historically Controlled Study/ (0)
 71 Interrupted Time Series Analysis/ (6)
 72 Comparative Study.pt. (768)
 73 case control\$.tw. (182)
 74 case series.tw. (139)
 75 (cohort adj (study or studies)).tw. (561)
 76 cohort analy\$.tw. (22)
 77 (follow up adj (study or studies)).tw. (40)
 78 (observational adj (study or studies)).tw. (253)
 79 longitudinal.tw. (429)
 80 prospective.tw. (778)
 81 retrospective.tw. (1032)
 82 cross sectional.tw. (739)
 83 or/63-82 (5471)
 84 54 or 58 or 62 or 83 (12581)
 85 48 and 84 (3)
 86 limit 85 to (letter or historical article or comment or editorial or news or case reports) (0)
 87 85 not 86 (3)

Database: Embase

Platform: Ovid

Version: Embase <1974 to 2020 July 22>

Search date: 23 July 2020

Number of results retrieved: 1207

Search strategy:

Database: Embase <1974 to 2020 July 22>

Search Strategy:

1 exp Gender Dysphoria/ (5399)
 2 Gender Identity/ (16820)
 3 "Sexual and Gender Disorders"/ (24689)
 4 Transsexualism/ (3869)
 5 exp Transgender/ (6597)

6 Health Services for Transgender Persons/ (158848)
7 exp Sex Reassignment Procedures/ (1108)
8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or
9 queer*)).tw. (12470)
10 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or
11 transmen* or transperson* or transpeopl*).tw. (22509)
12 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw.
13 (154446)
14 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (10327)
15 (male-to-female or m2f or female-to-male or f2m).tw. (200166)
16 or/1-12 (581748)
17 exp juvenile/ or Child Behavior/ or Child Welfare/ or Child Health/ or infant welfare/ or
18 "minor (person)"/ or elementary student/ or adolescent health/ or middle school student/ or
19 high school student/ (3440943)
20 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born*
21 or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn.
22 (1186161)
23 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (3586795)
24 exp pediatrics/ (106214)
25 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (1491597)
26 exp adolescence/ or exp adolescent behavior/ or adolescent health/ or high school
27 student/ or middle school student/ (105108)
28 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert*
29 or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn.
30 (641660)
31 school/ or high school/ or kindergarten/ or middle school/ or primary school/ or nursery
32 school/ or day care/ (103791)
33 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or
34 pupil* or student*).ti,ab,jn. (687437)
35 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen"
36 or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or
37 aged)).ti,ab. (138908)
38 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19")
39 adj2 (year or years or age or ages or aged)).ti,ab. (1562903)
40 or/14-24 (7130881)
41 13 and 25 (181778)
42 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw.
43 (17)
44 26 or 27 (181778)
45 hormone/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po,
46 pa, pr, sc, li, th, tp, td (5160)
47 exp progesterone derivative/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip,
48 ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (23479)
49 exp estrogen/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi,
50 po, pa, pr, sc, li, th, tp, td (57641)
51 steroid hormone/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve,
52 vi, po, pa, pr, sc, li, th, tp, td (372)
53 sex hormone/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi,
54 po, pa, pr, sc, li, th, tp, td (1984)
55 hormonal therapy/ (42222)
56 (progesteron* or oestrogen* or estrogen*).tw. (254142)
57 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or
58 treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (1224)
59 exp estradiol derivative/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va,
60 iv, ve, vi, po, pa, pr, sc, li, th, tp, td (30740)

38 exp testosterone derivative/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut,
 va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (15868)
 39 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or
 testocaps* or nebido or testavan).tw. (99596)
 40 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or
 progynova or zumenon or bedol or femseven or nuvelle).tw. (114290)
 41 or/29-40 (438737)
 42 28 and 41 (6053)
 43 limit 42 to yr="2000 -Current" (4741)
 44 nonhuman/ not human/ (4649157)
 45 43 not 44 (3636)
 46 limit 45 to english language (3513)
 47 (MEDLINE or pubmed).tw. (261145)
 48 exp systematic review/ or systematic review.tw. (302985)
 49 meta-analysis/ (191173)
 50 intervention\$.ti. (200041)
 51 or/47-50 (660206)
 52 random:.tw. (1552336)
 53 placebo:.mp. (455979)
 54 double-blind:.tw. (210671)
 55 or/52-54 (1807280)
 56 cohort analysis/ (596360)
 57 exp epidemiology/ (3434332)
 58 exp clinical trial/ (1504711)
 59 evaluation study/ (45870)
 60 statistics/ (301181)
 61 ((control and (group* or study)) or (time and factors)).mp. (3324555)
 62 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-
 up*).mp. (6067112)
 63 or/56-62 (11048972)
 64 Clinical study/ (155444)
 65 Case control study/ (157943)
 66 Family study/ (26047)
 67 Longitudinal study/ (141660)
 68 Retrospective study/ (937696)
 69 comparative study/ (859061)
 70 Prospective study/ (613138)
 71 Randomized controlled trials/ (182542)
 72 70 not 71 (606604)
 73 Cohort analysis/ (596360)
 74 cohort analy\$.tw. (13020)
 75 (Cohort adj (study or studies)).tw. (302159)
 76 (Case control\$ adj (study or studies)).tw. (137432)
 77 (follow up adj (study or studies)).tw. (63423)
 78 (observational adj (study or studies)).tw. (168428)
 79 (epidemiologic\$ adj (study or studies)).tw. (106448)
 80 (cross sectional adj (study or studies)).tw. (220073)
 81 case series.tw. (104089)
 82 prospective.tw. (861922)
 83 retrospective.tw. (886445)
 84 or/64-69,72-83 (4047788)
 85 51 or 55 or 63 or 84 (12494560)
 86 46 and 85 (2151)
 87 86 not (letter or editorial).pt. (2137)

88 87 not (conference abstract or conference paper or conference proceeding or "conference review").pt. (1207)

Database: APA PsycInfo

Platform: Ovid

Version: APA PsycInfo <1806 to July Week 2 2020>

Search date: 22 July 2020

Number of results retrieved: 581

Search strategy:

Database: APA PsycInfo <1806 to July Week 2 2020>

Search Strategy:

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1  Gender Dysphoria/ (936)
2  Gender Identity/ (8648)
3  Transsexualism/ (2825)
4  Transgender/ (5257)
5  exp Gender Reassignment/ (568)
6  (gender* adj3 (dysphori* or incongruen* or identi* or disorder* or confus* or minorit* or
  queer*)).tw. (15276)
7  (transgend* or transex* or transsex* or transfem* or transwom* or transma* or
  transmen* or transperson* or transpeopl*).tw. (13028)
8  (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw.
  (7679)
9  ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (5796)
10 (male-to-female or m2f or female-to-male or f2m).tw. (63688)
11 or/1-10 (99498)
12 exp Infant Development/ (21841)
13 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born*
  or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn.
  (150219)
14 Child Characteristics/ or exp Child Behavior/ or Child Psychology/ or exp Child
  Welfare/ or Child Psychiatry/ (23423)
15 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (984230)
16 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (78962)
17 Adolescent Psychiatry/ or Adolescent Behavior/ or Adolescent Development/ or
  Adolescent Psychology/ or Adolescent Characteristics/ or Adolescent Health/ (62142)
18 Puberty/ (2753)
19 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert*
  or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn.
  (347604)
20 Schools/ (29181)
21 Child Day Care/ or Nursery Schools/ (2836)
22 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or
  pupil* or student*).ti,ab,jn. (772814)
23 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen"
  or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or
  aged)).ti,ab. (21475)
24 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19")
  adj2 (year or years or age or ages or aged)).ti,ab. (285697)
25 or/12-24 (1765408)
26 11 and 25 (49560)
27 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw.
  (14)

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28 26 or 27 (49561)
 29 hormones/ (8408)
 30 sex hormones/ (1777)
 31 exp progestational hormones/ (2409)
 32 estrogens/ (3889)
 33 steroids/ (3797)
 34 (progesteron* or oestrogen* or estrogen*).tw. (11188)
 35 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or
 treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (457)
 36 estradiol/ (3120)
 37 testosterone/ (5606)
 38 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or
 testocaps* or nebido or testavan).tw. (9625)
 39 (oestrad* or estrad* or evorel or ethinyloestradiol* or ethinylestradiol* or elleste or
 progynova or zumenon or bedol or femseven or nuvelle).tw. (6741)
 40 or/29-39 (30344)
 41 28 and 40 (1005)
 42 limit 41 to yr="2000 -Current" (749)
 43 limit 42 to english language (692)
 44 limit 43 to ("0200 book" or "0240 authored book" or "0280 edited book" or "0300
 encyclopedia" or "0400 dissertation abstract") (111)
 45 43 not 44 (581)

**Database: Cochrane Library – incorporating Cochrane Database of Systematic
Reviews (CDSR); CENTRAL**

Platform: Wiley

Version:

CDSR – Issue 7 of 12, July 2020

CENTRAL – Issue 7 of 12, July 2020

Search date: 22 July 2020

Number of results retrieved: CDSR 0 ; CENTRAL 67.

ID	Search Hits
#1	MeSH descriptor: [Gender Dysphoria] this term only 3
#2	MeSH descriptor: [Gender Identity] this term only 227
#3	MeSH descriptor: [Sexual and Gender Disorders] this term only 2
#4	MeSH descriptor: [Transsexualism] this term only 27
#5	MeSH descriptor: [Transgender Persons] this term only 36
#6	MeSH descriptor: [Health Services for Transgender Persons] this term only 0
#7	MeSH descriptor: [Sex Reassignment Procedures] explode all trees 4
#8	(gender* near/3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)):ti,ab,kw 702
#9	(transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*):ti,ab,kw 959
#10	(trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*):ti,ab,kw 3969
#11	((sex or gender*) near/3 (reassign* or chang* or transform* or transition*)):ti,ab,kw 524
#12	(male-to-female or m2f or female-to-male or f2m):ti,ab,kw 516
#13	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 6413
#14	MeSH descriptor: [Infant] explode all trees 28440
#15	MeSH descriptor: [Infant Health] this term only 49
#16	MeSH descriptor: [Infant Welfare] this term only 82

- #17 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*):ti,ab,kw,so 89530
- #18 MeSH descriptor: [Child] explode all trees 44089
- #19 MeSH descriptor: [Child Behavior] explode all trees 2061
- #20 MeSH descriptor: [Child Health] this term only 98
- #21 MeSH descriptor: [Child Welfare] this term only 325
- #22 MeSH descriptor: [Minors] this term only 8
- #23 (child* or minor or minors or boy* or girl* or kid or kids or young*):ti,ab,kw,so 265417
- #24 MeSH descriptor: [Pediatrics] explode all trees 661
- #25 (pediatric* or paediatric* or peadiatric*):ti,ab,kw,so 57725
- #26 MeSH descriptor: [Adolescent] this term only 102154
- #27 MeSH descriptor: [Adolescent Behavior] this term only 1358
- #28 MeSH descriptor: [Adolescent Health] this term only 29
- #29 MeSH descriptor: [Puberty] this term only 295
- #30 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*):ti,ab,kw,so 140927
- #31 MeSH descriptor: [Schools] this term only 1914
- #32 MeSH descriptor: [Child Day Care Centers] this term only 231
- #33 MeSH descriptor: [Nurseries, Infant] explode all trees 17
- #34 MeSH descriptor: [Schools, Nursery] this term only 37
- #35 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*):ti,ab,kw,so 97810
- #36 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") near/2 (year or years or age or ages or aged)):ti,ab 6710
- #37 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") near/2 (year or years or age or ages or aged)):ti,ab 196881
- #38 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 516067
- #39 #13 and #38 2488
- #40 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*):ti,ab,kw 0
- #41 #39 or #40 2488
- #42 MeSH descriptor: [Hormones] this term only 2241
- #43 MeSH descriptor: [Progesterone] explode all trees 3135
- #44 MeSH descriptor: [Estrogens] explode all trees 1841
- #45 MeSH descriptor: [Gonadal Steroid Hormones] explode all trees 10747
- #46 (progesteron* or oestrogen* or estrogen*):ti,ab,kw 18387
- #47 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)):ti,ab,kw 24
- #48 MeSH descriptor: [Estradiol] explode all trees 4434
- #49 MeSH descriptor: [Testosterone] explode all trees 2945
- #50 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan):ti,ab,kw 7386
- #51 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle):ti,ab,kw 11410
- #52 #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 31870
- #53 #41 and #52 121
- #54 "conference":pt or (clinicaltrials or trialsearch):so 492465
- #55 #53 not #54 72

Database: HTA

Platform: Wiley
Version: up to 2018
Search date: 22nd July 2020
Number of results retrieved: 4
Search strategy:

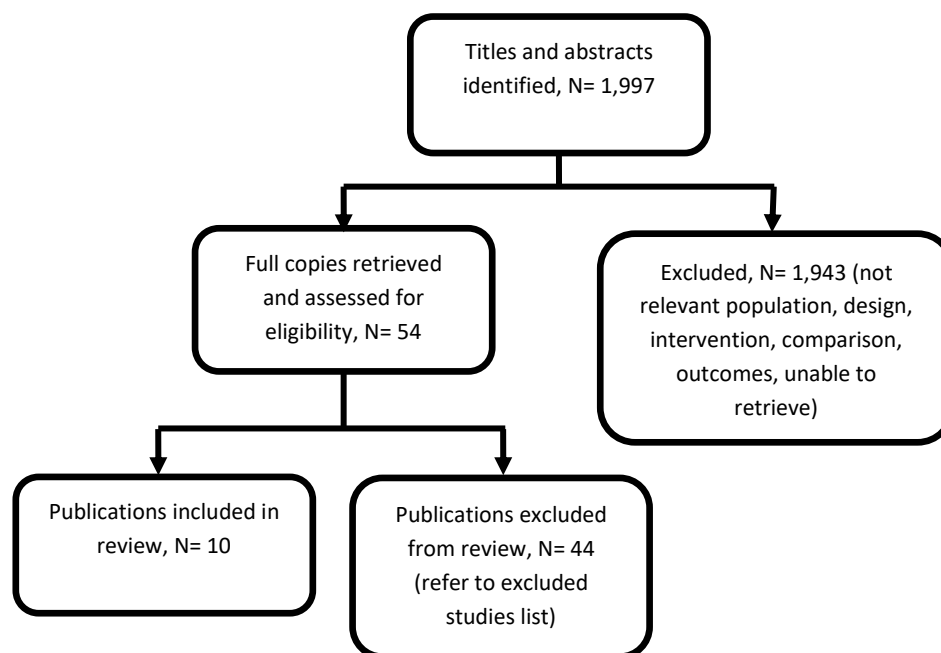
```
#1 MeSH DESCRIPTOR Gender Dysphoria 0
#2 MeSH DESCRIPTOR Gender Identity 12
#3 MeSH DESCRIPTOR Sexual and Gender Disorders 2
#4 MeSH DESCRIPTOR Transsexualism 12
#5 MeSH DESCRIPTOR Transgender Persons 3
#6 MeSH DESCRIPTOR Health Services for Transgender Persons 0
#7 MeSH DESCRIPTOR Sex Reassignment Procedures EXPLODE ALL TREES 1
#8 ((gender* near3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit*
or queer*))) 28
#9 ((transgend* or transex* or transsex* or transfem* or transwom* or transma* or
transmen* or transperson* or transpeopl*)) 76
#10 ((trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*))
83
#11 (((sex or gender*) near3 (reassign* or chang* or transform* or transition*))) 24
#12 ((male-to-female or m2f or female-to-male or f2m)) 86
#13 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
261
#14 MeSH DESCRIPTOR Infant EXPLODE ALL TREES 2964
#15 MeSH DESCRIPTOR Infant Health 0
#16 MeSH DESCRIPTOR Infant Welfare 22
#17 ((prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-
born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*))
5510
#18 MeSH DESCRIPTOR Child EXPLODE ALL TREES 4935
#19 MeSH DESCRIPTOR Child Behavior EXPLODE ALL TREES 64
#20 MeSH DESCRIPTOR Child Health 2
#21 MeSH DESCRIPTOR Child Welfare 80
#22 MeSH DESCRIPTOR Minors 2
#23 ((child* or minor or minors or boy* or girl* or kid or kids or young*)) 13575
#24 MeSH DESCRIPTOR Pediatrics EXPLODE ALL TREES 119
#25 ((pediatric* or paediatric* or peadiatric*)) 2842
#26 MeSH DESCRIPTOR Adolescent 4594
#27 MeSH DESCRIPTOR Adolescent Behavior 94
#28 MeSH DESCRIPTOR Adolescent Health 0
#29 MeSH DESCRIPTOR Puberty 3
#30 ((adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or
prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or
under*age*)) 5621
#31 MeSH DESCRIPTOR Schools 168
#32 MeSH DESCRIPTOR Child Day Care Centers 12
#33 MeSH DESCRIPTOR Schools, Nursery 3
#34 ((pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school*
or pupil* or student*)) 4454
#35 (((("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen"
or "sixteen" or "seventeen" or "eighteen" or "nineteen") near2 (year or years or age or ages
or aged))) 380
#36 (((("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or
"19") near2 (year or years or age or ages or aged))) 7996
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#37 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR
 #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR
 #35 OR #36 22640
 #38 #13 AND #37 116
 #39 (#13 AND #37) IN HTA 4

Appendix C Evidence selection

The literature searches identified 1,997 references. These were screened using their titles and abstracts and 54 references were obtained and assessed for relevance. Of these, 10 references are included in the evidence review. The remaining 44 references were excluded and are listed in [appendix D](#).

Figure 1 – Study selection flow diagram



References submitted with Preliminary Policy Proposal

There is no preliminary policy proposal for this policy.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Aranda G, Mora M, Hanzu FA et al. (2019) Effects of sex steroids on cardiovascular risk profile in transgender men under gender affirming hormone therapy. <i>Endocrinologia, diabetes y nutricion</i> 66(6): 385–392	Excluded on population – adult study, participants not 18 years or less (mean age 27.1 years).
Arnold, Justin D, Sarkodie, Eleanor P, Coleman, Megan E et al. (2016) Incidence of Venous Thromboembolism in Transgender Women	Excluded on population – adult study, participants not 18 years or less (mean age 33.2 years).

Study reference	Reason for exclusion
Receiving Oral Estradiol. The journal of sexual medicine 13(11): 1773–1777	
Asscheman, Henk, Giltay, Erik J, Megens, Jos A J et al. (2011) A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. European journal of endocrinology 164(4): 635–42	Excluded on population – although some participants started gender-affirming hormones when young, the study does not report the proportion who started treatment when 18 years or less. Mean ages at start of treatment were 31.4 years (transfemales) and 26.1 years (transmales), suggesting the majority of participants were older than 18 years at the start of treatment. Outcomes not reported separately for people aged 18 years or less.
Author not, found (2014) Hormone therapy for the treatment of gender dysphoria. Lansdale, PA: HAYES, Inc	Full text paper not available.
Baba, T., Endo, T., Honnma, H. et al. (2007) Association between polycystic ovary syndrome and female-to-male transsexuality. Human Reproduction 22(4): 1011–1016	Excluded on population – although study included some younger people (age range 17 to 47), most participants were adults (mean age around 25 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.
Becerra-Fernandez A, Perez-Lopez G, Roman MM et al. (2014) Prevalence of hyperandrogenism and polycystic ovary syndrome in female to male transsexuals. Endocrinologia y Nutricion: Organo de la Sociedad Espanola de Endocrinologia y Nutricion 61(7): 351–8	Excluded on population – although study included some younger people (age range 18 to 45), most participants were adults (mean age around 25 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.
Becker I, Auer M, Barkmann C et al. (2018) A Cross-Sectional Multicenter Study of Multidimensional Body Image in Adolescents and Adults with Gender Dysphoria Before and After Transition-Related Medical Interventions. Archives of Sexual Behavior 47(8): 2335–2347	Excluded on population – study included people aged 14 to 21 years. Outcomes not reported separately for people aged 18 years or less. Better evidence available – only 11 participants received gender-affirming hormones. The majority of the study cohort were either pre-treatment, received puberty suppression alone, or received hormones and underwent surgery.
Chew D, Anderson J, Williams K et al. (2018) Hormonal Treatment in Young People With Gender Dysphoria: A Systematic Review. Pediatrics 141(4): e20173742	Excluded on better available evidence - systematic review did not meta-analyse results from. Individual studies from this systematic review are either

Study reference	Reason for exclusion
	included, or excluded because they did not meet the PICO criteria.
Connolly MD, Zervos MJ, Barone CJ 2nd et al. (2016) The Mental Health of Transgender Youth: Advances in Understanding. The Journal of Adolescent Health: Official Publication of the Society for Adolescent Medicine 59(5): 489–495	Excluded on intervention - review did not investigate gender-affirming hormones
de Vries ALC, McGuire JK, Steensma TD et al. (2014) Young adult psychological outcome after puberty suppression and gender reassignment. Pediatrics 134(4): 696–704	Exclude on intervention – all participants had surgery after gender-affirming hormones. Unable to determine whether changes were due to hormones or surgery. Complete data only available for 40 patients. Details of gender-affirming hormones are poorly reported. Outcomes reported in other study (with a population that more closely matches PICO)
Elamin MB, Garcia MZ, Murad MH et al. (2010) Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. Clinical Endocrinology 72(1): 1–10	Exclude on population – all included studies conducted in adult population. Unclear whether hormones were started when participants were aged 18 years or less. Outcomes not reported by age at treatment initiation.
Fernandez JD and Tannock LR (2016) Metabolic effects of hormone therapy in transgender patients. Endocrine Practice: Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 22(4): 383–8	Excluded on population – adult study, participants not 18 years or less (mean ages 31 and 27 years).
Figuera TM, Ziegelmann PK, Da Silva TR et al. (2019) Bone mass effects of cross-sex hormone therapy in transgender people: Updated systematic review and meta-analysis. Journal of the Endocrine Society 3(5): 943–964	Excluded on population – all included studies conducted in adult population. Unclear whether hormones were started when participants were aged 18 years or less. Outcomes not reported by age at treatment initiation.
Getahun D, Nash R, Flanders WD et al. (2018) Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons: A Cohort Study. Annals of Internal Medicine 169(4): 205–213	Excluded on population – adult study, participants not 18 years or less.
Gomez-Gil E, Zubiaurre-Elorza L, de Antonio IE et al. (2014) Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. Quality of Life Research: an International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation 23(2): 669–76	Excluded on population – although study included some younger people (age range 16 to 67), most participants were adults (mean age 31.2 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.
Gomez-Gil E, Zubiaurre-Elorza L, Esteva I et al. (2012) Hormone-treated transsexuals report less	Excluded on population – adult study, participants not 18 years or less (mean age 24.6 years).

Study reference	Reason for exclusion
social distress, anxiety and depression. Psychoneuroendocrinology 37(5): 662–70	
Gooren LJ, van Trotsenburg MAA, Giltay EJ et al. (2013) Breast cancer development in transsexual subjects receiving cross-sex hormone treatment. The Journal of Sexual Medicine 10(12): 3129–34	Excluded on population – study reports on cancer rates in people aged 18-80 years. The 3 cases of cancer all started gender-affirming hormone treatment >18 years.
Grimstad FW, Boskey E, Grey M (2020) New-Onset Abdominopelvic Pain After Initiation of Testosterone Therapy Among TransMasculine Persons: A Community-Based Exploratory Survey. LGBT health 7(5): Published Online:13 Jul 2020 https://doi.org/10.1089/lgbt.2019.0258	Excluded on population – adult study, participants not 18 years or less.
Hannema SE, Schagen SEE, Cohen-Kettenis PT et al. (2017) Efficacy and Safety of Pubertal Induction Using 17beta-Estradiol in Transgirls. The Journal of Clinical Endocrinology and Metabolism 102(7): 2356–2363	Excluded on better evidence available – small study (n=28) with high drop-out rate (n=16 at final follow-up). Same outcomes reported in larger studies.
Jarín J, Pine-Twaddell E, Trotman G et al. (2017) Cross-Sex Hormones and Metabolic Parameters in Adolescents With Gender Dysphoria. Pediatrics 139(5)	Excluded on population and better evidence available. Although the study included some younger people (age range 13 to 25; mean age 16 and 18), the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less. Outcomes were limited to physiological results (including haemoglobin, lipids and BMI). Follow-up only 6 months, other included studies report same outcomes with longer follow-up (12 to 31 months).
Keo-Meier CL, Herman LI, Reisner SL et al. (2015) Testosterone treatment and MMPI-2 improvement in transgender men: a prospective controlled study. Journal of consulting and clinical psychology 83(1): 143–56	Excluded on population – although study included some younger people (age range 18 to 54), most participants were adults (mean age 26.6 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.
Klaver M, de Mutsert R, Wiepjes CM et al. (2018) Early Hormonal Treatment Affects Body Composition and Body Shape in Young Transgender Adolescents. The Journal of Sexual Medicine 15(2): 251–260	Excluded on outcomes – reported outcomes not included in PICO document. The risk of obesity with gender-affirmed hormones was reported in an included study.
McFarlane T, Zajac JD, Cheung AS (2018) Gender-affirming hormone therapy and the risk of sex hormone-dependent tumours in transgender individuals-A systematic review. Clinical Endocrinology 89(6): 700-711	Exclude on population – all included studies conducted in adult population.

Study reference	Reason for exclusion
Meriggiola MC, Armillotta F, Costantino A et al. (2008) Effects of testosterone undecanoate administered alone or in combination with letrozole or dutasteride in female to male transsexuals. The Journal of Sexual Medicine 5(10): 2442–53	Excluded on population – adult study, participants not 18 years or less.
Nota NM, Wiepjes CM, de Blok, CJM et al. (2018) The occurrence of benign brain tumours in transgender individuals during cross-sex hormone treatment. Brain: A Journal of Neurology 141(7): 2047–2054	Excluded on population – adult study, participants not 18 years or less.
Oda H and Kinoshita T (2017) Efficacy of hormonal and mental treatments with MMPI in FtM individuals: Cross-sectional and longitudinal studies. BMC Psychiatry 17(1): 256	Excluded on population – although study included some younger people (age range 15 to 43), most participants were adults (mean age around 25.6 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.
Olson-Kennedy J, Okonta V, Clark LF et al. (2018) Physiologic Response to Gender-Affirming Hormones Among Transgender Youth. The Journal of Adolescent Health: Official Publication of the Society for Adolescent Medicine 62(4): 397–401	Excluded on population – although study included some younger people (age range 12 to 23; mean age 18 years). Outcomes not reported separately for people aged 18 years or less. Outcomes limited to physiological results (including haemoglobin, lipids, liver enzymes and BMI). Same outcomes reported in included studies that had a less indirect population and a longer follow-up.
Ott J, Kaufmann U, Bentz K et al. (2010) Incidence of thrombophilia and venous thrombosis in transsexuals under cross-sex hormone therapy. Fertility and sterility 93(4): 1267–72	Excluded on population – adult study, participants not 18 years or less.
Pakpoor J, Wotton CJ, Schmierer K et al. (2016) Gender identity disorders and multiple sclerosis risk: A national record-linkage study. Multiple sclerosis. Multiple Sclerosis Journal. 22(13): 1759–1762	Excluded on population – although study included some younger people, outcomes not reported separately for people aged 18 years or less. Also exclude for intervention – unclear if people received gender-affirming hormones.
Pyra M, Casimiro I, Rusie L et al. (2020) An Observational Study of Hypertension and Thromboembolism among Transgender Patients Using Gender-Affirming Hormone Therapy. Transgender Health 5(1): 1–9	Excluded on population – adult study (age range 20-70). Age at which gender-affirming hormones started not reported.
Quiros C, Patrascioiu I, Mora M et al. (2015) Effect of cross-sex hormone treatment on cardiovascular risk factors in transsexual individuals. Experience in a specialized unit in Catalonia. Endocrinologia y nutricion : organo de la Sociedad Espanola de Endocrinologia y Nutricion 62(5): 210–6	Excluded on population – adult study, participants not 18 years or less.

Study reference	Reason for exclusion
Rowniak S, Bolt L, Sharifi C (2019) Effect of cross-sex hormones on the quality of life, depression and anxiety of transgender individuals: A quantitative systematic review. JBI Database of Systematic Reviews and Implementation Reports 17(9): 1826–1854	Exclude on population – all included studies conducted in adult population.
Sequeira GM, Kidd K, El Nokali NE et al. (2019) Early Effects of Testosterone Initiation on Body Mass Index in Transmasculine Adolescents. Journal of Adolescent Health 65(6): 818–820	Exclude on outcome - study only reports BMI z-score over 12 month testosterone treatment. BMI not listed as an outcome of interest in the PICO document. Other included studies have investigated the impact of gender-affirming hormone treatment on CV risk profile, including longer term obesity rates, with a longer follow-up and more participants.
Shim JY, Laufer MR, Grimstad FW (2020) Dysmenorrhea and Endometriosis in Transgender Adolescents. Journal of Pediatric and Adolescent Gynecology. Available online 11 June 2020. https://doi.org/10.1016/j.jpag.2020.06.001	Exclude on population – only 2 participants taking testosterone before diagnosis of dysmenorrhea.
Slabbekoorn D, Van Goozen SHM, Gooren, LJG et al. (2001) Effects of cross-sex hormone treatment on emotionality in transsexuals. International Journal of Transgenderism 5(3): http://www.symposion.com/ijt/ijtvo05no03_02.htm	Excluded on population – adult study (age range 21 to 28 years)
Smith YLS., Van Goozen SHM, Kuiper AJ et al. (2005) Sex reassignment: Outcomes and predictors of treatment for adolescent and adult transsexuals. Psychological Medicine 35(1): 89–99	Excluded on population – results on adults only used to assess hormone treatment.
Sutherland N, Espinel W, Grotzke M et al. (2020) Unanswered Questions: Hereditary breast and gynecological cancer risk assessment in transgender adolescents and young adults. Journal of Genetic Counseling 29(4): 625–633	Excluded on study type – narrative review of 3 case reports.
van Velzen DM, Paldino A, Klaver M et al. (2019) Cardiometabolic Effects of Testosterone in Transmen and Estrogen Plus Cyproterone Acetate in Transwomen. The Journal of Clinical Endocrinology and Metabolism 104(6): 1937–1947	Excluded on population – adult study, participants not 18 years or less.
White Hughto JM and Reisner SL (2016) A Systematic Review of the Effects of Hormone Therapy on Psychological Functioning and Quality of Life in Transgender Individuals. Transgender Health 1(1): 21–31	Exclude on population – all included studies conducted in adult population.
Wiepjes CM, de Blok CJM, Staphorsius AS et al. (2020) Fracture Risk in Trans Women and Trans Men Using Long-Term Gender-Affirming Hormonal Treatment: A Nationwide Cohort Study. Journal of Bone and Mineral Research 35(1): 64–70	Excluded on population – adult study, all participants started gender-affirming hormones after 18 years.
Wierckx K, Mueller S, Weyers S et al. (2012) Long-term evaluation of cross-sex hormone treatment in	Excluded on population – adult study, participants not 18 years or less.

Study reference	Reason for exclusion
transsexual persons. The Journal of Sexual Medicine 9(10): 2641–51	
Wierckx K, Van Caenegem E, Schreiner T et al. (2014) Cross-sex hormone therapy in trans persons is safe and effective at short-time follow-up: results from the European network for the investigation of gender incongruence. The journal of sexual medicine 11(8): 1999–2011	Excluded on population – adult study, participants not 18 years or less.
Wilson R, Jenkins C, Miller H et al. (2006) The effect of oestrogen on cytokine and antioxidant levels in male to female transsexual patients. Maturitas 55(1): 14–8	Excluded on population – adult study, participants not 18 years or less.
Witcomb GL, Bouman WP, Claes L et al. (2018) Levels of depression in transgender people and its predictors: Results of a large matched control study with transgender people accessing clinical services. Journal of Affective Disorders 235: 308–315	Excluded on population – although study included some younger people (age range 15 to 79), most participants were adults (mean age around 30.4 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.

Appendix E Evidence tables

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Achille, C., Taggart, T., Eaton, N.R. et al. (2020) Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: Preliminary results. International Journal of Pediatric Endocrinology 2020(1): 8 Study location Single centre, New York, United States Study type Prospective longitudinal study Study aim To assess the psychological wellbeing and quality of life in children and adolescents who have sought endocrine	Inclusion and exclusion not reported- it appears from the description in the publication that all people referred for gender dysphoria were invited to participate, and the vast majority agreed. Of the 95 treatment naïve people who entered the study, 50 people completed all follow-up questionnaires and were included in the analysis. No description of the 45 people without follow-up data reported. The study included 50 children, adolescents and young adults with gender dysphoria.	Intervention Endocrine interventions (the collective term used by authors for puberty suppression and gender-affirming hormones) were introduced as per Endocrine Society and the World Professional Association for	Critical Outcomes Impact on mental health Depression symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CESD-R). Statistically significant improvements in CESD-R score were observed from baseline (initial assessment; 21.4 points) to about 12 months follow-up (13.9 points; $p < 0.001$). Regression analysis, controlling for reported medicines for mental health problems and engagement in counselling, found no statistically significant change from baseline in transfemales ($p = 0.27$) and transmales ($p = 0.43$). The Patient Health Questionnaire Modified for Teens (PHQ 9_Modified for Teens) was also used to assess depression symptoms. Depression scores improved from baseline ($p < 0.001$; absolute scores not reported numerically). Regression analysis, controlling for reported medicines for mental health problems and engagement in counselling, found no statistically significant change from baseline in transfemales ($p = 0.07$) and transmales ($p = 0.67$). Suicidal ideation measured using the additional questions from the PHQ 9_Modified for Teens, was presented in 10% (5/50) of	This study was appraised using the Newcastle-Ottawa tool for cohort studies. Domain 1: Selection domain b) somewhat representative c) no-non exposed cohort a) secure record b) no Domain 2: Comparability c) no comparator Domain 3: Outcome c) self-report a) yes – 6 monthly assessment up to 12 months (preliminary results from an ongoing study) c) Follow up rate less than 80% and no description of those lost Overall quality is assessed as poor Other comments: Although regression analysis results for some outcomes were controlled for use of medicines for mental health problems,

intervention to help with gender dysphoria. Study dates Study recruitment ran from December 2013 to December 2018; study is ongoing	17 transfemales and 33 transmales. Diagnostic criteria for gender dysphoria not reported. Mean age at baseline was 16.2 years (SD 2.2). Mean age at the start of gender-affirming hormone treatment not reported.	Transgender Health (WPATH) guidelines. Puberty suppression was: - GnRH agonist and/or anti-androgens (transfemales) - GnRH agonist or medroxyprogesterone (transmales) Average duration of GnRH analogue treatment not reported. Once eligible, gender-affirming hormones were offered, these were: - Oestradiol (transfemales) - Testosterone (transmales) Doses and route of administration not reported. After about 12-months treatment ('wave 3' in the study): 24 people (48%) were on gender-affirming hormones alone 12 people (24%) were on puberty suppression alone	participants at baseline and 6% (3/50) at about 12-month follow-up, no statistical analysis reported. The study also reported results by gender: In transfemales, 11.8% (2/17) had suicidal ideation at baseline compared with 5.9% (1/17) at 12-month follow-up (no statistically analysis reported) In transmales, 9.1% (3/33) had suicidal ideation at baseline compared with 6.1% (2/33) at 12-month follow-up (no statistically analysis reported) Impact on quality of life Quality of Life Enjoyment and Satisfaction Questionnaire (QLES-Q-SF) scores: there was no statistically significant change in score from baseline to about 12-months ($p=0.085$; absolute scores not reported numerically). Regression analysis, controlling for reported medicines for mental health problems and engagement in counselling, found not statistically significant change from baseline in transfemales ($p=0.06$) and transmales ($p=0.08$). <i>No other critical or important outcomes reported</i>	details of these is not reported. Other co-morbidities not reported. Source of funding: None

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
		11 people (22%) were on both gender-affirming hormones and puberty suppression 3 people (6%) were on no endocrine intervention Results not represented separately for the sub-group of people who received gender-affirming hormones. Average duration of treatment with gender-affirming hormones not reported. Comparison No comparison group. Change overtime reported.		

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Allen, LR, Watson, LB, Egan, AM et al. (2019) Well-being and suicidality among transgender youth after gender-affirming hormones. Clinical Practice in Pediatric	The study included adolescents and young adults (age range 13-20 years) who received services for gender dysphoria in a clinic in the United States. Participants were required to have received gender-	39 participants received gender-affirming hormones only 8 participants received a GnRH analogue followed by gender-affirming hormones.	Critical Outcomes <i>Impact on mental health</i> The Ask Suicide-Screening Questions (ASQ) instrument was used to assess suicidality. Following an average of about 12 months treatment with gender-affirming hormones, adjusted mean ASQ score was statistically significantly lower (from 1.11 [standard error	This study was appraised using the Newcastle-Ottawa tool for cohort studies. Domain 1: Selection domain b) somewhat representative c) no-non exposed cohort

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Psychology 7(3): 302-311 Study location Single centre, Kansas City, United States Study type Retrospective longitudinal study Study aim To examine suicidality and general well-being following administration of gender-affirming hormones. Study dates Participants first presented to the clinic between 2015 and 2018.	affirming hormones for at least 3 months, and have pre-test and final assessment data points. No exclusion criteria reported. In total 47 adolescents and young adults with gender dysphoria were included: 14 transfemales (sex assigned at birth male) and 33 transmales (sex assigned at birth female). Diagnostic criteria for gender dysphoria not reported. Mean age at pre-test (before administration of gender-affirming hormones) was 16.59 years (range 13.73 to 19.04). Mean age at the start of treatment in the sub-group who received gender-affirming hormones-only was 16.72 years. Mean age at the start of treatment with gender-affirming hormones in people who previously	Mean duration of treatment in the gender-affirming hormones only subgroup was 366 days. Mean duration of gender-affirming hormone treatment in people who had previously received a GnRH analogue was not reported. Mean duration of treatment with a GnRH analogue was not reported. Participants were assessed at the start of treatment and at least 3 months after treatment.	(SE) 0.22] at baseline to 0.27 [SE 0.12] at final assessment; $p<0.001$). The authors also reported change in ASQ separately for transfemales (from 1.21 [SE 0.36] at baseline to 0.24 [SE 0.19] at final assessment) and transmales (from 1.01 [SE 0.36] at baseline to 0.29 [0.13] at final assessment). There was no statistically significant difference in change from baseline between transfemales and transmales ($p=0.79$) Impact on quality of life Assessed using the General Well-Being Scale (GWBS) of the Pediatric Quality of Life Inventory. Following an average of about 12 months treatment with gender-affirming hormones, adjusted mean GWBS score was statistically significantly higher (from 61.7 [SE 2.43] at baseline to 70.23 [2.15] at final assessment; $p<0.002$). The authors also reported change in GWBS of the Pediatric Quality of Life Inventory for transfemales (from 58.44 [SE 4.09] at baseline to 69.52 [SE 3.62] at final assessment) and transmales (from 64.95 [SE 2.66] at baseline to 70.94 [2.35] at final assessment). There was no statistically significant difference in change from baseline between transfemales and transmales ($p=0.32$) <i>No other critical or important outcomes reported</i>	3. a) secure record 4. b) no Domain 2: Comparability 2. c) no comparator Domain 3: Outcome 1. b) record linkage 2. a) yes – mean duration of treatment was 366 days 3. a) complete follow up - all subjects accounted for Overall quality is assessed as poor Other comments: None Source of funding: Not reported

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
	received a GnRH analogue was not reported.			

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Kaltiala, R., Heino, E., Tyolajarvi, M. et al. (2020) Adolescent development and psychosocial functioning after starting cross-sex hormones for gender dysphoria. Nordic Journal of Psychiatry 74(3): 213-219 Study location Single centre, Tampere, Finland Study type Retrospective chart review Study aim To evaluate the psychosocial functioning and need for mental health treatment during the gender identity diagnostic phase and after about	The study included adolescents who were referred to the gender identity service before they 18 years old, were diagnosed with gender dysphoria, received gender-affirming hormones and completed a follow-up of approximately 12 months after starting hormones. In total 52 adolescents were included, comprising of 11 transfemales and 41 transmales. Gender dysphoria was diagnosed according to International Classification of Disease 10 (ICD-10). The authors state that the corresponding diagnosis to 'gender dysphoria' in	Intervention referred to as 'hormonal sex reassignment treatment' – details of intervention not reported, although gender-affirming hormones were prescribed to all participants. It is not clear from the study whether additional interventions were prescribed. Medical records reviewed for the 'real-life phase' – the approximately 12 months follow-up period for this population in Finland.	Critical Outcomes <i>Impact on mental health</i> Of the 52 people who received gender-affirming hormones, 50% (26/52) needed mental health treatment before or during the assessment and 46% (24/51) needed mental health treatment during the 12-month 'real life' phase (no statistically significant difference). For specific symptoms / conditions: - depression: 54% (28/52) needed treatment before or during the assessment and 15% (8/52) needed treatment during the 12-month 'real life' phase (statistically significant reduction, $p<0.001$) - anxiety: 48% (25/52) needed treatment before or during the assessment and 15% (8/52) needed treatment during the 12-month 'real life' phase (statistically significant reduction, $p<0.001$) - suicidality/self-harm: 35% (18/52) needed treatment before or during the assessment and 4% (2/52) needed treatment during the 12-month 'real life' phase (statistically significant reduction, $p<0.001$) - conduct problems/antisocial: 14% (7/52) needed treatment before or during the	This study was appraised using the Newcastle-Ottawa tool for cohort studies. Domain 1: Selection domain b) somewhat representative c) no-non exposed cohort a) secure record b) no Domain 2: Comparability c) cohorts are not comparable on the basis of the design or analysis controlled for confounders Domain 3: Outcome b) record linkage a) yes – 12 month follow-up a) complete follow up - all subjects accounted for Overall quality is assessed as poor

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
a year on gender-affirming hormones. Study dates 2011 to 2017	the ICD-10 is 'transsexualism'. Mean age at diagnosis 18.1 years (range 15.2 to 19.9)		assessment and 6% (3/52) needed treatment during the 12-month 'real life' phase (no statistically significant difference, $p=0.18$) - psychotic symptoms/psychosis: 2% (1/52) needed treatment before or during the assessment and 4% (2/52) needed treatment during the 12-month 'real life' phase (no statistically significant difference, $p=0.56$) - substance abuse: 4% (2/52) needed treatment before or during the assessment and 2% (1/52) needed treatment during the 12-month 'real life' phase (no statistically significant difference, $p=0.56$) - autism: 12% (6/52) needed treatment before or during the assessment and 6% (3/52) needed treatment during the 12-month 'real life' phase (no statistically significant difference, $p=0.30$) - ADHD: 10% (5/52) needed treatment before or during the assessment and 2% (1/52) needed treatment during the 12-month 'real life' phase (no statistically significant difference, $p=0.09$) - eating disorder: 2% (1/52) needed treatment before or during the assessment and 2% (1/52) needed treatment during the 12-month 'real life' phase (no statistically significant difference, $p=1.0$). No details of actual treatment reported. Important Outcomes <i>Psychosocial Impact</i> Study reported on measures of functioning in different domains of adolescent development,	Other comments: None Source of funding: No source of funding reported

			reported over the approximately 12-month period after starting gender-affirming hormones (referred to as the 'real-life phase' in Finland) Significantly fewer participants were living with parent(s)/ guardians during the real-life phase (40%; 21/50) compared with during gender identity assessment (73%; 38/52; $p=0.001$)) There was a statistically significant reduction in the number of participants with normative peer contacts, from gender identity assessment (89%; 46/52) to the real-life phase (81%; 42/52; $p<0.001$). There was no significant difference in the number of participants who were progressing normally in school or work during gender identity assessment (64%; 33/52) compared with the real-life phase (60%; 31/52). There was no significant difference in the number of participants who have been dating or were in steady relationships during gender identity assessment (62%; 32/50) compared with the real-life phase (58%; 30/52). There was no significant difference in the number of participants who were able to deal with matters outside of the home in an age-appropriate manner during gender identity assessment (81% (42/52) compared with the real-life phase (81%; 42/52)	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			No other critical or important outcomes reported	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Khatchadourian K, Amed S, Metzger DL (2014) Clinical management of youth with gender dysphoria in Vancouver. The Journal of pediatrics 164(4): 906-11 Study location Single centre study, Vancouver, Canada Study type Retrospective chart review Study aim To describe the patient characteristics, clinical management, and response to treatment in a cohort of people seen in a single clinic. Study dates 1998 to 2011	Inclusion criteria were at least Tanner stage 2 pubertal development, previous assessment by a mental health professional and a confirmed diagnosis of gender dysphoria (diagnostic criteria not specified). No exclusion criteria are specified. 63 children, adolescents and young people with gender dysphoria who started gender-affirming hormones, out of 84 young people seen in the unit between 1998 and 2011. 39 transfemales and 24 transmales. Diagnostic criteria for gender dysphoria not reported. Mean age at the start of gender-affirming hormone treatment was 17.4 years (SD 1.9).	Intervention Transfemales: Oestrogen (oral micronized 17β-oestradiol) Transmales: Testosterone (injectable testosterone enanthate and/or cypionate) 19 participants (30%) had previously received a GnRH analogue. The median time from start of gender-affirming hormones was 11.3 months (range 2.2 to 42.0). 11 participants continued GnRH analogues after starting gender-affirming hormones. Average duration of treatment with a GnRH analogue not reported Comparison No comparator	Critical Outcomes No critical outcomes assessed. Important outcomes Safety Of the 63 participants who received gender-affirming hormones: - No participants permanently discontinued gender-affirming hormones 3 participants (5%) temporarily discontinued treatment: 2 transmales due to concomitant mental health comorbidities 1 transmale due to androgenic alopecia. - No transfemale stopped treatment. The authors report that all patients eventually restarted gender-affirming hormones, although they do not report how long treatment was	This study was appraised using the Newcastle-Ottawa tool for cohort studies. Domain 1: Selection domain b) somewhat representative c) no-non exposed cohort a) secure record* b) no Domain 2: Comparability c) cohorts are not comparable on the basis of the design or analysis controlled for confounders Domain 3: Outcome b) record linkage b) no – although follow-up time is reported for patients with more than 1 clinic visit, duration of treatment with gender-affirming hormones is not reported c) incomplete - missing data Overall quality is assessed as poor

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			stopped for, or what the effect of stopped treatment was. - No participants reported major complications 12 participants (19%) had minor complications: 7 transmales had severe acne (requiring isotretinoin) 1 transmale had androgenic alopecia 3 transmales had mild dyslipidaemia (levels not reported) 1 transmale had significant mood swings - No transfemales had minor complications	Other comments: Mental health comorbidity was reported for all participants but not for the gender-affirming hormone cohort separately. Concomitant use of other medicines was not reported. Source of funding: No source of funding identified.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Klaver, Maartje, de Mutsert, Renee, van der Loos, Maria A T C et al. (2020) Hormonal Treatment and Cardiovascular Risk Profile in Transgender Adolescents. Pediatrics 145(3) Study location Single centre, Amsterdam, Netherlands	Participants were included if i) they had started GnRH analogue treatment before 18 years, ii) if whole body dual-energy radiograph absorptiometry was performed at least once during treatment (4 months before or after the start of GnRH analogues or gender-affirming hormones, or	Transfemales: Oestrogen (17-β oestradiol [E2]) orally, starting with 5 mcg/kg body weight per day, which was increased every 6 months until the maintenance dose of 2 mg per day was reached. Transmales: mixed testosterone esters (Sustanon), 25 mg/m² body surface area every 2 weeks intramuscularly,	Critical Outcomes No critical outcomes assessed. Important outcomes Safety Safety outcomes reported separately for transfemales and transmales. For transfemales, from the start of gender-affirming hormone treatment to age 22 years: Mean BMI statistically significantly increased (mean change +1.9, 95% CI 0.6 to 3.2, p<0.005; mean BMI at	This study was appraised using the Newcastle-Ottawa tool for cohort studies. Domain 1: Selection domain b) somewhat representative c) no-non exposed cohort a) secure record* b) no Domain 2: Comparability c) cohorts are not comparable on the basis

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Study type Retrospective chart review Study aim To examine the effects of treatment on changes in cardiovascular risk factors, including BMI, blood pressure, insulin sensitivity, and lipid levels. Study dates 1998-2015	within 1.5 years before or after the 22nd birthday), iii) if they were likely to have had at least 1 medical consultation in young adulthood. The study included 192 young people with dysphoria who met the above inclusion criteria: 71 transfemales and 121 transmales. Gender dysphoria was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria. Mean age at the start of gender-affirming hormones was 16.4 years (SD 1.1) for transfemales and 16.9 years (SD 0.9) for transmales.	increased every 6 months to maintenance dose of 250 mg every 3 to 4 weeks. When GnRH analogues were started after the age of 16 years a different hormone starter dose was used (1 mg oestrogen daily and 75 mg testosterone weekly). Median (IQR) duration of GnRH analogue (monotherapy) was 2.1 years (1.0 to 2.7) in transfemales and 1.0 (0.5 to 2.9) for transmales.	22 years= 23.2, 95% CI 21.6 to 24.8). At age 22 years, 9.9% of the cohort were obese, compared with 3.0% in reference cisgender population¹. • Mean systolic blood pressure (SBP) did not significantly change (mean change - 3 mmHg, 95% CI -8 to 2; mean SBP at 22 years= 117 mmHg, 95% CI 113 to 122) • Mean diastolic blood pressure (DBP) statistically significantly increased (mean change +6 mmHg, 95% CI 3 to 10, $p<0.001$; mean DBP at 22 years= 75 mmHg, 95% CI 72 to 78) • Mean glucose level did not significantly change (mean change +0.1 mmol/L, 95% CI -0.1 to 0.2; mean glucose level at 22 years= 5.0 mmol/L, 95% CI 4.8 to 5.1) • Mean insulin level did not significantly change (mean change +2.7 mU/L, 95% CI -1.7 to 7.1; mean insulin level at 22 years= 5.0 mU/L (4.8 to 5.1) • Insulin resistance (mean Homeostatic Model Assessment of Insulin Resistance [HOMA-IR]) did not significantly change (mean change +0.7, 95% CI -0.2 to 1.5; mean HOMA-IR at 22 years 2.9, 95% CI 1.9 to 3.9) • Mean total cholesterol did not significantly change (mean change +0.1 mmol/L, 95% CI -0.2 to 0.4; mean total cholesterol at 22 years 4.1 mmol/L, 95% CI 3.8 to 4.4) • Mean HDL cholesterol did not significantly change (mean change +0.0 mmol/L, 95% CI -0.1 to 0.2; mean HDL cholesterol at 22 years 1.6 mmol/L, 95% CI 1.4 to 1.7) • Mean LDL cholesterol did not significantly change (mean change +0.0 mmol/L, 95%	of the design or analysis controlled for confounders Domain 3: Outcome 1. b) record linkage 2. a) yes- follow-up from start of gender-affirming hormones to age 22 years, around 5 years 3. a) complete follow up - all subjects accounted for Overall quality is assessed as poor Other comments: None Source of funding: No external funding

			CI -0.3 to 0.2; mean LDL cholesterol at 22 years 2.0 mmol/L, 95% CI 1.8 to 2.3) • Mean triglycerides statistically significantly increased (mean change +0.2 mmol/L, 95% CI 0.0 to 0.5, $p < 0.05$; triglyceride level at 22 years 1.1 mmol/L, 95% CI 0.9 to 1.4) For transmales, from the start of gender-affirming hormone treatment to age 22 years: • Mean BMI statistically significantly increased (mean change +1.4, 95% CI 0.8 to 2.0, $p < 0.005$; mean BMI at 22 years= 23.9, 95% CI 23.0 to 24.7). At age 22 years, 6.6% of the cohort were obese, compared with 2.2% in reference cisgender population¹. • Mean systolic blood pressure (SBP) statistically significantly increased (mean change +5 mmHg, 95% CI 1 to 9; mean SBP at 22 years= 126 mmHg, 95% CI 122 to 130) • Mean diastolic blood pressure (DBP) statistically significantly increased (mean change +6 mmHg, 95% CI 4 to 9, $p < 0.001$; mean DBP at 22 years= 74 mmHg, 95% CI 72 to 77) • Mean glucose level did not significantly change (mean change 0.0 mmol/L, 95% CI -0.2 to 0.2; mean glucose level at 22 years= 4.8 mmol/L, 95% CI 4.7 to 5.0) • Mean insulin level statistically significantly decreased (mean change -2.1 mU/L, 95% CI -3.9 to -0.3, $p < 0.05$; mean insulin level at 22 years= 8.6 mU/L (6.9 to 10.2) • Insulin resistance (mean Homeostatic Model Assessment of Insulin Resistance [HOMA-IR]) statistically significantly	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			decreased (mean change -0.5, 95% CI -1.0 to -0.1, $p < 0.05$; mean HOMA-IR at 22 years 1.8, 95% CI 1.4 to 2.2) • Mean total cholesterol statistically significantly increased (mean change +0.4 mmol/L, 95% CI 0.2 to 0.6, $p < 0.001$; mean total cholesterol at 22 years 4.6 mmol/L, 95% CI 4.3 to 4.8) • Mean HDL cholesterol statistically significantly decreased (mean change -0.3 mmol/L, 95% CI -0.4 to -0.2, $p < 0.001$; mean HDL cholesterol at 22 years 1.3 mmol/L, 95% CI 1.2 to 1.3) • Mean LDL cholesterol statistically significantly increased (mean change +0.4 mmol/L, 95% CI 0.2 to 0.6, $p < 0.001$; mean LDL cholesterol at 22 years 2.6 mmol/L, 95% CI 2.4 to 2.8) • Mean triglycerides statistically significantly increased (mean change +0.5 mmol/L, 95% CI 0.3 to 0.7, $p < 0.001$; triglyceride level at 22 years 1.3 mmol/L, 95% CI 1.1 to 1.5)	

¹ Reference population taken from [Fredriks et al. \(2000\)](#)

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Klink D, Caris M, Heijboer A et al. (2015) Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. The Journal of Clinical Endocrinology and Metabolism 100(2): e270-5 Study location Single centre, Amsterdam, Netherlands Study type Retrospective longitudinal study Study aim To assess peak bone mass in young adults with gender dysphoria who had received GnRH analogues and gender-affirming hormones during their pubertal years. Study dates	34 young people with gender dysphoria who received GnRH analogues, gender-affirming hormones and gonadectomy. The study included 15 transfemales and 19 transmales; mean age at start of gender-affirming hormones was 16.6 years (SD 1.4) and 16.4 years (SD 2.3) respectively. Participants were required to meet the DSM-IV-TR criteria for gender identity disorder of adolescence. Participants were included if they had undergone gonadectomy between June 1998 and August 2012, and they were at least 21 years old when they had the surgery. Bone mineral density data were also required at the start of GnRH analogue, gender-affirming hormones and at the age of 22 years. No concomitant treatments were reported.	Intervention Transfemales - oral 17-β oestradiol (incremental dosing) Transmales – IM testosterone (Sustanon 250 mg/ml; incremental dosing) Median duration of treatment with gender-affirming hormones for transfemales was 5.8 years (range 3.0 to 8.0) and for transmales was 5.4 years (range 2.8 to 7.8). The GnRH analogue was SC triptorelin 3.75 mg every 4 weeks. No details of gonadectomy reported. Comparison No comparison group. Comparison over time reported.	Critical outcomes No critical outcomes reported Important outcomes Safety Bone density: lumbar spine Lumbar spine bone mineral apparent density (BMAD) Change from starting gender-affirming hormones to age 22 years in transfemales-Mean (SD); g/m³ - Start of gender-affirming hormones: 0.22 (0.02) - Age 22 years: 0.23 (0.03) - p=0.003 z-score (range) - Start of gender-affirming hormones: -0.90 (0.80) - Age 22 years: -0.78 (1.03) - No statistically significant difference Change from starting gender-affirming hormones to age 22 years in transmales-Mean (SD); g/m³ - Start of gender-affirming hormones: 0.24 (0.02) - Age 22 years: 0.25 (0.28) - p=0.001 z-score (SD) - Start of gender-affirming hormones: -0.50 (0.81) - Age 22 years: -0.033 (0.95) - p=0.002	This study was appraised using the Newcastle-Ottawa tool for cohort studies. Domain 1: Selection domain b) somewhat representative c) no-non exposed cohort a) secure record* b) no Domain 2: Comparability c) cohorts are not comparable on the basis of the design or analysis controlled for confounders Domain 3: Outcome b) record linkage a) yes – mean duration of gender-affirming hormone treatment was 5.8 and 5.4 years. c) follow-up rate variable across timepoints and no description of those lost Overall quality is assessed as poor Other comments: Within person comparison. Small numbers of participants in each subgroup. No

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Gonadectomy took place between June 1998 and August 2012	At the start of gender-affirming hormone treatment, in the transfemale subgroup the median Tanner P was 4 (IQR 2) and the median Tanner G was 12 (IQR 11). In the transmale subgroup the median Tanner B was 5 (IQR 2) and the median Tanner P was 5 (IQR 0).		Lumbar spine bone mineral density (BMD) Change from starting gender-affirming hormones to age 22 years in transfemales-Mean (SD); g/m² • Start of gender-affirming hormones: 0.84 (0.11) • Age 22 years: 0.93 (0.10) • p<0.001 z-score (range) • Start of gender-affirming hormones: -1.01 (0.98) • Age 22 years: -1.36 (0.83) • No statistically significant difference Change from starting gender-affirming hormones to age 22 years in transmales-Mean (SD); g/m² • Start of gender-affirming hormones: 0.91 (0.10) • Age 22 years: 0.99 (0.13) • P<0.001 z-score (range) • Start of gender-affirming hormones: -0.72 (0.99) • Age 22 years: -0.33 (1.12) • No statistically significant difference Bone density: femoral region, nondominant side Femoral region, nondominant side BMAD Change from starting gender-affirming hormones to age 22 years in transfemales-Mean (SD); g/m³ • Start of gender-affirming hormones: 0.26 (0.04) • Age 22 years: 0.28 (0.05)	concomitant treatments or comorbidities were reported. Source of funding: None disclosed

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			• No statistically significant difference z-score (SD) • Start of gender-affirming hormones: -1.57 (1.74) • Age 22 years: Not reported • No statistical analysis reported Change from starting gender-affirming hormones to age 22 years in transmales-Mean (SD); g/m³ • Start of gender-affirming hormones: 0.31 (0.04) • Age 22 years: 0.33 (0.05) • p=0.010 z-score (SD) • Start of gender-affirming hormones: -0.28 (0.74) • Age 22 years: Not reported • No statistical analysis reported Femoral region, nondominant side BMD Change from starting gender-affirming hormones to age 22 years in transfemales-Mean (SD); g/m² • Start of gender-affirming hormones: 0.87 (0.08) • Age 22 years: 0.94 (0.11) • P=0.009 z-score (SD) • Start of gender-affirming hormones: -0.95 (0.63) • Age 22 years: -0.69 (0.74) • No statistically significant difference Change from starting gender-affirming hormones to age 22 years in transmales-Mean (SD); g/m² • Start of gender-affirming hormones: 0.88 (0.09) • Age 22 years: 0.95 (0.10)	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			• $P < 0.001$ • z-score (SD) • Start of gender-affirming hormones: -0.35 (0.79) • Age 22 years: -0.35 (0.74) • $p = 0.006$	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Kuper, Laura E, Stewart, Sunita, Preston, Stephanie et al. (2020) Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy. Pediatrics 145(4) Study location Single centre, Texas, USA Study type Prospective longitudinal study Study aim To: • explore how baseline body dissatisfaction, depression, and anxiety symptoms vary by gender,	148 children and adolescents with gender dysphoria, $n = 148$, of whom: • 25 received puberty suppression only • 93 received gender-affirming hormone therapy only • 30 received both Results for treatments reported separately. Mean age at initial assessment was 15.4 years (range 9 to 18). Mean age at start of gender-affirming hormone therapy was 16.2 years (range 13.2 to 18.6). All participants met the Diagnostic and Statistical	Hormone therapy, guided by Endocrine Society Clinical Practice Guidelines Follow-up at least 18 months from initial assessment at the clinic. Mean duration of gender-affirming hormone therapy before follow-up was 10.9 months (range 1 to 18; SD 3.3)	Critical Outcomes <i>Impact on mental health</i> Mean depression score, assessed using the Quick Inventory of Depressive Symptoms (QIDS), self-reported was 9.6 (SD 5.0) at baseline and 7.4 (SD 4.5) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant. Mean depression score, assessed using the QIDS, clinician-reported was 5.9 (SD 4.1) at baseline and 6.0 (SD 3.8) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant. Mean anxiety score, assessed using the Screen for Child Anxiety Related Emotional Disorders (SCARED) questionnaire was 32.6 (SD 16.3) at baseline and 28.4 (SD 15.9) at	This study was appraised using the Newcastle-Ottawa tool for cohort studies. Domain 1: Selection domain 1. b) somewhat representative 2. c) no-non exposed cohort 3. a) secure record 4. b) no Domain 2: Comparability 1. c) cohorts are not comparable on the basis of the design or analysis controlled for confounders Domain 3: Outcome 1. d) assessors not blinded to treatment 2. a) yes – follow-up at least 18 months from initial assessment. Mean duration of gender-affirming hormone

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
age at initial assessment, and Tanner stage at first medical visit - examine how body dissatisfaction, depression, and anxiety symptoms change over the first year of gender-affirming hormone treatment - explore how any changes vary by affirmed gender, Tanner stage, age, type of treatment, months on gender-affirming hormone therapy, mental health treatment received, and whether chest surgery was also obtained (among transmales). Study dates Initial participant assessments took place between August 2014 and March 2018.	Manual of Mental Disorders, Fifth Edition criteria for gender dysphoria. Specific inclusion and exclusion criteria for the study are not reported. It would appear that all children and adolescents eligible for gender-affirming hormones were considered eligible for the study. The authors state that before initial assessment with a psychologist, psychiatrist, and/or clinical therapist, parents completed a phone intake survey. Around one-third of families did not follow-up after the phone intake.		follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant. Mean panic score, assessed using specific questions from the SCARED questionnaire was 8.1 (SD 6.3) at baseline and 7.1 (SD 6.5) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant. Mean generalised anxiety score, assessed using specific questions from the SCARED questionnaire was 10.0 (SD 5.1) at baseline and 8.8 (SD 6.5) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant. Mean social anxiety score, assessed using specific questions from the SCARED questionnaire was 8.5 (SD 4.1) at baseline and 7.7 (SD 4.2) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant. Mean separation anxiety score, assessed using specific questions from the SCARED	treatment was 10.9 months. 3. c) patient numbers vary by outcome with no explanation Overall quality is assessed as poor Other comments: None Source of funding: Supported by Children's Health. The Research Electronic Data Capture database was funded by the Clinical and Translational Science Awards program

			questionnaire was 3.5 (SD 3.0) at baseline and 3.1 (SD 2.5) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant. Mean school avoidance score, assessed using specific questions from the SCARED questionnaire was 2.6 (SD 2.1) at baseline and 2.0 (SD 2.0) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant. The authors also reported results separately for transfemales and transmales: Transfemales No statistical analyses were reported for this sub-group and it is unclear whether any changes in score were statistically significant. • Mean depression symptoms, assessed using the QIDS, self-reported was 7.5 (SD 4.9) at baseline and 6.6 (SD 4.4) at follow-up. • Mean depression symptoms, assessed using the QIDS, clinician-reported was 4.2 (SD 3.2) at baseline and 5.4 (SD 3.4) at follow-up. • Mean anxiety symptoms, assessed using the SCARED questionnaire was 26.4 (SD 14.2) at baseline and 24.3 (SD 15.4) at follow-up.	

			• Mean panic symptoms, assessed using specific questions from the SCARED questionnaire was 5.7 (SD 4.9) at baseline and 5.1 (SD 4.9) at follow-up. • Mean generalised anxiety symptoms, assessed using specific questions from the SCARED questionnaire was 8.6 (SD 5.1) at baseline and 8.0 (SD 5.1) at follow-up. • Mean social anxiety symptoms, assessed using specific questions from the SCARED questionnaire was 7.1 (SD 3.9) at baseline and 6.8 (SD 4.4) at follow-up. • Mean separation anxiety symptoms, assessed using specific questions from the SCARED questionnaire was 3.4 (SD 3.3) at baseline and 2.7 (SD 2.3) at follow-up. • Mean school avoidance symptoms, assessed using specific questions from the SCARED questionnaire was 1.8 (SD 1.7) at baseline and 1.9 (SD 2.1) at follow-up. Transmales No statistical analyses were reported for this sub-group and it is unclear whether any changes in score were statistically significant. • Mean depression symptoms, assessed using the QIDS, self-reported was 10.4 (SD 5.0) at baseline and 7.5 (SD 4.5) at follow-up. • Mean depression symptoms, assessed using the QIDS, clinician-reported was 6.7 (SD 4.4) at baseline and 6.2 (SD 4.1) at follow-up. • Mean anxiety symptoms, assessed using the SCARED questionnaire was 35.4 (SD	

			16.5) at baseline and 29.8 (SD 15.5) at follow-up. • Mean panic symptoms, assessed using specific questions from the SCARED questionnaire was 9.3 (SD 6.5) at baseline and 7.9 (SD 6.5) at follow-up. • Mean generalised anxiety symptoms, assessed using specific questions from the SCARED questionnaire was 10.4 (SD 5.0) at baseline and 9.0 (SD 5.1) at follow-up. • Mean social anxiety symptoms, assessed using specific questions from the SCARED questionnaire was 8.5 (SD 4.0) at baseline and 7.8 (SD 4.1) at follow-up. • Mean separation anxiety symptoms, assessed using specific questions from the SCARED questionnaire was 4.2 (SD 3.4) at baseline and 3.4 (SD 2.6) at follow-up. • Mean school avoidance symptoms, assessed using specific questions from the SCARED questionnaire was 2.6 (SD 2.1) at baseline and 2.0 (SD 2.0) at follow-up. No difference in impact on mental health found by Tanner age. Numerical results, statistical analysis and information on specific outcomes not reported. It is unclear from the paper whether Tanner age is at initial assessment, start of GnRH analogues, start of gender-affirming hormones, or another timepoint. Important Outcomes <i>Impact on body image</i>	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			Mean Body Image Scale (BIS) score was 70.7 (SD 15.2) at baseline and 51.4 (SD 18.3) at follow-up. The authors do not present statistical analysis for this population and it is unclear whether the change in score was statistically significant. The authors also reported body image results separately for transfemales and transmales. No statistical analyses were reported for this sub-groups and it is unclear whether changes in score were statistically significant. • In transfemales, BIS score was 67.5 (SD 19.5) at baseline and 49.0 (SD 21.6) at follow-up. • In transmales, BIS score was 71.1 (SD 13.4) at baseline and 52.9 (SD 16.8) at follow-up. No difference in body image score found by Tanner age. Numerical results, statistical analysis and information on specific outcomes not reported. It is unclear from the paper whether Tanner age is at initial assessment, start of GnRH analogues, start of gender-affirming hormones, or another timepoint. <i>No other critical or important outcomes reported</i>	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Study dates Lopez de Lara, D., Perez Rodriguez, O., Cuellar Flores, I. et al. (2020) Psychosocial assessment in transgender adolescents. Anales de Pediatria Study location Single centre in Madrid, Spain Study type Prospective analytical study Study aim To assess the psychosocial status of patients seeking care in the paediatric endocrinology clinic for gender dysphoria, and the impact on psychosocial status of gender-affirming hormone therapy at 12 months of treatment Study dates Not reported	23 adolescents with gender dysphoria; 16 transmale and 7 transfemale. Participants were required to be at a stage of pubertal development of Tanner 2 or higher. People with mental health comorbidity that could affect the experience of gender dysphoria were excluded. Mean age at baseline was 16 years (range 14 to 18). 30 cisgender controls, matched for age, ethnicity, and socioeconomic status	Gender-affirming hormones- • Oral oestradiol • Intramuscular testosterone Participants had previously received gonadotropin-releasing hormone (GnRH) analogues in the intermediate pubertal stages (Tanner 2---3).	Critical Outcomes <i>Impact on gender dysphoria</i> Following gender-affirming hormones for 12 months, mean ($\pm$SD) Utrecht Gender Dysphoria Scale (UGDS) score statistically significantly improved, from 57.1 ($\pm$4.1) at baseline to 14.7 ($\pm$3.2; $p < 0.001$) <i>Impact on mental health</i> Mean depression score statistically significantly improved following treatment with gender-affirming hormones. Mean Beck Depression Inventory II (BDI-II) score ($\pm$SD) reduced from 19.3 points ($\pm$5.5) at baseline to 9.7 points ($\pm$3.9) at 12 months ($p < 0.001$). Mean anxiety scores statistically significantly improved following treatment with gender-affirming hormones. Mean ($\pm$SD) State-Trait Anxiety Inventory (STAI) State subscale score improved from 33.3 points ($\pm$9.1) at baseline to 16.8 points ($\pm$8.1) at 12 months ($p < 0.001$). Mean ($\pm$SD) State-Trait Anxiety Inventory (STAI) Trait subscale score improved from 33.0 points ($\pm$7.2) at baseline to 18.5 points ($\pm$8.4) at 12 months ($p < 0.001$). Important Outcomes <i>Psychosocial Impact</i> There was not change in family functioning, measured using the Family APGAR test, from baseline (17.9 points) to 1 year after starting	This study was appraised using the Newcastle-Ottawa tool for cohort studies. Domain 1: Selection domain 1. b) somewhat representative 2. Not applicable – although a control group is reported on, people in this group did not have gender dysphoria. 3. a) secure record* 4. b) no Domain 2: Comparability 1. Not applicable – although a control group is reported on, people in this group did not have gender dysphoria. Domain 3: Outcome 1. d) assessors not blinded to treatment 2. a) yes – 12 months treatment with gender-affirming hormones 3. a) complete follow up - all subjects accounted for Overall quality is assessed as poor

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			gender-affirming hormones (18.0 points; no statistical analysis reported). Results from the Strengths and Difficulties Questionnaire, Spanish Version (SDQ-Cas) showed statistically significant improvements from baseline (14.7 points; SD±3.3) to 12 months after gender-affirming hormones (10.3 points; SD±2.9; p<0.001) <i>No other critical or important outcomes reported</i>	Other comments: None Source of funding: Not reported

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Stoffers, Iris E; de Vries, Martine C; Hannema, Sabine E (2019) Physical changes, laboratory parameters, and bone mineral density during testosterone treatment in adolescents with gender dysphoria. The journal of sexual medicine 16(9): 1459-1468 Study location Single centre, Leiden, Netherlands Study type Retrospective chart review Study aim To report changes in height, BMI, blood pressure, laboratory parameters and bone density. Study dates November 2010 to August 2018	62 transmales with gender dysphoria. participants were required to have been receiving testosterone therapy for at least 6 months. Further inclusion or exclusion criteria not reported. Gender dysphoria was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria.	Testosterone intramuscular injection (Sustanon 250 mg). Dose escalated every 6 months up to the standard adult dose of 125 mg every 2 weeks or 250 mg every 3-4 weeks. A more rapid dose escalation was using in patients who started GnRH analogue treatment at 16 years or older. Median age at start of testosterone treatment was 17.2 years (range 14.9 to 18.4) Median duration of testosterone treatment was 12 months (range 5 to 33) Median duration of GnRH analogue treatment was 8 months (range 3 to 39)	Critical Outcomes No critical outcomes assessed. Important outcomes Safety Bone mineral density (BMD): lumbar spine There was no statistically significant difference in lumbar spine bone mineral density (BMD) from start of testosterone treatment to any timepoint, up to 24 months follow-up. Mean ($\pm$SD), g/cm²: - Start of testosterone: 0.90 ($\pm$0.11) 6 months: 0.94 ($\pm$0.10) 12 months: 0.95 ($\pm$0.09) 24 months: 0.95 ($\pm$0.11) z-score ($\pm$SD): - Start of testosterone: -0.81 ($\pm$1.02) 6 months: -0.67 ($\pm$0.95) 12 months: -0.66 ($\pm$0.81) 24 months: -0.74 ($\pm$1.17) Bone mineral density (BMD): femoral neck (hip) There was no statistically significant difference in right or left femoral neck (hip) bone mineral density (BMD) from start of	This study was appraised using the Newcastle-Ottawa tool for cohort studies. Domain 1: Selection domain b) somewhat representative c) no-non exposed cohort a) secure record* b) no Domain 2: Comparability c) cohorts are not comparable on the basis of the design or analysis controlled for confounders Domain 3: Outcome b) record linkage a) yes – mean duration of gender-affirming hormone treatment was 5.8 and 5.4 years. a) complete follow up - all subjects accounted for Overall quality is assessed as poor Other comments: None Source of funding: None

			testosterone treatment to any timepoint, up to 24 months follow-up. Right Mean ($\pm$SD), g/cm²: • Start of testosterone: 0.77 ($\pm$0.08) • 6 months: 0.84 ($\pm$0.11) • 12 months: 0.82 ($\pm$0.08) • 24 months: 0.85 ($\pm$0.11) z-score ($\pm$SD): • Start of testosterone: -0.97 (0.79) • 6 months: -0.54 ($\pm$0.96) • 12 months: -0.80 ($\pm$0.69) • 24 months: -0.31 ($\pm$0.84) Left Mean ($\pm$SD), g/cm²: • Start of testosterone: 0.76 ($\pm$0.09) • 6 months: 0.83 ($\pm$0.12) • 12 months: 0.81 ($\pm$0.08) • 24 months: 0.86 ($\pm$0.09) z-score ($\pm$SD): • Start of testosterone: -1.07 (0.85) • 6 months: -0.62 ($\pm$1.12) • 12 months: -0.93 ($\pm$0.63) • 24 months: -0.20 ($\pm$0.70) <i>Other safety-related outcomes</i> • Alkaline phosphatase: statistically significant increases observed from start of testosterone treatment to 6 months and 12 months ($p < 0.001$), although difference at 24 months was not statistically significant. Median (IQR), U/L ○ Start of testosterone: 102 (78 to 136) ○ 6 months: 115 (102 to 147) ○ 12 months: 112 (88 to 143) ○ 24 months: 81 (range 69 to 98) • Creatinine: statistically significant increases observed from start of	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			testosterone treatment to 6, 12 and 24 months ($p < 0.001$). Mean ($\pm$SD), umol/L ○ Start of testosterone: 62 ($\pm$7) ○ 6 months: 70 ($\pm$9) ○ 12 months: 74 ($\pm$10) ○ 24 months: 81 ($\pm$10) There was no statistically significant change from start of testosterone treatment in: • HbA1c • Aspartate aminotransferase (AST) • Alanine aminotransferase (ALT) • Gamma-glutamyl transferase • Urea Numerical results, follow-up duration and further details of statistical analysis not reported.	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Vlot MC, Klink DT, den Heijer M et al. (2017) Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. Bone 95: 11-19 Study location Single centre, Amsterdam, Netherlands Study type Retrospective chart review Study aim To investigate the impact of GnRH analogues and gender-affirming hormones on bone mineral apparent density (BMAD) in transgender adolescents. The study also report on levels of bone turnover markers, although the authors concluded that the	70 adolescents with gender dysphoria (42 transmales and 28 transfemales). Median age (range) at the start of gender-affirming hormones was 16.3 years (15.9 to 19.5) for transmales and 16.0 years (14.0 to 18.9) for transfemales. Participants were included if they had a diagnosis of gender dysphoria according to DSM-IV-TR criteria who received GnRH analogues and then gender-affirming hormones. No concomitant treatments were reported. The study categorised participants into a young and old pubertal group, based on their bone age. The young transmales had a bone age of <14 years and the old transmales had a bone age of ≥14 years. The young transfemales	Transfemales: Oestradiol oral Dose escalated every 6 months until standard adult dose of 2 mg daily was reached Transmales: Testosterone intramuscular injection (Sustanon 250 mg). Dose escalated every 6 months up to the standard adult dose of 250 mg every 4 weeks or 250 mg every 3-4 weeks. All participants previously received a GnRH analogue (triptorelin 3.75 mg subcutaneously every 4 weeks) Median duration of GnRH analogue therapy not reported.	Critical outcomes No critical outcomes reported Important outcomes Bone density: lumbar spine Lumbar spine bone mineral apparent density (BMAD) Transfemales (bone age <15 years), change from starting gender-affirming hormones to 24 months follow-up. Median (range), g/m³ - Start of gender-affirming hormones (C0): 0.20 (0.18 to 0.24) 24-month follow-up (C24): 0.22 (0.19 to 0.27) - Statistically significant increase ($p \leq 0.01$) z-score (range) - Start of gender-affirming hormones (C0): -1.52 (-2.36 to 0.42) 24-month follow-up (C24): - Statistically significant increase ($p \leq 0.05$) Transfemales (bone age ≥15 years), change from starting gender-affirming hormones to 24 months follow-up. Median (range), g/m³ - Start of gender-affirming hormones: 0.22 (0.19 to 0.24) 24-months: 0.23 (0.21 to 0.26) - Statistically significant increase ($p \leq 0.05$) z-score (range) - Start of gender-affirming hormones: -1.15 (-2.21 to 0.08) 24-months: -0.66 (-1.66 to 0.54)	This study was appraised using the Newcastle-Ottawa tool for cohort studies. Domain 1: Selection domain b) somewhat representative c) no-non exposed cohort a) secure record* b) no Domain 2: Comparability c) cohorts are not comparable on the basis of the design or analysis controlled for confounders Domain 3: Outcome b) record linkage a) yes- 24 month follow-up a) complete follow up - all subjects accounted for Overall quality is assessed as poor. Other comments: None Source of funding: grant from Abbott diagnostics

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
added value of these seems to be limited. Study dates Participants started gender-affirming therapy between 2001 and 2011	group had a bone age of <15 years and the old transfemales group ≥15 years.		Statistically significant increase ($p \leq 0.05$) Transmales (bone age <14 years), change from starting gender-affirming hormones to 24 months follow-up. Median (range), g/m³ • Start of gender-affirming hormones: 0.23 (0.19 to 0.28) • 24-months: 0.25 (0.22 to 0.28) • Statistically significant increase ($p \leq 0.01$) z-score (range) • Start of gender-affirming hormones: -0.84 (-2.2 to 0.87) • 24-months: -0.15 (-1.38 to 0.94) Statistically significant increase ($p \leq 0.01$) Transmales (bone age ≥14 years), change from starting gender-affirming hormones to 24 months follow-up. Median (range), g/m³ • Start of gender-affirming hormones: 0.24 (0.20 to 0.28) • 24-months: 0.25 (0.21 to 0.30) • Statistically significant increase ($p \leq 0.01$) z-score (range) • Start of gender-affirming hormones: -0.29 (-2.28 to 0.90) • 24-months: -0.06 (-1.75 to 1.61) Statistically significant increase ($p \leq 0.01$) Bone density: femoral neck Femoral neck BMAD Transfemales (bone age <15 years), change from starting gender-affirming hormones to 24 months follow-up.	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			Median (range), g/m³ • Start of gender-affirming hormones: 0.27 (0.20 to 0.33) • 24-months: 0.27 (0.20 to 0.36) • No statistically significant change z-score (range) • Start of gender-affirming hormones: -1.32 (-3.39 to 0.21) • 24-months: -1.30 (-3.51 to 0.92) • No statistically significant change Transfemales (bone age ≥15 years), change from starting gender-affirming hormones to 24 months follow-up. Median (range), g/m³ • Start of gender-affirming hormones: 0.30 (0.26 to 0.34) • 24-months: 0.29 (0.24 to 0.38) • No statistically significant change z-score (range) • Start of gender-affirming hormones: -0.36 (-1.50 to 0.46) • 24-months: -0.56 (-2.17 to 1.29) • No statistically significant change Transmales (bone age <14 years), change from starting gender-affirming hormones to 24 months follow-up. Median (range), g/m³ • Start of gender-affirming hormones: 0.30 (0.22 to 0.35) • 24-months: 0.33 (0.23 to 0.37) • Statistically significant increase (p≤0.01) z-score (range) • Start of gender-affirming hormones: -0.37 (-2.28 to 0.47) • 24-months: -0.37 (-2.03 to 0.85)	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			- Statistically significant increase ($p \leq 0.01$) Transmales (bone age ≥ 14 years), change from starting gender-affirming hormones to 24 months follow-up. - Start of gender-affirming hormones: 0.30 (0.23 to 0.41) 24-months: 0.32 (0.23 to 0.41) - Statistically significant increase ($p \leq 0.01$) z-score (range) - Start of gender-affirming hormones: -0.27 (-1.91 to 1.29) 24-months: 0.02 (-2.1 to 1.35) - Statistically significant increase ($p \leq 0.05$)	

Appendix F Quality appraisal checklists

Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

- 1) Representativeness of the exposed cohort
 - a) Truly representative (one star)
 - b) Somewhat representative (one star)
 - c) Selected group
 - d) No description of the derivation of the cohort
- 2) Selection of the non-exposed cohort
 - a) Drawn from the same community as the exposed cohort (one star)
 - b) Drawn from a different source
 - c) No description of the derivation of the non exposed cohort
- 3) Ascertainment of exposure
 - a) Secure record (e.g., surgical record) (one star)
 - b) Structured interview (one star)
 - c) Written self report
 - d) No description
 - e) Other
- 4) Demonstration that outcome of interest was not present at start of study
 - a) Yes (one star)
 - b) No

Comparability

- 1) Comparability of cohorts on the basis of the design or analysis controlled for confounders
 - a) The study controls for age, sex and marital status (one star)
 - b) Study controls for other factors (list) _____
(one star)
 - c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcome

- 1) Assessment of outcome
 - a) Independent blind assessment (one star)
 - b) Record linkage (one star)
 - c) Self report
 - d) No description
 - e) Other
- 2) Was follow-up long enough for outcomes to occur
 - a) Yes (one star)
 - b) No

Indicate the median duration of follow-up and a brief rationale for the assessment above: _____
- 3) Adequacy of follow-up of cohorts
 - a) Complete follow up- all subject accounted for (one star)

- b) Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. (one star)
- c) Follow up rate less than 80% and no description of those lost
- d) No statement

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Appendix G Grade profiles

Table 2: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? - Gender dysphoria

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
<i>Impact on gender dysphoria (1 uncontrolled, prospective observational study)</i>									
<i>Change from baseline in mean gender dysphoria score, measured using the UGDS (duration of treatment 12 months). Higher scores indicate greater gender dysphoria.</i>									
1 cohort study Lopez de Lara et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=23	None	T0 (baseline) = 57.1 (SD 4.1) T1 (12 months) = 14.7 (SD 3.2) Statistically significant improvement, p<0.001	Critical	VERY LOW

Abbreviations: p: p-value; SD: standard deviation; UGDS: Utrecht Gender Dysphoria Scale

1 Downgraded 1 level - the cohort study by Lopez de Lara et al. 2020 was assessed at high risk of bias (poor quality overall; lack of blinding and no control group)

Table 3: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Mental health

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
<i>Impact on mental health (3 uncontrolled, prospective observational studies and 2 uncontrolled, retrospective observational studies)</i>									
<i>Change from baseline in mean depression score, measured using the BDI-II (duration of treatment 12 months). Higher scores indicate more severe depression.</i>									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 cohort study Lopez de Lara et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=23	None	T0 (baseline) = 19.3 (SD 5.5) T1 (12 months) = 9.7 (SD 3.9) Statistically significant improvement, p<0.001	Critical	VERY LOW
Change from baseline in mean depression score, measured using the CESD-R (approximately 12-month follow-up). Higher scores indicate more severe depression.									
1 cohort study Achille et al. 2020	Serious limitations ²	Serious indirectness ³	No serious inconsistency	Not calculable	N=50	None	Wave 1 (baseline) = 21.4 Wave 3 (approx. 12 months) = 13.9 Statistically significant improvement (p<0.001)	Critical	VERY LOW
Change from baseline in depression score, measured using the Patient Health Questionnaire Modified for Teens (PHQ 9_Modified for Teens) (approximately 12-month follow-up). Higher scores indicate more severe depression.									
1 cohort study Achille et al. 2020	Serious limitations ²	Serious indirectness ³	No serious inconsistency	Not calculable	N=50	None	Statistically significant reductions in mean score, p<0.001 Results presented diagrammatically, numerical results for mean score not reported	Critical	VERY LOW
Change from baseline in depression symptoms, measured using the Quick Inventory of Depressive Symptoms (QIDS), self-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.									
1 cohort study Kuper et al. 2020	Serious limitations ⁴	No serious indirectness	No serious inconsistency	Not calculable	N=105	None	Baseline = 9.6 (SD 5.0) Follow-up = 7.4 (SD 4.5) No statistical analysis reported for the sub-group of participants receiving gender-affirming hormones	Critical	VERY LOW
Change from baseline in depression symptoms, measured using the Quick Inventory of Depressive Symptoms (QIDS), clinician-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.									
1 cohort study	Serious limitations ⁴	No serious indirectness	No serious inconsistency	Not calculable	N=106	None	Baseline = 5.9 (SD 4.1) Follow-up = 6.0 (SD 3.8)	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Kuper et al. 2020							No statistical analysis reported for the sub-group of participants who received gender-affirming hormones		
<i>Need for treatment due to depression, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)</i>									
1 cohort study Kaltiala et al. 2020	Serious limitations ⁷	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 54% (28/52) During real life phase 15% (8/52) Statistically significant reduction (p<0.001)	Critical	VERY LOW
<i>Change from baseline in anxiety score, measured using the STAI-State subscale (duration of treatment 12 months). Higher scores indicate more severe anxiety.</i>									
1 cohort study Lopez de Lara et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=23	None	T0 (baseline) = 33.3 (SD 9.1) T1 (12 months) = 16.8 (SD 8.1) Statistically significant improvement, p<0.001	Critical	VERY LOW
<i>Change from baseline in anxiety score, measured using the STAI-Trait subscale (duration of treatment 12 months). Higher scores indicate more severe anxiety.</i>									
1 cohort study Lopez de Lara et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=23	None	T0 (baseline) = 33.0 (SD 7.2) T1 (12 months) = 18.5 (SD 8.4) Statistically significant improvement, p<0.001	Critical	VERY LOW
<i>Change from baseline in anxiety symptoms, measured using the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe anxiety.</i>									
1 cohort study Kuper et al. 2020	Serious limitations ⁴	No serious indirectness	No serious inconsistency	Not calculable	N=80	None	Baseline = 32.6 (SD 16.3) Follow-up = 28.4 (SD 15.9) No statistical analysis reported for the sub-group of participants	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							who received gender-affirming hormones		
Change from baseline in panic symptoms, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations ⁴	No serious indirectness	No serious inconsistency	Not calculable	N=82	None	Baseline = 8.1 (SD 6.3) Follow-up = 7.1 (SD 6.5) No statistical analysis reported for the sub-group of participants who received gender-affirming hormones	Critical	VERY LOW
Change from baseline in generalised anxiety symptoms, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations ⁴	No serious indirectness	No serious inconsistency	Not calculable	N=82	None	Baseline = 10.0 (SD 5.1) Follow-up = 8.8 (SD 5.0) No statistical analysis reported for the sub-group of participants who received gender-affirming hormones	Critical	VERY LOW
Change from baseline in social anxiety symptoms, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations ⁴	No serious indirectness	No serious inconsistency	Not calculable	N=82	None	Baseline = 8.5 (SD 4.1) Follow-up = 7.7 (SD 4.2) No statistical analysis reported for the sub-group of participants who received gender-affirming hormones	Critical	VERY LOW
Change from baseline in separation anxiety symptoms, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations ⁴	No serious indirectness	No serious inconsistency	Not calculable	N=81	None	Baseline = 3.5 (SD 3.0) Follow-up = 3.1 (SD 2.5) No statistical analysis reported for the sub-group of participants	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							who received gender-affirming hormones		
Change from baseline in school avoidance, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations ⁴	No serious indirectness	No serious inconsistency	Not calculable	N=80	None	Baseline = 2.6 (SD 2.1) Follow-up = 2.0 (SD 2.0) No statistical analysis reported for the sub-group of participants who received gender-affirming hormones	Critical	VERY LOW
Need for treatment due to anxiety, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations ⁷	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 48% (25/52) During real life phase 15% (8/52) Statistically significant reduction (p<0.001)	Critical	VERY LOW
Change from baseline in adjusted mean suicidality score, measured using the ASQ instrument (mean treatment duration 349 days). Higher scores indicate a greater degree of suicidality.									
1 cohort study Allen et al. 2019	Serious limitations ⁵	No serious indirectness	No serious inconsistency	Not calculable	N=39	None	T0 (baseline) = 1.11 (SE 0.22) T1 (final assessment) = 0.27 (SE 0.12) Statistically significant improvement in score from T0 to T1, p<0.001	Critical	VERY LOW
Change from baseline in percentage of participants with suicidal ideation, measured using the additional questions from the PHQ 9_Modified for Teens (approximately 12-month follow-up)									
1 cohort study Achille et al. 2020	Serious limitations ²	Serious indirectness ³	No serious inconsistency	Not calculable	N=50	None	Wave 1 (baseline) = 10% (5/50) Wave 3 (approx. 12 months) = 6% (3/50)	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							No statistical analysis reported		
<i>Change from baseline in suicidal ideation (passive), information on which was collected by clinician, exact methods / tools not reported (mean duration of gender-affirming hormone treatment was 10.9 months)</i>									
1 cohort study Kuper et al. 2020	Serious limitations ⁴	Serious indirectness ⁶	No serious inconsistency	Not calculable	N=130	None	Lifetime = 81% (105 people) 1 month before initial assessment = 25% (33 people) Follow-up period = 38% (51 people) No statistical analysis reported	Critical	VERY LOW
<i>Change from baseline in suicide attempts, information on which was collected by clinician, exact methods / tools not reported (mean duration of gender-affirming hormone treatment was 10.9 months)</i>									
1 cohort study Kuper et al. 2020	Serious limitations ⁴	Serious indirectness ⁶	No serious inconsistency	Not calculable	N=130	None	Lifetime = 15% (20 people) 3 months before initial assessment = 2% (3 people) Follow-up period = 5% (6 people) No statistical analysis reported	Critical	VERY LOW
<i>Change from baseline in non-suicidal self-injury, information on which was collected by clinician, exact methods / tools not reported (mean duration of gender-affirming hormone treatment was 10.9 months)</i>									
1 cohort study Kuper et al. 2020	Serious limitations ⁴	Serious indirectness ⁶	No serious inconsistency	Not calculable	N=130	None	Lifetime = 52% (68 people) 3 months before initial assessment = 10% (13 people) Follow-up period = 17% (23 people) No statistical analysis reported	Critical	VERY LOW
<i>Need for treatment due to suicidality / self-harm, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)</i>									
1 cohort study Kaltiala et al. 2020	Serious limitations ⁷	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 35% (18/52) During real life phase	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							4% (2/52) Statistically significant reduction (p<0.001)		
<i>Need for mental health treatment, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)</i>									
1 cohort study Kaltiala et al. 2020	Serious limitations ⁷	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 50% (26/52) During real life phase 46% (24/51) No statistically significant difference (p= 0.77)	Critical	VERY LOW
<i>Need for treatment due to conduct problems / antisocial, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)</i>									
1 cohort study Kaltiala et al. 2020	Serious limitations ⁷	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 14% (7/52) During real life phase 6% (3/52) No statistically significant difference (p= 0.18)	Critical	VERY LOW
<i>Need for treatment due to psychotic symptoms or psychosis, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)</i>									
1 cohort study Kaltiala et al. 2020	Serious limitations ⁷	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 2% (1/52) During real life phase 4% (2/52) No statistically significant difference (p= 0.56)	Critical	VERY LOW
<i>Need for treatment due to substance abuse, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)</i>									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 cohort study Kaltiala et al. 2020	Serious limitations ⁷	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 4% (2/52) During real life phase 2% (1/52) No statistically significant difference (p= 0.56)	Critical	VERY LOW
<i>Need for treatment due to autism, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)</i>									
1 cohort study Kaltiala et al. 2020	Serious limitations ⁷	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 12% (6/52) During real life phase 6% (3/52) No statistically significant difference (p= 0.30)	Critical	VERY LOW
<i>Need for treatment due to ADHD, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)</i>									
1 cohort study Kaltiala et al. 2020	Serious limitations ⁷	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 10% (5/52) During real life phase 2% (1/52) No statistically significant difference (p= 0.09)	Critical	VERY LOW
<i>Need for treatment due to eating disorder, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)</i>									
1 cohort study Kaltiala et al. 2020	Serious limitations ⁷	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 2% (1/52)	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							During real life phase 2% (1/52) No statistically significant difference (p=1.0)		

Abbreviations: ADHD: attention deficit hyperactivity disorder; ASQ: Ask Suicide-Screening Questions; CESD-R: Center for Epidemiologic Studies Depression Scale; BDI-II: Beck Depression Inventory II (BDI-II); p: p-value; PHQ 9_Modified for Teens: Patient Health Questionnaire Modified for Teens; SCARED: Screen for Child Anxiety Related Emotional Disorders; SD: standard deviation; STAI: State-Trait Anxiety Inventory

1 Downgraded 1 level - the cohort study by Lopez de Lara et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding and no control group).

2 Downgraded 1 level - the cohort study by Achille et al (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).

3 Serious indirectness in Achille 2020- Outcome reported for full study cohort, of whom 30% were taking no treatment or puberty suppression alone at follow-up. Results for people taking gender-affirming hormones not reported separately.⁴ Downgraded 1 level - the cohort study by Kuper et al. (2020) was assessed at high risk of bias (poor quality).

5 Downgraded 1 level - the cohort study by Allen et al. (2019) was assessed at high risk of bias (poor quality; lack of blinding and no control group).

6 Serious indirectness in Kuper et al. 2020- Outcome reported for full study cohort, of whom approximately 17% received puberty suppression alone and did not receive gender-affirming hormones

7 Downgraded 1 level - the cohort study by Kaltiala et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding and no control group).

Table 4: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Quality of life

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on quality of life (1 uncontrolled, prospective observational study and 1 uncontrolled, retrospective observational study)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Change from baseline in mean quality of life score, measured using the QLES-Q-SF) (approximately 12-month follow-up). Higher scores indicated better quality of life.									
1 cohort study Achille et al. 2020	Serious limitations ¹	Serious indirectness ²	No serious inconsistency	Not calculable	N=50	None	Numerical improvements in mean score reported from wave 1 (baseline) to wave 3 (approx. 12 months), but difference not statistically significant (p = 0.085) Results presented diagrammatically, numerical results for mean score not reported	Critical	VERY LOW
Change from baseline in adjusted mean well-being score, measured using the GWBS of the Pediatric Quality of Life Inventory (mean treatment duration 349 days). Higher scores indicated better well-being.									
1 cohort study Allen et al. 2019	Serious limitations ³	No serious indirectness	No serious inconsistency	Not calculable	N=39	None	T0 (baseline) = 61.70 (SE 2.43) T1 (final assessment) = 70.23 (SE 2.15) Statistically significant improvement in well-being score, p<0.002	Critical	VERY LOW

Abbreviations: GWBS: General Well-Being Scale; p: p-value; QLES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire; SE: standard error

1 Downgraded 1 level - the cohort study by Achille et al (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).

2 Serious indirectness in Achille et al. 2020 - Outcome reported for full study cohort, of whom 30% were taking no treatment or puberty suppression alone at follow-up. Results for people taking gender-affirming hormones not reported separately.

3 Downgraded 1 level - the cohort study by Allen et al. (2019) was assessed at high risk of bias (poor quality; lack of blinding and no control group).

Table 5: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Body image

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY

					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on body image (1 uncontrolled, prospective observational study)									
Change from baseline in mean body image, measured using the BIS (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores represent a higher degree of body dissatisfaction.									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=86	None	Baseline = 70.7 (SD 15.2) Follow-up = 51.4 (SD 18.3) No statistical analysis reported for the sub-group of participants who received gender-affirming hormones	Important	VERY LOW

Abbreviations: BIS: Body Image Scale; p: p-value; SD: standard deviation

¹ Downgraded 1 level - the cohort study by Kuper et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).

Table 6: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Psychological impact

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Psychosocial Impact (1 uncontrolled, prospective observational study and 1 uncontrolled, retrospective observational study)									
Change from baseline in family functioning, measured using the Family APGAR test. Higher scores suggest more family dysfunction.									
1 cohort study Lopez de Lara et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=23	None	T0 (baseline) = 17.9 T1 (12 months) = 18.0 No statistical analysis reported	Important	VERY LOW
Change from baseline in mean patient strengths and difficulties score, measured using the SDQ, Spanish Version (total difficulties score) (duration of treatment 12 months). Higher scores suggest the presence of a behavioural disorder.									
1 cohort study	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=23	None	T0 (baseline) = 14.7 (SD 3.3) T1 (12 months) = 10.3 (SD 2.9)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Lopez de Lara et al. 2020							Statistically significant improvement p<0.001		
Functioning in adolescent development: Living with parent(s)/ guardians ² (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the ‘real-life phase’ in Finland). Not living with parent(s) or guardian in your early 20s is a marker of age-appropriate functioning in Finnish culture.									
1 cohort study Kaltiala et al. 2020	Serious limitations ³	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During gender identity assessment = 73% (38/52) During real life phase = 40% (21/50) Statistically significant reduction (p=0.001)	Important	VERY LOW
Functioning in adolescent development: Normative peer contacts ⁴ (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the ‘real-life phase’ in Finland)									
1 cohort study Kaltiala et al. 2020	Serious limitations ³	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During gender identity assessment = 89% (46/52) During real life phase = 81% (42/52) Statistically significant reduction (p<0.001)	Important	VERY LOW
Functioning in adolescent development: Progresses normatively in school/ work ⁵ (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the ‘real-life phase’ in Finland)									
1 cohort study Kaltiala et al. 2020	Serious limitations ³	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During gender identity assessment = 64% (33/52) During real life phase = 60% (31/52) No statistically significant difference (p=0.69)	Important	VERY LOW
Functioning in adolescent development: Has been dating or had steady relationships ⁶ (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the ‘real-life phase’ in Finland)									
1 cohort study	Serious limitations ³	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During gender identity assessment = 62% (32/50)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Kaltiala et al. 2020							During real life phase = 58% (30/52) No statistically significant difference (p=0.51)		
Functioning in adolescent development: Is age-appropriately able to deal with matters outside of the home ⁷ (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the ‘real-life phase’ in Finland)									
1 cohort study Kaltiala et al. 2020	Serious limitations ²	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During gender identity assessment = 81% (42/52) During real life phase = 81% (42/52) No statistically significant difference (p=1.00)	Important	VERY LOW

Abbreviations: APGAR: Adaptability, Partnership, Growth, Affection and Resolve; p: p-value; SD: standard deviation; SDQ: Strengths and Difficulties Questionnaire

1 Downgraded 1 level - the cohort study by Lopez de Lara et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding and no control group).

2 Living arrangements were classified as (1) living with at least one parent/guardian, (2) living in a boarding school, with an adult relative, in some form of supported accommodation or the like, where supervision and guidance by a responsible adult is provided, (3) independently alone or in a shared household with a peer, (4) with a romantic partner. In the analyses dichotomised living arrangements as (a) parent(s)/guardian(s) vs. in other arrangements.

3 Downgraded 1 level - the cohort study by Kaltiala et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding and no control group).

4 Peer relationships were classified as: (1) socialises with friends in leisure time, outside of activities supervised by adults, (2) socialises with peers only at school or in the context of rehabilitative activity, (3) spends time close to peers, for example in school or rehabilitative activity, but does not connect with them, (4) does not meet peers at all. In the analyses, peer relationships during (a) gender identity assessment and (b) the real-life phase were dichotomized to age-appropriate (normative) (1) vs. restricted or lacking (2–4).

5 School/work participation was classified as (1) age appropriate participation in mainstream curriculum, progresses without difficulties, (2) participates in mainstream curriculum with difficulty, (3) participates in rehabilitative educational or work activity, (4) not involved in education and working life. Age-appropriate participation during (1) was recorded if the adolescent attended mainstream secondary education or upper secondary education at a regular rate (a class per year in comprehensive school; has not changed more than once between tracks in upper secondary education) or had proceeded to work life after completing vocational education. Participation with difficulty (2) was recorded if the adolescent was enrolled in mainstream education but had to repeat a class, studied with special arrangements (for example, in a special small group), or followed some form of adjusted curriculum. In the analyses, school/work life during (a) gender identity assessment and (b) real-life phase was dichotomised to normative (1) vs. any other (2, 3 or 4).

6 Romantic involvement was recorded (1) has or has had a dating or steady relationship, not only online, (2) has had a romantic relationship only online, (3) has not had dating or steady relationships. In the analyses we compared has or has had (1) vs. has not had (2,3) a dating or steady relationship during (a) gender identity assessment and (b) real-life phase. Sexual history was recorded in more detail in case histories during gender identity assessment, and for this period we also collected the experiences of (French) kissing (yes/no), intercourse (yes/no) and experience of any genitally intimate contact with a partner (petting under clothes or naked, intercourse, oral sex) (yes/no).

7 In recording age-appropriate competence in managing everyday matters it was expected that early adolescents (up to 14 years) would be able, for example, to do shopping and travel alone on local public transport, and to help with household duties assigned by their parents. Middle adolescents (15–17 years) were further assumed, for example, to be able make telephone calls in matters important to them (for example, when seeking a summer job), to deal with school-related issues with school personnel without parental participation, to select and start new hobbies independently and to fulfil their role in summer jobs and in similar responsibilities of young people. Late adolescents (18 years and over), legally adults, were expected to have, in addition to the above, competence to talk to authorities such as professionals in health and social services, employment or educational institutions, to deal with banks or health insurance, to manage their financial issues and to manage their housekeeping if they chose to move to live independently of parents/guardians. Competence in managing everyday matters was recorded as follows: (1) the adolescent is able to cope age appropriately outside home, (2) the adolescent needs support in age-appropriate matters outside home but functions age-appropriately in the home (manages her/his own hygiene, clothing and nutrition, participates in (younger subjects) or takes responsibility for (older subjects) housekeeping) and (3) the adolescent's functioning is inadequate both at home and outside home. For the analyses, participants were determined to be able to age-appropriately cope with matters outside of the home (1) vs. not (2,3).

Table 7: Question 2: For children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Bone density

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Lumbar spine bone mineral apparent density (BMAD) (2 uncontrolled, retrospective observational studies)									
Change from start of gender-affirming hormones to age 22 years in lumbar spine BMAD in transfemales									
1 cohort study Klink et al. 2015	Serious limitations ¹	Serious indirectness ²	Not applicable	Not calculable	N=13 (Mean) N=14 (z-score)	None	Mean (SD), g/m ³ Start of gender-affirming hormones: 0.22 (0.02) Age 22 years: 0.23 (0.03) P=0.003 z-score (SD) Start of gender-affirming hormones: -0.90 (0.80) Age 22 years: -0.78 (1.03) No statistically significant difference	Important	VERY LOW
Change from baseline in lumbar spine BMAD in transfemales with a bone age less than 15 years ('young'; 24 months follow-up)									
1 cohort study Vlot et al. 2017	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	N=15	None	Median (range), g/m ³ Start of gender-affirming hormones (C0): 0.20 (0.18 to 0.24)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							24-month follow-up (C24): 0.22 (0.19 to 0.27) Statistically significant increase ($p \leq 0.01$) z-score (range) Start of gender-affirming hormones (C0): -1.52 (-2.36 to 0.42) 24-month follow-up (C24): -1.10 (-2.44 to 0.69) Statistically significant increase ($p \leq 0.05$)		
Change from baseline in lumbar spine BMAD in transfemales with a bone age of 15 years or more ('old'; 24 months follow-up)									
1 cohort study Vlot et al. 2017	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	N=5	None	Median (range), g/m ³ Start of gender-affirming hormones (C0): 0.22 (0.19 to 0.24) 24-month follow-up (C24): 0.23 (0.21 to 0.26) Statistically significant increase ($p \leq 0.05$) z-score (range) Start of gender-affirming hormones (C0): -1.15 (-2.21 to 0.08) 24-month follow-up (C24): -0.66 (-1.66 to 0.54) Statistically significant increase ($p \leq 0.05$)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in lumber spine BMAD in transmales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
1 cohort study Klink et al. 2015	Serious limitations ¹	Serious indirectness ²	Not applicable	Not calculable	N=19 (Mean and z-score)	None	Mean (SD), g/m ³ Start of gender-affirming hormones: 0.24 (0.02) Age 22 years: 0.25 (0.28) P=0.001 z-score Start of gender-affirming hormones: -0.50 (0.81) Age 22 years: -0.033 (0.95) P=0.002	Important	VERY LOW
Change from baseline in lumbar spine BMAD in transmales with a bone age of less than 14 years ('young'; 24 months follow-up)									
1 cohort study Vlot et al. 2017	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	N=11	None	Median (range), g/m ³ Start of gender-affirming hormones (C0): 0.23 (0.19 to 0.28) 24-month follow-up (C24): 0.25 (0.22 to 0.28) Statistically significant increase (p≤0.01) z-score (range) Start of gender-affirming hormones (C0): -0.84 (-2.2 to 0.87) 24-month follow-up (C24): -0.15 (-1.38 to 0.94) Statistically significant increase (p≤0.01)	Important	VERY LOW
Change from baseline in lumbar spine BMAD in transmales with a bone age of 14 years or more ('old'; 24 months follow-up)									
1 cohort study	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	N=23	None	Median (range), g/m ³	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Vlot et al. 2017							Start of gender-affirming hormones (C0): 0.24 (0.20 to 0.28) 24-month follow-up (C24): 0.25 (0.21 to 0.30) Statistically significant increase (p≤0.01) z-score (range) Start of gender-affirming hormones (C0): -0.29 (-2.28 to 0.90) 24-month follow-up (C24): -0.06 (-1.75 to 1.61) Statistically significant increase (p≤0.01)		
Change in femoral neck BMAD (2 uncontrolled, retrospective observational studies)									
Change from start of gender-affirming hormones to age 22 years in femoral neck BMAD in transfemales									
1 cohort study Klink et al. 2015	Serious limitations ¹	Serious indirectness ²	Not applicable	Not calculable	N=14 (Mean) N=10 (z-score)	None	Mean (SD), g/m ³ Start of gender-affirming hormones: 0.26 (0.04) Age 22 years: 0.28 (0.05) No statistically significant difference z-score (SD) Start of gender-affirming hormones: -1.57 (1.74) Age 22 years: Not reported	Important	VERY LOW
Change from baseline in femoral neck BMAD in transfemales with a bone age less than 15 years ('young'; 24 months follow-up)									
1 cohort study	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	N=16	None	Median (range), g/m ³ C0: 0.27 (0.20 to 0.33) C24: 0.27 (0.20 to 0.36)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Vlot et al. 2017							No statistically significant change z-score (range) C0: -1.32 (-3.39 to 0.21) C24: -1.30 (-3.51 to 0.92) No statistically significant change		
Change from baseline in femoral neck BMAD in transfemales with a bone age of 15 years or more ('old'; 24 months follow-up)									
1 cohort study Vlot et al. 2017	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	N=6	None	Median (range), g/m ³ C0: 0.30 (0.26 to 0.34) C24: 0.29 (0.24 to 0.38) No statistically significant change z-score (range) C0: -0.36 (-1.50 to 0.46) C24: -0.56 (-2.17 to 1.29) No statistically significant change	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in femoral neck BMAD in transmales									
1 cohort study Klink et al. 2015	Serious limitations ¹	Serious indirectness ²	Not applicable	Not calculable	N=19 (Mean) N=18 (z-score)	None	Mean (SD), g/m ³ Start of gender-affirming hormones: 0.31 (0.04) Age 22 years: 0.33 (0.05) P=0.010 z-score (SD) Start of gender-affirming hormones: -0.28 (0.74) Age 22 years: Not reported	Important	VERY LOW
Change from baseline in femoral neck BMAD in transmales with a bone age of less than 14 years ('young'; 24 months follow-up)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
1 cohort study Vlot et al. 2017	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	N=10	None	Median (range), g/m ³ C0: 0.30 (0.22 to 0.35) C24: 0.33 (0.23 to 0.37) Statistically significant increase (p≤0.01) z-score (range) C0: -0.37 (-2.28 to 0.47) C24: -0.37 (-2.03 to 0.85) Statistically significant increase (p≤0.01)	Important	VERY LOW
Change from baseline in femoral neck BMAD in transmales with a bone age of 14 years or more ('old'; 24 months follow-up)									
1 cohort study Vlot et al. 2017	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	N=23	None	Median (range), g/m ³ C0: 0.30 (0.23 to 0.41) C24: 0.32 (0.23 to 0.41) Statistically significant increase (p≤0.01) z-score (range) C0: -0.27 (-1.91 to 1.29) C24: 0.02 (-2.1 to 1.35) Statistically significant increase (p≤0.05)	Important	VERY LOW
Change in lumbar spine BMD (2 uncontrolled, retrospective observational studies)									
Change from start of gender-affirming hormones to age 22 years in lumbar spine BMD in transfemales									
1 cohort study Klink et al. 2015	Serious limitations ¹	Serious indirectness ²	Not applicable	Not calculable	N=15 (Mean) N=13 (z-score)	None	Mean (SD), g/m ² Start of gender-affirming hormones: 0.84 (0.11) Age 22 years: 0.93 (0.10) P<0.001 z-score (SD)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							Start of gender-affirming hormones: -1.01 (0.98) Age 22 years: -1.36 (0.83) No statistically significant difference		
Change from start of gender-affirming hormones to age 22 years in lumbar spine BMD in transmales									
1 cohort study Klink et al. 2015	Serious limitations ¹	Serious indirectness ²	Not applicable	Not calculable	N=19 (Mean and z-score)	None	Mean (SD), g/m ² Start of gender-affirming hormones: 0.91 (0.10) Age 22 years: 0.99 (0.13) P<0.001 z-score (SD) Start of gender-affirming hormones: -0.72 (0.99) Age 22 years: -0.33 (1.12) No statistically significant difference	Important	VERY LOW
Change from start of testosterone treatment in lumbar spine BMD in transmen (follow-up 6 to 24 months)									
1 cohort study Stoffers et al. 2019	Serious limitations ⁴	No serious indirectness	Not applicable	Not calculable	N=62 (T0 and T6) N=37 (T12) N=15 (T24)	None	Mean (SD), g/cm ² T0: 0.90 (0.11) T6: 0.94 (0.10) T12: 0.95 (0.09) T24: 0.95 (0.11) No statistically significant difference from T0 to any timepoint z-score (SD) T0: -0.81 (1.02) T6: -0.67 (0.95) T12: -0.66 (0.81) T24: -0.74 (1.17)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							No statistically significant difference from T0 to any timepoint		
Change in femoral neck BMD (2 uncontrolled, retrospective observational studies)									
Change from start of gender-affirming hormones to age 22 years in femoral neck BMD in transfemales									
1 cohort study Klink et al. 2015	Serious limitations ¹	Serious indirectness ²	Not applicable	Not calculable	N=15 (Mean) N=11 (z-score)	None	Mean (SD), g/m ² Start of gender-affirming hormones: 0.87 (0.08) Age 22 years: 0.94 (0.11) P=0.009 z-score (SD) Start of gender-affirming hormones: -0.95 (0.63) Age 22 years: -0.69 (0.74) No statistically significant difference	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in femoral neck BMD in transmales									
1 cohort study Klink et al. 2015	Serious limitations ¹	Serious indirectness ²	Not applicable	Not calculable	N=19 (Mean) N=16 (z-score)	None	Mean (SD), g/m ² Start of gender-affirming hormones: 0.88 (0.09) Age 22 years: 0.95 (0.10) P<0.001 z-score (SD) Start of gender-affirming hormones: -0.35 (0.79) Age 22 years: -0.35 (0.74) P=0.006	Important	VERY LOW
Change from start of testosterone treatment in right femoral neck (hip) BMD in transmales (follow-up 6 to 24 months)									
1 cohort study	Serious limitations ⁴	No serious indirectness	Not applicable	Not calculable	N=62 (T0 and T6)	None	Mean (SD), g/cm ² T0: 0.77 (0.08)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Stoffers et al. 2019					N=37 (T12) N=15 (T24)		T6: 0.84 (0.11) T12: 0.82 (0.08) T24: 0.85 (0.11) No statistically significant difference from T0 to any timepoint z-score (SD) T0: -0.97 (0.79) T6: -0.54 (0.96) T12: -0.80 (0.69) T24: -0.31 (0.84) No statistically significant difference from T0 to any timepoint		
Change from start of testosterone treatment in left femoral neck (hip) BMD in transmales (follow-up 6 to 24 months)									
1 cohort study Stoffers et al. 2019	Serious limitations ⁴	No serious indirectness	Not applicable	Not calculable	N=62 (T0 and T6) N=37 (T12) N=15 (T24)	None	Mean (SD), g/cm ² T0: 0.76 (0.09) T6: 0.83 (0.12) T12: 0.81 (0.08) T24: 0.86 (0.09) No statistically significant difference from T0 to any timepoint z-score (SD) T0: -1.07 (0.85) T6: -0.62 (1.12) T12: -0.93 (0.63) T24: -0.20 (0.70) No statistically significant difference from T0 to any timepoint	Important	VERY LOW

Abbreviations: BMAD: bone mineral apparent density; BMD: bone mineral density; g: grams; m: metre; SD: standard deviation

1 Downgraded 1 level - the cohort study by Klink et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding, no control group and high number of participants lost to follow-up)

2 Outcomes reported after gender reassignment surgery and not after gender-affirming hormones alone. Unclear whether observed changes are due to hormones or surgery

3 Downgraded 1 level - the cohort study by Vlot et al. (2017) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control)

4 Downgraded 1 level - the cohort study by Stoffers et al. (2019) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group)

Table 8: Question 2: For children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Cardiovascular risk factors

QUALITY					Summary of findings		IMPORTANCE	CERTAINTY
					No of patients	Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)	
Change in body mass index (1 uncontrolled, retrospective observational study)								
Change from start of gender-affirming hormones to age 22 years in BMI in transfemales								
1 cohort study Klaver et al. 2020	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI) +1.9 (0.6 to 3.2) Statistically significant increase (p<0.005) Mean BMI at 22 years (95% CI): 23.2 (21.6 to 24.8)	Important VERY LOW
Change from start of gender-affirming hormones to age 22 years in BMI in transmales								
1 cohort study Klaver et al. 2020	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI) +1.4 (0.8 to 2.0) Statistically significant increase (p<0.005) Mean BMI at 22 years (95% CI): 23.9 (23.0 to 24.7)	Important VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
<i>Obesity rates at age 22 years (1 uncontrolled, retrospective observational study)</i>									
<i>Obesity rates at age 22 years in transfemales who started gender-affirming hormones as adolescents (1 uncontrolled, retrospective observational study)</i>									
1 cohort study Klaver et al. 2020	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=71	None	At 22 years, 9.9% of transfemales were obese, compared with 3.0% in reference cisgender population No statistically analysis reported	Important	VERY LOW
<i>Obesity rates at age 22 years in transfemales who started gender-affirming hormones as adolescents (1 uncontrolled, retrospective observational study)</i>									
1 cohort study Klaver et al. 2020	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=121	None	At 22 years, 6.6% of transmales were obese, compared with 2.2% in reference cisgender population No statistically analysis reported	Important	VERY LOW
<i>Change in blood pressure (1 uncontrolled, retrospective observational study)</i>									
<i>Change from start of gender-affirming hormones to age 22 years in systolic blood pressure (SBP) in transfemales</i>									
1 cohort study Klaver et al. 2020	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI) -3 (-8 to 2) No statistically significant difference Mean SBP at 22 years (95% CI): 117 (113 to 122)	Important	VERY LOW
<i>Change from start of gender-affirming hormones to age 22 years in diastolic blood pressure (DBP) in transfemales</i>									

QUALITY					Summary of findings		IMPORTANCE	CERTAINTY
					No of patients	Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)	
1 cohort study Klaver et al. 2020	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI) +6 (3 to 10) Statistically significant increase (p<0.001) Mean DBP at 22 years (95% CI): 75 (72 to 78)	Important VERY LOW
Change from start of gender-affirming hormones to age 22 years in systolic blood pressure (SBP) in transmales								
1 cohort study Klaver et al. 2020	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI): +5 (1 to 9) Statistically significant increase (p<0.05) Mean SBP at 22 years (95% CI): 126 (122 to 130)	Important VERY LOW
Change from start of gender-affirming hormones to age 22 years in diastolic blood pressure (DBP) in transmales								
1 cohort study Klaver et al. 2020	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI): +6 (4 to 9) Statistically significant increase (p<0.001) Mean DBP at 22 years (95% CI): 74 (72 to 77)	Important VERY LOW
Change in glucose levels, insulin levels, insulin resistance and HbA1c (2 uncontrolled, retrospective observational studies)								
Change from start of gender-affirming hormones to age 22 years in glucose level (mmol/L) in transfemales								
1 cohort study Klaver et al. 2020	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI): +0.1 (-0.1 to 0.2)	Important VERY LOW

QUALITY					Summary of findings		IMPORTANCE	CERTAINTY
					No of patients	Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)	
							No statistically significant difference Mean glucose level at 22 years (95% CI): 5.0 (4.8 to 5.1)	
Change from start of gender-affirming hormones to age 22 years in insulin level (mU/L) in transfemales								
1 cohort study Klaver et al. 2020	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI) +2.7 (-1.7 to 7.1) No statistically significant difference Mean insulin level at 22 years (95% CI): 13.0 (8.4 to 17.6)	Important VERY LOW
Change from start of gender-affirming hormones to age 22 years in insulin resistance (HOMA-IR) in transfemales. Higher scores indicate more insulin resistance.								
1 cohort study Klaver et al. 2020	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI) +0.7 (-0.2 to 1.5) No statistically significant difference Mean HOMA-IR at 22 years (95% CI): 2.9 (1.9 to 3.9)	Important VERY LOW
Change from start of gender-affirming hormones to age 22 years in glucose level (mmol/L) in transmales								
1 cohort study Klaver et al. 2020	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI) 0.0 (-0.2 to 0.2) No statistically significant difference	Important VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							Mean glucose level at 22 years (95% CI): 4.8 (4.7 to 5.0)		
Change from start of gender-affirming hormones to age 22 years in insulin level (mU/L) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI) -2.1 (-3.9 to -0.3) Statistically significant decrease (p<0.05) Mean insulin level at 22 years (95% CI): 8.6 (6.9 to 10.2)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in insulin resistance (HOMA-IR) in transmales. Higher scores indicate more insulin resistance.									
1 cohort study Klaver et al. 2020	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI): -0.5 (-1.0 to -0.1) Statistically significant decrease (p<0.05) Mean HOMA-IR at 22 years (95% CI): 1.8 (1.4 to 2.2)	Important	VERY LOW
Change from start of testosterone in HbA1c in transmales (up to 24 months follow-up)									
1 cohort study Stoffers et al. 2019	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N= Not reported	None	No statistically significant change from start of testosterone treatment Numerical results, follow-up duration and further details of	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							statistical analysis not reported.		
Change in lipid profile (1 uncontrolled, retrospective observational study)									
Change from start of gender-affirming hormones to age 22 years in total cholesterol (mmol/L) in transfemales									
1 cohort study Klaver et al. 2020	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI): +0.1 (-0.2 to 0.4) No statistically significant difference Mean total cholesterol at 22 years (95% CI): 4.1 (3.8 to 4.4)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in HDL cholesterol (mmol/L) in transfemales									
1 cohort study Klaver et al. 2020	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI): 0.0 (-0.1 to 0.2) No statistically significant difference Mean HDL cholesterol at 22 years (95% CI): 1.6 (1.4 to 1.7)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in LDL cholesterol (mmol/L) in transfemales									
1 cohort study Klaver et al. 2020	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI): 0.0 (-0.3 to 0.2) No statistically significant difference Mean LDL cholesterol at 22 years (95% CI): 2.0 (1.8 to 2.3)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Change from start of gender-affirming hormones to age 22 years in triglycerides (mmol/L) in transfemales									
1 cohort study Klaver et al. 2020	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI): +0.2 (0.0 to 0.5) Statistically significant increase (p<0.05) Mean triglycerides at 22 years (95% CI): 1.1 (0.9 to 1.4)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in total cholesterol (mmol/L) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI): +0.4 (0.2 to 0.6) Statistically significant increase (p<0.001) Mean total cholesterol at 22 years (95% CI): 4.6 (4.3 to 4.8)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in HDL cholesterol (mmol/L) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI): -0.3 (-0.4 to -0.2) Statistically significant decrease (p<0.001) Mean HDL cholesterol at 22 years (95% CI): 1.3 (1.2 to 1.3)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in LDL cholesterol (mmol/L) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI): +0.4 (0.2 to 0.6)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							Statistically significant increase (p<0.001) Mean LDL cholesterol at 22 years (95% CI): 2.6 (2.4 to 2.8)		
Change from start of gender-affirming hormones to age 22 years in triglycerides (mmol/L) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI) +0.5 (0.3 to 0.7) Statistically significant increase (p<0.001) Mean triglycerides at 22 years (95% CI): 1.3 (1.1 to 1.5)	Important	VERY LOW

Abbreviations: BMI: body mass index; CI: confidence interval; DBP: diastolic blood pressure; HbA1c: glycated haemoglobin; HDL: high-density lipoproteins; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; LDL: low-density lipoproteins; mmol/L: millimoles per litre; mU/L: milliunits per litre; SBP: systolic blood pressure; SD: standard deviation

1 Downgraded 1 level - the cohort study by Klaver et al. (2020) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group)

2 Downgraded 1 level - the cohort study by Stoffers et al. (2019) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group)

Table 9: Question 2: For children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Other safety outcomes

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Liver enzymes (1 uncontrolled, retrospective observational study)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
<i>Change from start of testosterone in aspartate aminotransferase (AST) level in transmales (up to 24 months follow-up)</i>									
1 cohort study Stoffers et al. 2019	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N= Not reported	None	No statistically significant change from start of testosterone treatment Numerical results, follow-up duration and further details of statistical analysis not reported.	Important	VERY LOW
<i>Change from start of testosterone in alanine aminotransferase (ALT) level in transmales (up to 24 months follow-up)</i>									
1 cohort study Stoffers et al. 2019	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N= Not reported	None	No statistically significant change from start of testosterone treatment Numerical results, follow-up duration and further details of statistical analysis not reported.	Important	VERY LOW
<i>Change from start of testosterone in gamma-glutamyl transferase (GGT) level in transmales (up to 24 months follow-up)</i>									
1 cohort study Stoffers et al. 2019	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N= Not reported	None	No statistically significant change from start of testosterone treatment Numerical results, follow-up duration and further details of statistical analysis not reported.	Important	VERY LOW
<i>Change from start of testosterone in alkaline phosphatase (ALP) level in transmales (up to 24 months follow-up)</i>									
1 cohort study Stoffers et al. 2019	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=62 (T0 and T1) N=37 (T12)	None	Median (IQR), U/L T0: 102 (78 to 136) T6: 115 (102 to 147) T12: 112 (88 to 143) T24: 81 (range 69 to 98)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
					N-15 (T24)		Statistically significant increase from T0 at T6 and T12 (p<0.001)		
Kidney markers (1 uncontrolled, retrospective observational study)									
Change from start of testosterone in serum creatinine level in transmales (up to 24 months follow-up)									
1 cohort study Stoffers et al. 2019	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=62 (T0 and T1) N=37 (T12) N=15 (T24)	None	Mean (SD), umol/L T0: 62 (7) T6: 70 (9) T12: 74 (10) T24: 81 (10) Statistically significant increase from T0 at all timepoints (p<0.001)	Important	VERY LOW
Change from start of testosterone in serum urea² level in transmales (up to 24 months follow-up)									
1 cohort study Stoffers et al. 2019	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N= Not reported	None	No statistically significant change from start of testosterone treatment Numerical results, follow-up duration and further details of statistical analysis not reported.	Important	VERY LOW
Adverse effects (1 uncontrolled, retrospective observational study)									
Permanent discontinuation of gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3))									
1 cohort study Khatchadorian et al. 2014	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	N=63	None	No participants permanently discontinued gender-affirming hormones.	Important	VERY LOW
Temporary discontinuation of gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3))									
1 cohort study	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	N=63	None	3/37 transmales receiving testosterone temporarily	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Khatchadorian et al. 2014							discontinued treatment, 2 due to concomitant mental health comorbidities and 1 due to androgenic alopecia. All eventually resumed treatment. No transfemales receiving oestrogen temporarily discontinued treatment		
Minor complications during treatment with gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3))									
1 cohort study Khatchadorian et al. 2014	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	N=63	None	12/63 participants had minor complications during treatment with gender-affirming hormones All 12 were transfemales receiving testosterone. Complications were severe acne (n=7), androgenic alopecia (n=1) mild dyslipidaemia (n=3) and significant mood swings (n=1) No transfemales receiving oestrogen had minor complications	Important	VERY LOW
Severe complications during treatment with gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3))									
1 cohort study Khatchadorian et al. 2014	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	N=63	None	No severe complications reported during gender-affirming treatment	Important	VERY LOW

Abbreviations: ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; IQR: interquartile range; SD: standard deviation; U/L: units per litre; umol/L: micromole per litre

1 Downgraded 1 level - the cohort study by Stoffers et al. (2019) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group)

2 Referred to as 'ureum' in original publication

3 Downgraded 1 level - the cohort study by Khatchadourian et al. (2014) was assessed as at high risk of bias (poor quality overall; lack of blinding, no control group and high number of participants lost to follow-up)

Table 10: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Transfemales compared with transmales

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Transfemales	Transmales	Result (95% CI)		
Impact on mental health (1 uncontrolled, retrospective observational study)									
Change from baseline in adjusted mean suicidality score, measured using the ASQ tool (mean treatment duration 349 days). Higher scores indicate a greater degree of suicidality.									
1 cohort study Allen et al. 2019	Serious limitations ⁴	No serious indirectness	No serious inconsistency	Not calculable	N=14	N=33	Transfemales T0 (baseline) = 1.21 (SE 0.36) T1 (final assessment) = 0.24 (SE 0.19) Transmales T0 (baseline) = 1.01 (SE 0.23) T1 (final assessment) = 0.29 (SE 0.13) No statistically significant difference in change from baseline between transfemales and transmales (p=0.79)	Critical	VERY LOW
Impact on quality of life (1 uncontrolled, retrospective observational study)									
Change from baseline in adjusted mean well-being score, measured using the GWBS of the Pediatric Quality of Life Inventory (mean treatment duration 349 days). Higher scores indicate better well-being.									
1 cohort study Allen et al. 2019	Serious limitations ⁴	No serious indirectness	No serious inconsistency	Not calculable	N=14	N=33	Transfemales T0 (baseline) = 58.44 (SE 4.09) T1 (final assessment) = 69.52 (SE 3.62)	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Transfemales	Transmales	Result (95% CI)		
							Transmales T0 (baseline) = 64.95 (SE 2.66) T1 (final assessment) = 70.94 (SE 2.35) No statistically significant difference in change from baseline between transfemales and transmales (p=0.32)		

Abbreviations: ASQ: Ask Suicide-Screening Questions; GWBS: General Well-Being Scale; SE: standard error

¹ The cohort study by Allen et al. 2019 was assessed at high risk of bias (poor quality; lack of blinding and no control group).

Table 11: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Sex assigned at birth males (transfemales)

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
					Intervention	Comparator	Result (95% CI)		
Study type and number of studies Author year	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Change from baseline in mean depression symptoms in transfemales, measured using the Quick Inventory of Depressive Symptoms (QIDS), self-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more depression.									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=40	None	Baseline = 7.5 (SD 4.9) Follow-up = 6.6 (SD 4.4) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean depression symptoms in transfemales, measured using the Quick Inventory of Depressive Symptoms (QIDS), clinician-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.									
1 cohort study	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=45	None	Baseline = 4.2 (SD 3.2) Follow-up = 5.4 (SD 3.4)	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study type and number of studies Author year	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Kuper et al. 2020							No statistical analysis reported for this sub-group		
Change from baseline in mean anxiety symptoms in transfemales, measured using the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe anxiety.									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=33	None	Baseline = 26.4 (SD 14.2) Follow-up = 24.3 (SD 15.4) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean panic symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=34	None	Baseline = 5.7 (SD 4.9) Follow-up = 5.1 (SD 4.9) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean generalised anxiety symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=34	None	Baseline = 8.6 (SD 5.1) Follow-up = 8.0 (SD 5.1) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean social anxiety symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=34	None	Baseline = 7.1 (SD 3.9) Follow-up = 6.8 (SD 4.4) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean separation anxiety symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=34	None	Baseline = 3.4 (SD 3.3) Follow-up = 2.7 (SD 2.3) No statistical analysis reported for this sub-group	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study type and number of studies Author year	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
<i>Change from baseline in mean school avoidance symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.</i>									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=33	None	Baseline = 1.8 (SD 1.7) Follow-up = 1.9 (SD 2.1) No statistical analysis reported for this sub-group	Critical	VERY LOW
<i>Change from baseline in percentage of participants with suicidal ideation in transfemales, measured using the additional questions from the PHQ 9 Modified for Teens (approximately 12-month follow-up)</i>									
1 cohort study Achille et al. 2020	Serious limitations ²	Serious indirectness ²	No serious inconsistency	Not calculable	N=17	None	Wave 1 (baseline) = 11.8% (2/17) Wave 2 (approx. 12 months) = 5.9% (1/17) No statistical analysis reported	Critical	VERY LOW
<i>Impact on body image (1 uncontrolled, prospective observational study)</i>									
<i>Change from baseline in mean body image in transfemales, measured using the BIS (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores represent a higher degree of body dissatisfaction.</i>									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=30	None	Baseline = 67.5 (SD 19.5) Follow-up = 49.0 (SD 21.6) No statistical analysis reported for this sub-group	Important	VERY LOW

Abbreviations: BIS: Body Image Scale; PHQ 9: Patient Health Questionnaire 9; SCARED: Screen for Child Anxiety Related Emotional Disorders; SD: standard deviation

1 Downgraded 1 level - the cohort study by Kuper et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).

2 Downgraded 1 level - the cohort study by Achille et al. 2020 was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).

3 Serious indirectness in Achille 2020- Approximately 30% of the full sample received puberty suppression alone or were receiving no treatment at final follow-up.

Table 12: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Sex assigned at birth females (transmales)

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
<i>Change from baseline in mean depression symptoms in transmales, measured using the Quick Inventory of Depressive Symptoms (QIDS), self-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.</i>									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=76	None	Baseline = 10.4 (SD 5.0) Follow-up = 7.5 (SD 4.5) No statistical analysis reported for this sub-group	Critical	VERY LOW
<i>Change from baseline in mean depression symptoms in transmales, measured using the Quick Inventory of Depressive Symptoms (QIDS), clinician-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.</i>									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=78	None	Baseline = 6.7 (SD 4.4) Follow-up = 6.2 (SD 4.1) No statistical analysis reported for this sub-group	Critical	VERY LOW
<i>Change from baseline in mean anxiety symptoms in transmales, measured using the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe anxiety.</i>									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=65	None	Baseline = 35.4 (SD 16.5) Follow-up = 29.8 (SD 15.5) No statistical analysis reported for this sub-group	Critical	VERY LOW
<i>Change from baseline in mean panic symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe symptoms.</i>									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=66	None	Baseline = 9.3 (SD 6.5) Follow-up = 7.9 (SD 6.5) No statistical analysis reported for this sub-group	Critical	VERY LOW
<i>Change from baseline in mean generalised anxiety symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.</i>									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=66	None	Baseline = 10.4 (SD 5.0) Follow-up = 9.0 (SD 5.1) No statistical analysis reported for this sub-group	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
<i>Change from baseline in mean social anxiety symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.</i>									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=66	None	Baseline = 8.5 (SD 4.0) Follow-up = 7.8 (SD 4.1) No statistical analysis reported for this sub-group	Critical	VERY LOW
<i>Change from baseline in mean separation anxiety symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.</i>									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=65	None	Baseline = 4.2 (SD 3.4) Follow-up = 3.4 (SD 2.6) No statistical analysis reported for this sub-group	Critical	VERY LOW
<i>Change from baseline in mean school avoidance symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.</i>									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=65	None	Baseline = 2.9 (SD 2.3) Follow-up = 2.0 (SD 2.3) No statistical analysis reported for this sub-group	Critical	VERY LOW
<i>Change from baseline in percentage of participants with suicidal ideation in transmales, measured using the additional questions from the PHQ 9_Modified for Teens (approximately 12-month follow-up)</i>									
1 cohort study Achille et al. 2020	Serious limitations ²	Serious indirectness ³	No serious inconsistency	Not calculable	N=33	None	Wave 1 (baseline) = 9.1% (3/33) Wave 2 (approx. 12 months) = 6.1% (2/33) No statistical analysis reported	Critical	VERY LOW
<i>Impact on body image (1 uncontrolled, prospective observational study)</i>									
<i>Change from baseline in mean body image in transmales, measured using the BIS (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores represent a higher degree of body dissatisfaction.</i>									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=66	None	Baseline = 71.1 (SD 13.4) Follow-up = 52.9 (SD 16.8) No statistical analysis reported for this sub-group	Important	VERY LOW

Abbreviations: BIS: Body Image Scale; PHQ 9: Patient Health Questionnaire 9; SCARED: Screen for Child Anxiety Related Emotional Disorders; SD: standard deviation

1 Downgraded 1 level - the cohort study by Kuper et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).

2 Downgraded 1 level - the cohort study by Achille et al. 2020 was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).

3 Serious indirectness in Achille 2020- Approximately 30% of the full sample received puberty suppression alone or were receiving no treatment at final follow-up.

Table 14: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Outcomes controlled for concurrent counselling and medicines for mental health problems

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Impact on mental health (1 uncontrolled, retrospective observational study)									
Change from baseline in mean depression score in transfemales, measured using the CESD-R (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicate more depression.									
1 cohort study Achille et al. 2020	Serious limitations ¹	Serious indirectness ²	No serious inconsistency	Not calculable	N=17	None	No statistically significant change from baseline (p=0.27) Numerical scores not reported	Critical	VERY LOW
Change from baseline in mean depression score in transmales, measured using the CESD-R (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicate more severe depression.									
1 cohort study Achille et al. 2020	Serious limitations ¹	Serious indirectness ²	No serious inconsistency	Not calculable	N=33	None	No statistically significant change from baseline (p=0.43) Numerical scores not reported	Critical	VERY LOW
Change from baseline in depression score in transfemales, measured using the Patient Health Questionnaire Modified for Teens (PHQ 9 Modified for Teens) (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicate more severe depression.									
1 cohort study Achille et al. 2020	Serious limitations ¹	Serious indirectness ²	No serious inconsistency	Not calculable	N=17	None	No statistically significant change from baseline (p=0.07) Numerical scores not reported	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
<i>Change from baseline in depression score in transmales, measured using the Patient Health Questionnaire Modified for Teens (PHQ 9_Modified for Teens) (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicate more severe depression.</i>									
1 cohort study Achille et al. 2020	Serious limitations ¹	Serious indirectness ²	No serious inconsistency	Not calculable	N=33	None	No statistically significant change from baseline (p=0.67) Numerical scores not reported	Critical	VERY LOW
<i>Impact on quality of life (1 uncontrolled, retrospective observational study)</i>									
<i>Change from baseline in mean quality of life score in transfemales, measured using the QLES-Q-SF (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicated better quality of life.</i>									
1 cohort study Achille et al. 2020	Serious limitations ¹	Serious indirectness ²	No serious inconsistency	Not calculable	N=17	None	No statistically significant change from baseline (p=0.06)	Critical	VERY LOW
<i>Change from baseline in mean quality of life score in transmales, measured using the QLES-Q-SF (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicated better quality of life.</i>									
1 cohort study Achille et al. 2020	Serious limitations ¹	Serious indirectness ²	No serious inconsistency	Not calculable	N=33	None	No statistically significant change from baseline (p=0.08)	Critical	VERY LOW
<i>Psychosocial Impact (1 uncontrolled, retrospective observational study)</i>									
<i>Functioning in adolescent development: Progresses normatively in school/ work during the real-life phase – impact on need for mental health treatment before or during gender identity assessment</i>									
1 cohort study Kaltiala et al. 2020	Serious limitations ³	No serious indirectness	No serious inconsistency	Not calculable	N=49	None	Needed mental health treatment: 47% (15/32) functioning well Did not need mental health treatment: 82% (14/17) functioning well Statistically significant difference p=0.02	Important	VERY LOW
<i>Functioning in adolescent development: Is age-appropriately able to deal with matters outside of the home during the real-life phase – impact on need for mental health treatment before or during gender identity assessment</i>									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
1 cohort study Kaltiala et al. 2020	Serious limitations ³	No serious indirectness	No serious inconsistency	Not calculable	N=49	None	Needed mental health treatment: 72% (23/32) managing well Did not need mental health treatment: 94% (16/17) managing well No statistically significant difference p=0.06	Important	VERY LOW
Functioning in adolescent development: Progresses normatively in school/ work during the real-life phase – impact on need for mental health treatment during the real-life phase									
1 cohort study Kaltiala et al. 2020	Serious limitations ³	No serious indirectness	No serious inconsistency	Not calculable	N=51	None	Needed mental health treatment: 42% (10/24) functioning well Did not need mental health treatment: 74% (20/27) functioning well Statistically significant difference p=0.02	Important	VERY LOW
Functioning in adolescent development: Is age-appropriately able to deal with matters outside of the home during the real-life phase – impact on need for mental health treatment during the real-life phase									
1 cohort study Kaltiala et al. 2020	Serious limitations ³	No serious indirectness	No serious inconsistency	Not calculable	N=51	None	Needed mental health treatment: 67% (16/24) managing well Did not need mental health treatment: 93% (25/27) managing well Statistically significant difference p=0.02	Important	VERY LOW

Abbreviations: CESD-R: Center for Epidemiologic Studies Depression; p: p-value; PHQ 9: Patient Health Questionnaire 9; QLES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire

1 Downgraded 1 level - the cohort study by Achille et al 2020 was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).

2 Serious indirectness in Achilles 2020- Approximately 30% of the full sample received puberty suppression alone or were receiving no treatment at final follow-up.

3 Downgraded 1 level - the cohort study by Kaltiala et al. 2020 was assessed at high risk of bias (poor quality: lack of blinding and no control).

Table 15: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Tanner age

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Impact on mental health (1 uncontrolled, retrospective observational study)									
Change from baseline in mental health problems – depression, anxiety and anxiety-related symptoms (mean duration of gender-affirming hormone treatment was 10.9 months)									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=105	None	No difference in outcomes found by Tanner age. Numerical results, statistical analysis and information on specific outcomes not reported. It is unclear from the paper whether Tanner age is at initial assessment, start of GnRH analogues, start of gender-affirming hormones, or another timepoint	Critical	VERY LOW
Impact on body image (1 uncontrolled, prospective observational study)									
Change from baseline in mean body image, measured using the BIS (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores represent a higher degree of body dissatisfaction.									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=105	None	No difference in body image score found by Tanner age. Numerical results, statistical analysis and information on specific outcomes not reported.	Important	VERY LOW

							It is unclear from the paper whether Tanner age is at initial assessment, start of GnRH analogues, start of gender-affirming hormones, or another timepoint		

Abbreviations: BIS: Body Image Scale

1 Downgraded 1 level - the cohort study by Kuper et al. 2020 was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).

Glossary

Ask Suicide-Screening Questions (ASQ)	ASQ is a four-item dichotomous (yes, no) response measure with high sensitivity, designed to identify risk of suicide. A patient is considered to have screened positive if they answered yes to any item. The authors of Allen et al. 2019 altered the fourth item of the ASQ (“Have you ever tried to kill yourself?”) and prefaced it with “In the past few weeks . . .” as they were not investigating lifetime suicidality. A response of ‘no’ was scored as 0 and a response of ‘yes’ was scored as 1; each item was summed, generating an overall score for suicidality on a scale ranging from 0 to 4, with higher scores indicating greater levels of suicidal ideation.
Beck Depression Inventory-II (BDI-II)	The BDI-II is a tool for assessing depressive symptoms. There are no specific scores to categorise depression severity, but it is suggested that 0 to 13 is minimal symptoms, 14 to 19 is mild depression, 20 to 28 is moderate depression, and severe depression is 29 to 63.
Body Image Scale (BIS)	The BIS is used to measure body satisfaction. The scale consists of 30 body features, which the person rates on a 5-point scale. Each of the 30 items falls into one of 3 basic groups based on its relative importance as a gender-defining body feature: primary sex characteristics, secondary sex characteristics, and neutral body characteristics. A higher score indicates more dissatisfaction.
Bone mineral apparent density (BMAD)	BMAD is a size adjusted value of bone mineral density (BMD) incorporating bone size measurements using UK norms in growing adolescents.
Center for Epidemiologic Studies Depression scale (CESD-R)	The CESD-R is a valid, widely used tool to assess depressive symptoms. The CESD-R asks about how frequently a person has felt or behaved in a certain way; with 20 questions scored from 0 score is calculated as a sum of 20 questions, ranging from 0 (“not at all or less than one day”) to 3 (“5–7 days” and/or “nearly every day for 2 weeks”). Total score ranges from 0 to 60, with higher scores indicating more depressive symptoms.
Cisgender	Cisgender is a term for someone whose gender identity matches their birth-registered sex.
Family APGAR (Adaptability, Partnership, Growth, Affection and Resolve) test	The Family APGAR test is a 5-item questionnaire, with higher scores indicating better family functioning. The authors reported the following interpretation of the score: functional, 17-20 points; mildly dysfunctional, 16-13 points; moderately dysfunctional, 12-10 point; severely dysfunctional, <9 points.
Gender	The roles, behaviours, activities, attributes and opportunities that any society considers appropriate for girls and boys, and women and men.
Gender dysphoria	Discomfort or distress that is caused by a discrepancy between a person’s gender identity (how they see themselves regarding their gender) and that person’s sex assigned at birth (and the associated gender role, and/or primary and secondary sex characteristics).

General Well-Being Scale (GWBS) of the Pediatric Quality of Life Inventory score	The GWBS of the Pediatric Quality of Life Inventory uses a 5-point response scale, contains seven items, and measures two dimensions: general wellbeing (6 items) and general health (1 item). Each item is scored from 0 to 4, and the total score is linearly transformed to a 0 to 100 scale. High scores reflect fewer perceived problems and greater well-being.
GnRH analogue	GnRH analogues competitively block GnRH receptors to prevent the spontaneous release of two gonadotropin hormones, Follicular Stimulating Hormone (FSH) and Luteinising Hormone (LH) from the pituitary gland. The reduction in LH and FSH secretion reduces oestradiol secretion from the ovaries in those whose sex assigned at birth was female and testosterone secretion from the testes in those whose sex assigned at birth was male.
Patient Health Questionnaire Modified for Teens score (PHQ 9_Modified for Teens)	The PHQ 9_Modified for Teens is a validated tool to assess depression, dysthymia and suicide risk. The tool consists of 9 questions scored from 0 to 3 (total score 0 to 27), plus an additional 4 questions that are not scored. A score of 0 to 4 suggests no or minimal depressive symptoms, 5 to 9 mild, 10-14 moderate, 15-19 moderate and 20-27 severe symptoms.
Quick Inventory of Depressive Symptoms (QIDS)	Both the clinician- and self-reported QIDS are validated tools to assess depressive symptoms. The tool consists of 16 items, with the highest score for 9 items (sleep, weight, psychomotor changes, depressed mood, decreased interest, fatigue, guilt, concentration, and suicidal ideation) are added to give a total score ranging from 0 to 27. A score of 0 to 5 is suggestive of no depressive symptoms, 6 to 10 mild symptoms, 11 to 15 moderate symptoms, 16-20 severe symptoms and 21 to 27 very severe symptoms.
Quality of Life Enjoyment and Satisfaction Questionnaire (QLES-Q-SF)	QLES-Q-SF is a validated questionnaire, consisting of 15 questions that rate quality of life on a scale of 1 (poor) to 5 (very good).
Screen for Child Anxiety Related Emotional Disorders (SCARED) questionnaire	SCARED is a validated, 41-point questionnaire, with each item scored 0 to 2. A total score of 25 or more is suggestive of anxiety disorder, with scores above 30 being more specific. Certain scores for specific questions may indicate the presence of other anxiety-related disorders: A score of 7 or more in questions related to panic disorder or significant somatic symptoms may indicate the presence of these. A score of 9 or more in questions related to generalised anxiety disorder may indicate the presence of this. A score of 5 or more in questions related to separation anxiety may indicate the presence of this. A score of 8 or more in questions related to social anxiety disorder may indicate the presence of this. A score of 3 or more in questions related to significant school avoidance may indicate the presence of this.
State-Trait Anxiety Inventory (STAI) score	STAI is a validated and commonly used measure of state anxiety (current state of anxiety) and trait anxiety (general state of calmness, confidence and security). It has 40 items, the first 20 covering state anxiety, the second 20 covering trait anxiety. STAI

	can be used in clinical settings to diagnose anxiety and to distinguish it from depressive illness. Each subtest (state and trait) is scored between 20 and 80, with higher scores indicating greater anxiety. There is no published minimal clinically meaningful difference (MCID) for STAI or thresholds for anxiety severity.
Strengths and Difficulties Questionnaire (SDQ, Spanish version)	The SDQ, Spanish version includes 25-items covering emotional symptoms, conduct problems, hyperactivity/ inattention, peer relationship problems and prosocial behaviour. The authors state that a score of more than 20 is considered indicative of risk of having a disorder (normal: 0-15; borderline: 16-19, abnormal: 20-40).
Tanner stage	Tanner staging is a scale of physical development.
Transgender (including transmale and transfemale)	Transgender is a term for someone whose gender identity is not congruent with their birth-registered sex. A transfemale is a person who identifies as female and a transmale is a person who identifies as male.
Utrecht Gender Dysphoria Scale (UGDS)	The UGDS is a validated screening tool for both adolescents and adults to assess gender dysphoria. It consists of 12 items, to be answered on a 1- to 5-point scale, resulting in a sum score between 12 and 60. Higher scores indicate higher levels of gender dysphoria.

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Antiandrogen or estradiol treatment or both during hormone therapy in transitioning transgender women (Review)

Haupt C, Henke M, Kutschmar A, Hauser B, Baldinger S, Saenz SR, Schreiber G

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Antiandrogen or estradiol treatment or both during hormone therapy in transitioning transgender women
(Review)

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[Intervention Review]

Antiandrogen or estradiol treatment or both during hormone therapy in transitioning transgender women

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ABSTRACT

Background

Gender dysphoria is described as a mismatch between an individual's experienced or expressed gender and their assigned gender, based on primary or secondary sexual characteristics. Gender dysphoria can be associated with clinically significant psychological distress and may result in a desire to change sexual characteristics. The process of adapting a person's sexual characteristics to their desired sex is called 'transition.'

Current guidelines suggest hormonal and, if needed, surgical intervention to aid transition in transgender women, i.e. persons who aim to transition from male to female. In adults, hormone therapy aims to reverse the body's male attributes and to support the development of female attributes. It usually includes estradiol, antiandrogens, or a combination of both. Many individuals first receive hormone therapy alone, without surgical interventions. However, this is not always sufficient to change such attributes as facial bone structure, breasts, and genitalia, as desired. For these transgender women, surgery may then be used to support transition.

Objectives

We aimed to assess the efficacy and safety of hormone therapy with antiandrogens, estradiol, or both, compared to each other or placebo, in transgender women in transition.

Search methods

We searched MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Biosis Preview, PsycINFO, and PSYINDEX. We carried out our final searches on 19 December 2019.

Selection criteria

We aimed to include randomised controlled trials (RCTs), quasi-RCTs, and cohort studies that enrolled transgender women, age 16 years and over, in transition from male to female. Eligible studies investigated antiandrogen and estradiol hormone therapies alone or in combination, in comparison to another form of the active intervention, or placebo control.

Data collection and analysis

We used standard methodological procedures expected by Cochrane to establish study eligibility.

Main results

Our database searches identified 1057 references, and after removing duplicates we screened 787 of these. We checked 13 studies for eligibility at the full text screening stage. We excluded 12 studies and identified one as an ongoing study. We did not identify any completed studies that met our inclusion criteria. The single ongoing study is an RCT conducted in Thailand, comparing estradiol valerate plus cyproterone treatment with estradiol valerate plus spironolactone treatment. The primary outcome will be testosterone level at three month follow-up.

Authors' conclusions

We found insufficient evidence to determine the efficacy or safety of hormonal treatment approaches for transgender women in transition. This lack of studies shows a gap between current clinical practice and clinical research. Robust RCTs and controlled cohort studies are needed to assess the benefits and harms of hormone therapy (used alone or in combination) for transgender women in transition. Studies should specifically focus on short-, medium-, and long-term adverse effects, quality of life, and participant satisfaction with the change in male to female body characteristics of antiandrogen and estradiol therapy alone, and in combination. They should also focus on the relative effects of these hormones when administered orally, transdermally, and intramuscularly. We will include non-controlled cohort studies in the next iteration of this review, as our review has shown that such studies provide the highest quality evidence currently available in the field. We will take into account methodological limitations when doing so.

PLAIN LANGUAGE SUMMARY

Does hormone therapy help transgender women undergoing gender reassignment to transition?

Background

Transgender women may feel that they have been born in a body with the wrong sexual characteristics. This may result in significant psychological distress (gender dysphoria) and the desire to adapt their male physical and sexual characteristics to be more consistent with their experienced female gender. This is a process called transition. If measures to aid transition are not taken, this can result in greater psychological distress. One of the medical treatments given to help transgender women with male bodies to achieve transition is synthetic female hormones. These hormones can be taken by mouth, absorbed through the skin or injected into muscle.

Study characteristics

We looked for randomised controlled trials (RCTs) that included transgender women (age 16 and over) in transition from male to female. RCTs are a type of research study that can reduce the possibility of several types of bias. To be included in this review, studies needed to compare different hormone treatments used to support transgender women to transition (oestrogen alone, testosterone blockers alone, or oestrogen in combination with testosterone blockers), or compare these hormone treatments to placebos (fake or dummy treatments that appear to be the same as the actual treatment, but have no medical effects). We wanted to see whether hormone treatments help transgender women to make a transition that they are happy with. We also wanted to look at whether there were any health risks of the treatment.

Key results

We searched for studies up to 19 December 2019. We were unable to find any relevant completed studies that we could include. We did find one ongoing study that aimed to recruit all of the people taking part in the study by the end of 2020. This study is comparing the effects of estradiol valerate plus cyproterone treatment with estradiol valerate plus spironolactone treatment in transitioning transgender women in Thailand.

Quality of evidence

Our review found no RCTs that looked at whether hormone therapies are effective and safe when used to help transgender women to transition. Therefore, high-quality RCTs are needed to research these questions.

BACKGROUND

Description of the condition

There is a growing trend towards de-psychopathologisation of transgenderism ([Drescher 2014](#); [ATME 2015](#)). There is an emerging consensus that transgenderism is not a psychiatric disorder ([WPATH 2011](#)). For instance, the 11th Revision of the International Classification of Diseases (ICD-11) ([WHO 2018](#)) no longer classifies transgenderism as a behavioural and personality disorder, but has instead drafted the term "gender incongruence" to describe gender dysphoria.

In contrast, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) ([DSM-5 2013](#)) describes gender dysphoria as a "marked incongruence between one's experienced/expressed gender and assigned gender, of at least six months duration, as manifested by at least two of the following" characteristics:

- A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or, in young adolescents, the anticipated secondary sex characteristics);
- A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or, in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics);
- A strong desire for the primary and/or secondary sex characteristics of the other gender;
- A strong desire to be of the other gender (or some alternative gender different from one's assigned gender);
- A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender);
- A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).

Gender dysphoria has been defined as associated with "clinically significant distress or impairment in social, occupational or other important areas of functioning" ([Zucker 2016](#)), which may lead to substantial suffering in affected people ([Deutsch 2016a](#); [Soll 2018](#)). Gender dysphoria may result in the desire to modify one's physical and sexual characteristics to be consistent with those of the experienced gender. This process of adaptation is called transition.

The treatments applied in transition differ from those used for maintenance of the new sexual characteristics. Currently, there is uncertainty about the value of hormone therapy as a sole intervention, or when combined with surgery, for transition from male to female. This Cochrane Review specifically focuses on 'transgender women in transition from male to female,' a definition that includes biological males aiming to adapt their sexual characteristics to be consonant with those of females.

A meta-analysis that analyzed 21 studies on the prevalence of gender dysphoria (of which 12 studies contained evaluable data) estimated an overall prevalence of transgender women with gender dysphoria at 6.8 per 100,000 individuals ([Arcelus 2015](#)).

Description of the intervention

Current guidelines suggest hormonal and, if needed, surgical treatment of gender dysphoria in transgender women ([WPATH 2011](#)). Hormone therapy aims to suppress the development of, or to reverse, male attributes that have already developed. At the same time, hormones aim to develop female attributes. However, where male characteristics have already developed in adult males, such as in the bone structure of the face, hormones are not effective. Other treatments, such as surgery, would be required to change these ([WPATH 2011](#)).

The guidelines of the Endocrine Society working group suggest treatment with both oestrogens and antiandrogens ([Hembree 2017](#)). Oestrogens can be administered as either oral oestrogen, absorbed through transdermal estradiol patches, or by injection of estradiol valerate or estradiol cypionate. The application frequency differs depending on the patient's reaction to the agent and the administration regimen; it could be multiple times per day or once every two weeks. Meanwhile, antiandrogens such as spironolactone or cyproterone acetate (CPA) are commonly taken orally. Additionally, it is possible to block male puberty by treatment with gonadotropin-releasing hormone (GnRH) agonist injections ([Hembree 2017](#)).

While not every transgender woman undergoes hormone therapy in her transition, this intervention is still widely used ([Hembree 2017](#)). We know of no studies identifying the ratio of patients who undergo hormone therapy, nor do we know of studies investigating how much time passes between the start of transition (the decision to transition) and the start of hormone therapy. We are not aware of any studies on how often antiandrogens are being prescribed in addition to or instead of 17-beta-estradiol, how often they are being taken, or which kinds of androgens are in use besides CPA and spironolactone.

How the intervention might work

Several hormonal substances and combinations are used clinically for hormone therapy in transitioning women. CPA is a progestin, steroidal anti-androgen and anti-gonadotropin that blocks the receptors for testosterone (T) and dihydrotestosterone (DHT), and thereby prevents these steroidal hormones from exerting their androgenic effects. Hence, it stops processes like body hair growth, hair loss on the head, male body fat distribution and others ([Figg 2010](#); [WPATH 2011](#)). According to the World Professional Association for Transgender Health (WPATH) guidelines, it is possible to suppress puberty with GnRH analogues or progestins such as medroxyprogesterone ([WPATH 2011](#)).

Spironolactone acts as a weak androgen receptor antagonist ([Wenqing 2005](#)). It also causes an increase in oestradiol levels ([Thompson 1993](#)), so that further virilisation is prevented and feminisation occurs ([WPATH 2011](#)).

17-beta-estradiol is used to feminise the external appearance ([WPATH 2011](#)). It binds to oestrogen receptors and thus ensures gene expression, which in turn feminises appearance ([Hye-Rim 2012](#)). In addition, estradiol suppresses gonadal testosterone production via the control systems of the hypothalamus ([Hayes 2000](#)).

Feminisation therapy aims to adapt the physical appearance and experience of the male body to that of a female body, by

inducing breast growth, softening facial features, and inducing other physical changes commonly considered to comprise a feminine appearance (WPATH 2011). For this purpose, oral or transdermal oestrogen is recommended, and therapy with oestrogen in combination with antiandrogens is most common. Co-treatment with antiandrogens minimises the required dose of oestrogen, and thereby reduces the potential risks of oestrogen identified in previous studies (Schürmeyer 1986; Prior 1989). Some antiandrogens are approved by WPATH, such as spironolactone, cyproterone acetate, GnRH analogues like goserelin, and 5-alpha-reductase inhibitors like finasteride (WPATH 2011).

Why it is important to do this review

Antiandrogens like CPA and spironolactone are prescribed to transgender women in transition by clinicians, including gynaecologists and endocrinologists (Schneider 2006; Flütsch 2015), and they are commonly considered to be valuable drugs to support transition (WPATH 2011; Hembree 2017). However, clinical evidence suggests that taking these drugs can result in adverse events; for example, CPA has significant potential for causing depression and for worsening depressive symptoms (Seal 2012). There is also some concern that CPA can lead to other psychiatric, neurological, and metabolic disorders (Griard 1978; Ramsay 1990; Oberhammer 1996; Giltay 2000; Calderón 2009; Bessone 2015). The most common adverse effects of spironolactone are hyperkalaemia, dehydration and hyponatraemia (Greenblatt 1973). Furthermore, spironolactone might have an influence on feelings of anxiety (Fox 2016).

Other studies from the 1980s and 90s reported that there were adverse effects from high-dose estradiol, but these studies used ethinyl estradiol or equine premarin (equine estradiol) instead of bioidentical 17-beta-estradiol; and used progestins, instead of bioidentical progesterone. This may have contributed to the adverse effect profile of these specific treatments (Prior 1989). Unlike the bioidentical alternatives used today (hormone preparations made from plant sources that are similar or identical to human hormones), substances administered in the past (e.g. equine oestrogens, ethinyl estradiol) were associated with more diverse adverse effects like thrombophilia, cardiovascular problems, breast and prostate cancer, as well as liver, adrenal gland and neural dysfunction (Griard 1978; Calderón 2009; Asscheman 2011). The health risks attributed to estradiol doses high enough to suppress androgens have not been found in the parenteral or transdermal application of bioidentical estradiol (Hembree 2017). Thus, it is unclear why those estradiol doses should be kept low in order to make the addition of androgen antagonists like CPA or spironolactone necessary.

In light of discussions among experts (Seal 2012; Wierckx 2014), and current recommendations for hormonal gender affirmation treatment (WPATH 2011) (which are strongly based on the values and preferences of health consumers), it is necessary to review the evidence from trials that show results for outcomes such as feminisation, satisfactory sexual function, reduced gender dysphoria, and improved quality of life (e.g. Murad 2010).

In 2017, the overall quality of evidence relating to these outcomes was classified as low (Hembree 2017). In 2011, WPATH summarised the situation as follows. "There is a need for further research on the effects of hormone therapy without surgery, and without the goal of maximum physical feminisation or masculinisation" (WPATH

2011). It is necessary to determine whether subsequent trials have provided additional evidence for efficacy, or whether there is still a lack of evidence for these desired outcomes.

OBJECTIVES

We aimed to assess the efficacy and safety of hormone therapy with antiandrogens, estradiol, or both, compared to each other or placebo, in transgender women in transition.

METHODS

Criteria for considering studies for this review

Types of studies

We aimed to include randomised controlled trials (RCTs), quasi-RCTs and controlled cohort studies.

We chose to include quasi-RCTs and cohort studies due to the low prevalence of the condition and the consequent current scarcity of RCTs (WPATH 2011).

Types of participants

We aimed to include studies that enrolled transgender women, age 16 years and over, in transition from male to female. Transitioning is defined as the process of changing one's gender profile or sexual characteristics (or both) to accord with one's sense of gender identity (WPATH 2011). Transition as a concept thus encompasses several aspects, e.g. social, psychological, or physical aspects, or a combination of these. There is consistency in the literature on when the transition begins: namely, with the decision to change a person's gender assignment (Brown 1996). However, we did not differentiate among any supposed phases of the respective types of transitions. Depending on the personal situation, the process of transition (which may include the decision to transition, gathering of information, gathering of experience, medical treatment and change of social role), can take very different periods of time, usually several months to years. Therefore, it is difficult to distinguish certain 'phases' of this process. When focusing on hormone therapy, the transition term can be more precisely defined. The transition process lasts as long as patients are in the process of changing their sexual characteristics (WPATH 2011).

We aimed to include studies with participants age 16 years and older because, according to currently applied guidelines, this is the age when patients start being treated with hormone therapy. Patients below this age are usually being treated with puberty blockers, which are outside the scope of this review (WPATH 2011).

Types of interventions

We considered studies evaluating hormone-based interventions only, excluding those that examined combined hormonal and either psychological or surgical treatments. We aimed to include studies reporting treatment with the following experimental interventions.

- Antiandrogens (cyproterone acetate or spironolactone) and estradiol
- Antiandrogens (cyproterone acetate or spironolactone) alone
- Estradiol alone

For the above interventions, we considered all types of administration: oral, sublingual, transdermal, subdermal and intramuscular. For estradiol, we also considered bioidentical 17-beta-estradiol, as well as synthetic derivatives.

We aimed to include the following comparator interventions.

- Any of the active interventions listed above
- Placebo

Although we consider placebo-controlled studies to be unethical (Bostick 2008), we made them eligible for inclusion in this review so that we could consider the evidence in its entirety. We did not consider interventions consisting purely of psychological treatment, spiritual support, or conversion therapy.

Types of outcome measures

For studies with repeated follow-up (i.e. reporting of outcomes at multiple time points), we regarded follow-up at three to six months as short term, six months to two years as medium term, and more than two years as long term (WPATH 2011).

We intended to include in the descriptive section of the review all studies that met the criteria for type of study, participants, intervention and comparator, regardless of outcomes reported or missing data.

Primary outcomes

- Quality of life (QoL) as measured by validated generic instruments, e.g. Quality of Life Inventory (QOLI) (Frisch 2005); or specific instruments, e.g. for body image, the Body Image Quality of Life Inventory (BIQLI) (Cash 2004); or for sexual life the Sexual Satisfaction Scale for Women (SSS-W) (Meston 2005).
- Satisfaction with change of male to female body characteristics, as measured with validated instruments
- Adverse events specific to hormone therapy, including serious adverse events

Secondary outcomes

- Severity of gender dysphoria/gender incongruence, e.g. as measured with the Utrecht Gender Dysphoria Scale (UGDS) (Schneider 2016)
- Measures of specific body changes, including:
 - * breast size, e.g. by measurement of bust girth;
 - * skin thickness, e.g. by echographic measurement (Laurent 2007);
 - * skin sebum production, e.g. as measured by three-hour sebum collection with absorbent paper (Downing 1981; Giltay 2008; Ezerskaia 2016); and
 - * hair growth, including hair density, diameter, growth rate and anagen/telogen ratio (Giltay 2000; Hoffmann 2013).
- Incidence or severity of depression.

We did not include surrogate outcomes, such as serum hormone levels (e.g. 17-beta-estradiol or testosterone). While these measures can help with monitoring the progress of hormone therapy, they are of little interest of themselves, especially since individuals require varying levels of these hormones to achieve a certain level of feminisation (Gooren 2017).

Search methods for identification of studies

Electronic searches

We searched the following electronic databases for relevant trials up to 19 December 2019 with no restrictions based on language of publication, date of publication, or publication status:

- MEDLINE via PubMed
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Embase
- Biosis Preview
- PsycINFO
- PSYINDEX

Our search strategy is outlined in Appendix 1. We have successfully tested the screening methods for abstracts and titles.

Searching other resources

Had we identified any eligible studies through the electronic searches above we would have searched the reference lists of these in order to find additional relevant studies. We also searched the scientific abstracts of the last two meetings of each of the following organisations:

- American Association of Clinical Endocrinologists
- American Society of Andrology
- Berufsverband der deutschen Endokrinologen (Professional Association of the German Endocrinologists)
- Berufsverband der Frauenärzte e.V. (Professional Association of the Gynaecologists)
- Dachverband Reproduktionsbiologie und Medizin e.V. (Federal Association Reproductive Biology and Medicine)
- Deutsche Gesellschaft für Endokrinologie (German Society for Endocrinology)
- Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (German Society for Gynaecology and Obstetrics)
- Endocrine Society
- European Society of Gynaecological Oncology
- European Thyroid Association
- Nordrhein-Westfälische Gesellschaft für Endokrinologie und Diabetologie (North Rhine-Westphalian Society for Endocrinology and Diabetology)
- Royal College of Obstetricians and Gynaecologists
- Society for Endocrinology
- Society for Gynaecologic Investigation

We also searched the following grey literature databases:

- The New York Academy of Medicine Grey Literature Report (www.greylit.org/)
- OALster (www.oclc.org/oaister.en.html)
- OpenGrey (www.opengrey.eu/)

Finally, in order to identify completed but unpublished or ongoing studies, we searched the following trial registries.

- ClinicalTrials.gov (www.clinicaltrials.gov/)
- metaRegister of Controlled Trials (mRCT; www.controlledtrials.com/mrct/)

- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (www.who.int/trialsearch/)
- Drugs@FDA (www.accessdata.fda.gov/scripts/cder/drugsatfda/)
- European Public Assessment Reports (EPAR; www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp)

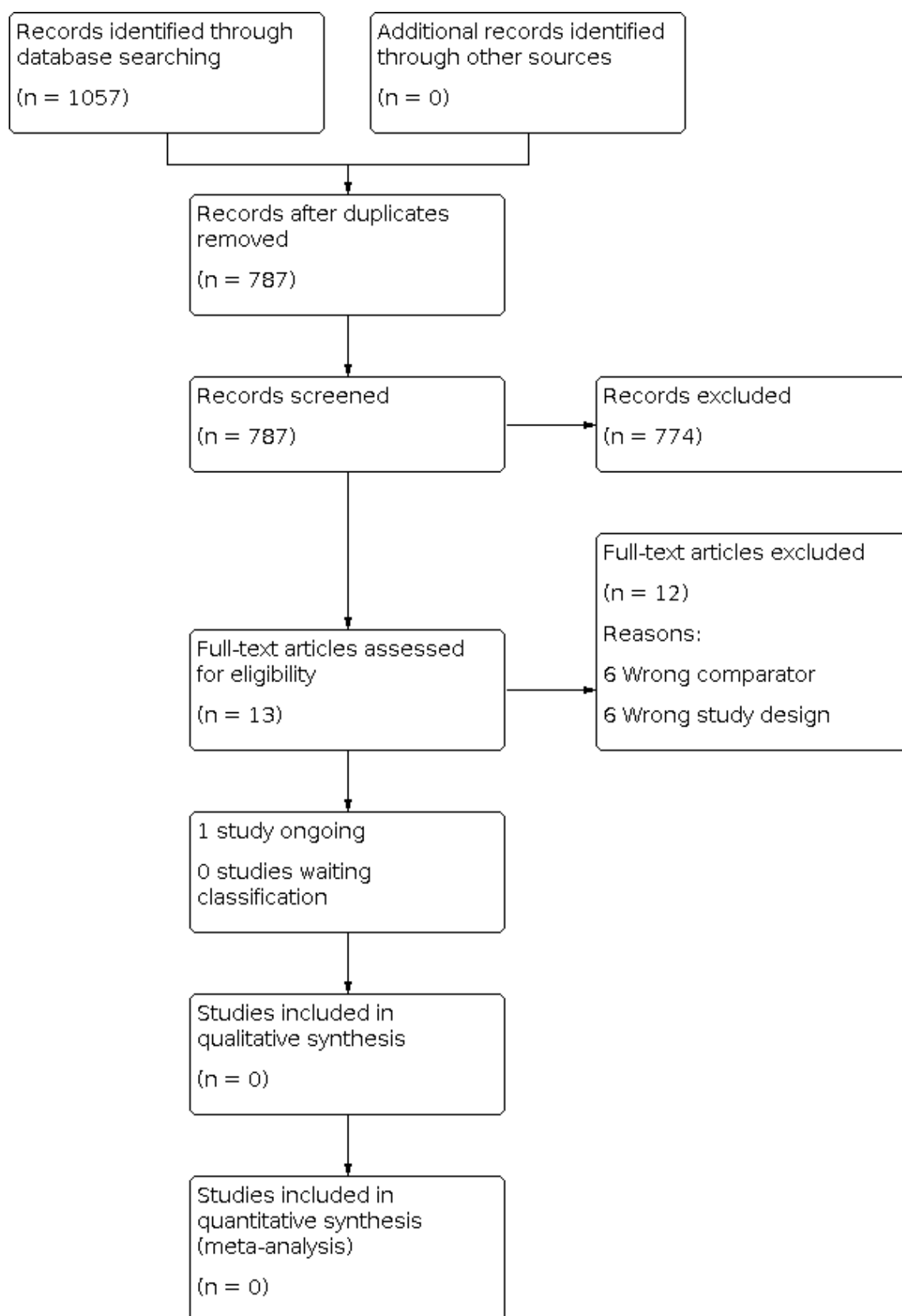
We contacted fifteen manufacturers of hormonal agents and experts in the field to identify unpublished or ongoing trials.

Data collection and analysis

Selection of studies

We used the reference management tool Covidence to identify and remove potential duplicate records of relevant studies (www.covidence.org). Two review authors (AKU and MHE)

independently scanned titles and abstracts of the remaining records to compile a list of potential papers to potentially be included in the review. After this, the same review authors investigated the references in detail (as full text articles or matched records to studies), and categorised these as 'included studies,' 'excluded studies,' 'studies awaiting classification' and 'ongoing studies.' We executed this task in accordance with the criteria provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). If there had been discrepancies or if a consensus could not be reached, a third review author would have adjudicated (CHA). There were no disagreements that could not be thus resolved. Had this been the case, we would have designated the study as 'awaiting classification' and contacted the study authors for clarification. We listed studies excluded during the full text review stage, and documented the reasons for exclusion in [Characteristics of excluded studies](#). We included an adapted PRISMA flow diagram outlining the study selection process (Moher 2009) (Figure 1).

Figure 1. Study Flow Diagram

Data extraction and management

If we had found relevant studies, two review authors (AKU and MHE) would have extracted data from all studies deemed eligible for inclusion independently, with the help of a standardized data extraction form that would have been pilot tested according to Chapter 7 of the *Cochrane Handbook* (Higgins 2011a). We have used Google Spreadsheets to manage all data gathered.

We would have collected data on the following items:

- General information on the study: first author, date of publication, study dates, publication type (full text article, abstract, unpublished), citation.
- Study methods: study design (e.g. parallel, factorial), number of study arms, study setting (single institution, multi-centre national, multi-centre international), study location, and length of follow-up.
- Participant characteristics: study inclusion/exclusion criteria, age (mean/median with range), ethnic distribution, number of participants randomised and included in analysis, participants lost to follow-up.
- Interventions: type of hormonal agents (for example CPA, estradiol, progesterone, spironolactone), dose, administration route, dosing schedule and any other associated therapies. We would have extracted data on the sample size for each intervention group.
- Outcomes: definition and method of assessment for each outcome (including the adverse event classification system used in individual studies), as well as any relevant subgroups. We would have extracted the number of events and participants per treatment group for dichotomous outcomes. We would also extract the mean, standard deviation or median and range, and number of participants per treatment group for continuous outcomes.
- Study funding sources.
- Declarations of potential conflicts of interest reported by study authors.

For each included study, we would have extracted the outcome data relevant for this review, and which would be required for the calculation of summary statistics and measures of variance. If there had been disagreements, we would have resolved them by discussion. If necessary, we would have consulted a third review author (CHA). We provided key information about potentially relevant ongoing studies, including trial identifiers, in the table of [Characteristics of ongoing studies](#). We would have attempted to contact authors of included studies to obtain missing key data if needed.

Assessment of risk of bias in included studies

If relevant studies had been found, two review authors (AKU and MHE) would have examined all included studies to assess risk of bias (assessment of methodological quality) independently. We would have used the Cochrane 'Risk of bias' tool for assessing risk of bias in RCTs, as described in the *Cochrane Handbook* (Higgins 2011b). We would have resolved disagreements by consensus or by consulting a third review author (CHA). Our summary judgement would have included a rating (low, high or unclear risk of bias) for each domain (Higgins 2011b). We would have assessed the risk of bias for the following domains:

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective reporting
- Other bias

We would have evaluated the risks of performance bias (blinding of participants and personnel) and detection bias (blinding of outcome assessment) separately for each outcome.

For any relevant cohort studies we would have used the ROBINS-I tool to assess risk of bias (Sterne 2016). We would have assessed each individual study in accordance with the guidance, documenting the results using a spreadsheet and providing details in 'Risk of bias' tables. We would have documented the reasons for our judgements, and would have included relevant quotations from the full-text articles or from information about the study provided by authors in the notes section of the 'Risk of bias' tables. We would have summarised the risk of bias across domains for each primary outcome in every included study, as well as across studies and domains for each primary outcome.

Measures of treatment effect

Dichotomous data

We planned to summarise dichotomous data using risk ratios (RRs), reported with 95% confidence intervals (CIs).

Continuous data

For continuous outcomes with a standard measure, we would have summarised the obtained data as mean differences (MDs) with 95% CIs. For continuous outcomes without a standard measure, we would have summarised data as standardized mean differences (SMDs) with 95% CIs. Alternatively, if the mean value and variance were missing, we would have estimated them using the methods described in Hozo 2005, which allows estimations for mean value and variance of a sample when only the median, range and size of the sample are known. We would also have considered the guidance in the *Cochrane Handbook* where appropriate (Higgins 2011c).

Unit of analysis issues

We planned to treat recurring events in individual participants as single events occurring in one participant (e.g. three episodes of major depressive disorder in one participant would have been recorded as one participant with major depressive disorder). We did not expect to include studies with interventions delivered at the cluster level.

Dealing with missing data

For studies with missing data, we would have followed the recommendations of the *Cochrane Handbook* (Higgins 2011d). We would have collected dropout rates for each study group and would have reported these in the 'Risk of bias' table. Our preferred option would have been to contact study authors in cases of missing data or statistics that were not due to participant dropout (e.g. missing statistics such as standard deviation (SD)). If missing outcome data were not provided, then we would have attempted to impute

data where possible and appropriate, and conduct sensitivity analyses to assess the effect of this on the analysis. However, where imputation is not appropriate, we would not have included the study in the respective meta-analysis, and would have discussed the potential impact of this in the text of the review. In the case of participants lost to follow-up, we would have performed meta-analyses on an intention-to-treat basis. We would have performed sensitivity analyses, excluding studies with missing outcome data, to evaluate the impact of missing data. We would have discussed the potential impact of missing data on review findings in the 'Discussion' section of the full review, using a summary table if appropriate.

Assessment of heterogeneity

We would have compared the characteristics of included studies to identify heterogeneity of content or methodology, and to determine the feasibility of performing a meta-analysis. We would have deemed meta-analyses unsuitable in cases where there was substantial content-related or methodological heterogeneity across studies. Instead, we would have used a narrative approach to data synthesis. Had meta-analyses been deemed appropriate, we would have assessed statistical heterogeneity by visually inspecting the scatter of individual study effect estimates on forest plots and by calculating the I^2 statistic (Higgins 2011c), which gives the percentage of variability in effect estimations that can be attributed to heterogeneity rather than to chance. We would have considered an I^2 of more than 50% to represent substantial heterogeneity. In the case of statistical heterogeneity, we would have conducted the prespecified subgroup and sensitivity analyses described below to investigate the source.

Assessment of reporting biases

If we had included 10 or more studies that investigated the same outcome, we would have used funnel plots to assess small-study effects and publication bias. Given that several explanations are possible for funnel plot asymmetry, we would have interpreted results carefully (Sterne 2011).

Data synthesis

Had we identified any eligible studies, we would have provided a narrative summary of the included studies. We would also have conducted meta-analyses of RCTs for all relevant outcomes, where possible, using data from studies that 1) compared the actual hormone therapy-relevant agents or combinations of agents to placebo, and 2) compared the actual hormone therapy-relevant agents or combinations of agents to other hormone therapy-agents or combinations of agents. Studies comparing two variations on the intervention would have been pooled separately to studies comparing the intervention to placebo. However, if there had been significant variability in the definition of outcomes across trials, we would have decided not to pool data.

Had we conducted meta-analyses, we would have used the Mantel-Haenszel approach to combine dichotomous data and calculate RRs with 95% CIs (Higgins 2011c). For continuous outcomes (e.g. quality of life) we would have calculated MDs or SMDs, with 95% CIs, using the inverse variance approach. Had studies reported the same outcome measure but some studies had reported data on the change from baseline (e.g. mean values and standard deviations) and others for final measurements of outcomes, they would have been placed in subgroups in the meta-analysis and

pooled according to guidance in the *Cochrane Handbook* (Higgins 2011c).

For meta-analyses, we would have used a random-effects model, expecting the true effects to be related, but not the same, across all studies. We would have interpreted random-effects meta-analyses with due consideration of the whole distribution of effects, ideally by presenting a prediction interval (Higgins 2009). A prediction interval specifies a predicted range for the true treatment effect in an individual study (Riley 2011). In addition, we would have performed statistical analyses according to the statistical guidelines contained in the *Cochrane Handbook* (Higgins 2011c).

We would have summarised outcome data from cohort studies (e.g. change scores) narratively.

Subgroup analysis and investigation of heterogeneity

Wherever possible, we would have considered subgroup analyses that are structured by the following characteristics.

- Type of application of intervention (oral, transdermal, intramuscular, subcutaneous)
- Orchiectomy before or during hormone therapy

The justification for these analyses is as follows. Pharmacokinetic mechanisms lead to significant differences in the absorption and metabolism of an active substance depending on the type of application. Therefore, we would, if possible, have formed appropriate subgroups based on the application method of the intervention. Also, patients who have undergone an orchiectomy could have different outcomes than those patients without orchiectomy (Defreyne 2017).

Sensitivity analysis

We would have conducted sensitivity analyses to investigate any potential effect of removing studies judged to be at high risk of bias from meta-analyses. We would have classified studies as being at high risk of bias overall if one or more domains were judged to be at high risk. If appropriate, we would also have conducted sensitivity analyses excluding studies with missing outcome data, or where missing data have been imputed by the review author team. We would also have conducted a sensitivity analysis to compare a fixed-effect model to a random effects model where the studies in a meta-analysis appear more homogeneous than expected.

Summary of findings and assessment of the certainty of the evidence

Following standard Cochrane methodology, had we identified any included studies, we would have created a 'Summary of findings' table for all three primary outcomes. Also following standard Cochrane methodology, we would have used the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome, and to draw conclusions about the quality of evidence within the text of the review.

RESULTS

Description of studies

Results of the search

We conducted our searches on 18 January 2019 and updated them on 19 December 2019. Through the database searches, we identified a total of 1057 references. After removing duplicates, we screened the titles and abstracts of 787 references. Through this screening, we identified 13 studies to assess as full text articles. We fully inspected these articles, and excluded 12 studies. The remaining study was still ongoing. Therefore, we did not include any studies in this review (Figure 1).

Of the manufacturers and experts in the field whom we contacted, 15 responded but did not report any additional studies.

Included studies

None of the reports retrieved met the inclusion criteria for this review. Suggestions for future studies are given in Table 1

Excluded studies

We excluded all 12 of the full-text articles that we had assessed for eligibility, either because they used an ineligible comparator or because they used an ineligible study design. See [Characteristics of excluded studies](#) for further details.

Ongoing studies

We identified one ongoing RCT in Thailand, comparing spironolactone with CPA ([Krasean 2019](#)). This study started in April 2019. We describe this study in [Characteristics of ongoing studies](#).

Risk of bias in included studies

As no studies met the inclusion criteria, it was not possible to assess risk of bias.

Effects of interventions

As no studies met the inclusion criteria, we were unable to calculate any effects of the interventions.

DISCUSSION

Summary of main results

No study met the inclusion criteria for this review. A total of 13 potentially eligible studies were identified, but ultimately all but one was excluded after we assessed the full text articles. The one remaining RCT is ongoing, and we are awaiting its publication ([Krasean 2019](#)). We conducted a comprehensive search to identify eligible studies for inclusion in this review. Despite more than four decades of ongoing efforts to improve the quality of hormone therapy for women in transition, we found that no RCTs or suitable cohort studies have yet been conducted to investigate the efficacy and safety of hormonal treatment approaches for transgender women in transition.

Overall completeness and applicability of evidence

The evidence is incomplete because no studies met the inclusion criteria for the review. This lack of studies shows a gap between current clinical practice and clinical research, which has

been repeatedly emphasised ([Hembree 2009](#); [Hembree 2017](#)). If hormone therapy is highly valued in the treatment of gender dysphoria ([Hembree 2009](#); [WPATH 2011](#); [Hembree 2017](#)), then this raises the question: why are there no RCTs or appropriate cohort studies for this clinical condition? There is also an ethical need for research into the efficacy and safety of hormone therapy, particularly comparing combination therapy with CPA/estradiol and spironolactone/estradiol to monotherapy with estradiol alone. In view of the reported but rather alarming side-effect profiles of CPA and spironolactone in other populations ([De Bastos 2014](#); [Khan 2016](#); [PG12 2019](#)), long-term clinical studies that aim to achieve adequate outcomes are urgently needed for the population of transgender women in transition. The lack of reliable data on hormone therapy for transitioning transgender women should encourage the development of well-planned RCTs and cohort studies to evaluate widespread empirical practice in the treatment of gender dysphoria.

The most common reason for the exclusion of studies from this review was the lack of a control group. We excluded some studies because they did not meet the eligibility requirements for study design (e.g. case series or case-control studies). Further, interventions were not clearly defined.

Among guideline developers in the field of transgender medicine, it has been discussed in recent years why the available evidence remains limited ([Deutsch 2016a Reilly 2019](#)). [Deutsch 2016a](#) has identified three main reasons, which they believe have hindered the development of evidence based healthcare guidelines. Firstly, a lack of research funding and institutional stigma means that the evidence currently centres around less robust study designs, such as retrospective studies, case series, and individual case reports ([Bockting 2016 Reisner 2016a](#)); secondly variation in the collection of gender identity data in observational data sets makes it difficult to identify relevant populations and monitor their health outcomes ([Deutsch 2013 Bauer 2009](#)); and finally, academic programmes focused on transgender medicine are in their infancy and few exist ([Reisner 2016b](#)), meaning there is a general lack of research and training on this topic.

Against this background, methodological problems such as inconsistent and missing comparison groups, uncontrolled confounding factors, small sample size, short follow-up time and difficulties in recording and evaluating a broad spectrum of health outcomes (physical and mental health, social functioning and QoL) have become apparent in hormone therapy ([Deutsch 2016b](#)). The performance of RCTs is controversial, especially with regard to placebo studies, and ethical and methodological objections have been raised (e.g. violation of the principle of equipoise, [Miller 2003](#)). However, the positive research potential of active-controlled RCTs is acknowledged, in order to compare different types, dosages and methods of administration of active treatments. Overall, there is a trend in the discussion to favour not only RCTs and quasi-RCTs, but also high-quality cohort studies conducted in a network of health centres, hospitals and practices ([Deutsch 2016a](#); [Deutsch 2016b](#)).

Quality of the evidence

We could not appraise the quality of the evidence because no studies met our review's inclusion criteria.

Potential biases in the review process

We consider our search to have been consistent and comprehensive (including the fifteen contacts with manufacturers and experts in the field). At each stage, the review authors independently applied the inclusion criteria before comparing their judgements. Reliability testing was performed in the screening phase. Even though we were unable to test for publication bias, we think it is unlikely that there are studies that have been conducted but remained unpublished. The experts in the field we interviewed believed that there was a general lack of research activity by treatment manufacturers, and considered it very likely that no phase IV studies have ever been conducted in this population. For example, one expert stated that there was probably "nothing to be kept secret."

Agreements and disagreements with other studies or reviews

There are currently no systematic reviews in the Cochrane Library that evaluate the effectiveness of hormone therapy for transgender women in transition, nor are there systematic reviews that evaluate the clinical and economic impact of hormone therapy on transgender women in transition. The Endocrine Society's 2009 and 2017 guidelines addressed endocrine treatment of gender-dysphoric/gender-incongruent persons (Hembree 2009; Hembree 2017). The literature search included in these guidelines did not identify any RCTs of hormone therapy in transitioning transgender women. In the context of the preparation of UK National Health Service (NHS) guidelines (PG12 2019), the NHS Guideline Panel also found no RCTs. However, PG12 2019 includes a recommendation for the prescription of hormone therapy for transitioning transgender women.

Of the potentially relevant studies we excluded, some reported on relevant questions. Asscheman 2011 focused on the important outcome of mortality. Fisher 2016 investigated the important relationship between hormone therapy-related body changes and psychobiological well-being. Giltay 2000 focused on body related outcomes such as hormone therapy's effects on the skin (hair growth rate, density, and shaft diameter by image analysis; and sebum production). Toorians 2003 focused on the outcomes of different interventions (estradiol alone compared with combination therapy estradiol and antiandrogens). Miles 2006 was based on a cross-over design with the intention of comparing groups of individuals on and off oestrogen. Due to the reported deficits, we excluded these studies, although they addressed important questions.

AUTHORS' CONCLUSIONS

Implications for practice

We found insufficient evidence to determine the efficacy or safety of hormonal treatment approaches (estradiol alone or

in combination with cyproterone acetate or spironolactone) for transgender women in transition. The evidence is very incomplete, demonstrating a gap between current clinical practice and clinical research.

Implications for research

This systematic review has shown that well-designed, sufficiently robust randomised controlled trials (RCTs) and controlled-cohort studies do not exist, and are needed, to assess the benefits and harms of hormone therapies (used alone or in combination) for transgender women in transition. The following questions should be addressed via RCTs and cohort studies:

1. What are the short-, medium-, and long-term effects (including adverse effects, benefits, and prognoses) of estradiol therapy alone, as opposed to combination therapy using estradiol together with cyproterone acetate or spironolactone?
2. What is the short-, medium-, and long-term clinical efficacy of hormone therapy when applied orally, transdermally, and intramuscularly?

Table 1 presents design components that we suggest could be used in future studies. Studies should be structured and reported according to the CONSORT Statement or the STROBE Statement in order to improve the quality of reporting on efficacy and to obtain better reports on harms in clinical research (von Elm 2007; Schulz 2010). There is an urgent need for research in this area, not least for ethical reasons.

We will include non-controlled cohort studies in the next iteration of this review, as this review has demonstrated that this is the highest quality evidence currently available in the field. We will take methodological limitations into account when doing so.

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CHARACTERISTICS OF STUDIES**Characteristics of excluded studies** [ordered by study ID]

Study	Reason for exclusion
Asscheman 2011	Mortality rates in transgender people receiving long-term cross-sex hormones. A cohort study. Adequate controls are missing. Interventions are not clearly defined
Colizzi 2015	Increased prevalence of metabolic syndrome among individuals with gender dysphoria treated by cross-sex hormonal treatment. Study without adequate comparator group.
Figuera 2018	Hormone therapy has been associated with changes in bone and lean/fat mass. This study assessed bone mineral density, appendicular lean mass, and total fat mass in transwomen undergoing cross-sex hormone therapy. Study without adequate comparator group.
Fisher 2014	This study aimed to assess differences in body uneasiness and psychiatric symptoms between gender dysphoria clients taking hormone therapy and those not taking hormones (no hormone therapy). A second aim was to assess whether length of hormone treatment and daily dose provided an explanation for levels of body uneasiness and psychiatric symptoms. Cross-sectional design.
Fisher 2016	The objective of the study was to assess whether hormone therapy-related body changes affect psychobiological well-being in gender dysphoria. Study without adequate comparator group.
Giltay 2000	Hormone therapy effects on the skin (hair growth rate, density, and shaft diameter by image analysis; and sebum production) of transsexual patients receiving cross-sex hormones. It is a case series, adequate controls are missing.
Haraldsen 2005	Hormone therapy effects on cognitive performance. Study without adequate comparator group.
Haraldsen 2007	The effects of cross-sex hormones on bone metabolism (bone mineral density, total body fat, total lean body mass) in patients with early onset gender identity disorder. Study without adequate comparator group.
Miles 2006	The study was designed to examine associations between oestrogen and cognition (memory, including visual, spatial, object and location memory, other cognitive abilities that show reliable sex

Study	Reason for exclusion
	differences, including verbal and visual-spatial abilities, and mood variables). The cross-over design used was comparative, but did not used randomization or quasi-randomisation.
Schlatterer 1998	This follow-up study was carried out to validate the effectiveness of cross-gender hormone therapy embedded in a multistep treatment concept for transgender patients. Study without adequate comparator group. This study lacks adequate controls.
Toorians 2003	To find an explanation for the different thrombotic risks of oral ethinyl estradiol and transdermal 17-beta-estradiol use, the researchers compared the effects of treatment of male-to-female transgender people with cyproterone acetate only, and with cyproterone acetate in combination with transdermal 17-beta-estradiol, oral ethinyl estradiol, or oral 17-beta-estradiol on a number of haemostatic variables. There is no adequate control group.
Van Goozen 1995	Effects of sex hormones to the establishment of gender differences in behaviour, a large battery of tests on aggression, sexual motivation and cognitive functioning was administered twice: shortly before and three months after the start of cross-sex hormone treatment. The study does not have an adequate comparator group.

Characteristics of ongoing studies *[ordered by study ID]*

[Krasean 2019](#)

Study name	Anti-androgenic effects comparison between cyproterone acetate and spironolactone in transgender women: a randomised controlled trial (Trial ID: TCTR20190404001)
Methods	Allocation: randomised Study design: randomised controlled trial Control: active Study endpoint classification: efficacy study Intervention model: Parallel Number of arms: 2 Masking: double blind (Masked roles: participant caregiver, investigator) Primary purpose: treatment Study phase: phase 4
Participants	Gender: male Age limit: minimum 18 years: maximum 40 years Condition: Gender dysphoria patients diagnosed from DSM V Male to female transgender Not undergone orchidectomy No psychological disease or mental disability
Interventions	Arm 1: Intervention name: cyproterone acetate Type: active comparator

Krasean 2019 (Continued)

	Classification: drug Descriptions: participants (gender dysphoria patients) will receive estradiol valerate (4 mg daily) combined with cyproterone acetate (25 mg daily) for cross-sex hormone treatment. Arm: 2 Intervention name: spironolactone Type: experimental Classification: drug Descriptions: participants (gender dysphoria patients) will be received estradiol valerate (4 mg daily) combined with spironolactone (100 mg daily) for cross-sex hormone treatment.
Outcomes	Primary outcome(s): Outcome name: testosterone level Measurement: Electrochemiluminescent Immunoassay (ECLIA) of total testosterone level Time point: three months after intervention Safety issue: no Key secondary outcomes: Outcome name: physical and metabolic changes Measurement: physical examination, metabolic profile parameters Time point: three months after intervention Safety Issue: no
Starting date	April 3, 2019 (estimated end date: June 16, 2020)
Contact information	Contact: Krasean Panyakhamlerd Degree: Assoc. Prof. Phone: 0926536415 Email: krasean@hotmail.com Postal Address: 1873 Rama 4 Road, Patumwan State/Province: Bangkok Postal Code: 10400 Country: Thailand
Notes	Source(s) of monetary or material supports: Ratchadapisek Sompoch Fund, Faculty of Medicine, Chulalongkorn University Declarations of interest not reported

ADDITIONAL TABLES

Table 1. Suggested design of future studies

Methods	RCT or controlled cohort study
Participants	Transgender women experiencing gender dysphoria, in transition N* Age: from the age of 16 years
Intervention	• Antiandrogens (cyproterone acetate or spironolactone) and estradiol • Antiandrogens (cyproterone acetate or spironolactone) alone • Estradiol alone All types of administration: oral, sublingual, transdermal, subdermal and intramuscular. For estradiol and bioidentical 17-beta-estradiol, as well as synthetic derivatives.
Comparator	Any of the active interventions listed above
Outcomes	Primary outcomes • Quality of life (QoL) • Satisfaction with change of male to female body characteristics, • Adverse events specific to hormone therapy, including serious adverse events
Notes	* Size of study with sufficient power to detect a ~ 10% difference between the two groups for primary outcome

APPENDICES

Appendix 1. OvidSP search strategy

Search	Query
#1	(transsexual* OR transgender OR "gender dysphoria" OR transident* OR "trans women" OR "trans woman").mp.
#2	("cyproterone acetate" OR CPA OR androcur).mp. or cyproterone Acetate/
#3	(spironolactone OR Aldactone OR Jenaspiron OR Osyrol OR Spirobene OR Verospiron OR Xenalon).mp. or spironolactone/
#4	(estradiol* OR oestradiol* OR estrifam OR gynocadin OR neofollin OR lenzetto).mp. or Estradiol/
#5	2 OR 3 OR 4
#6	1 AND 5

HISTORY

Protocol first published: Issue 10, 2018

Review first published: Issue 11, 2020

CONTRIBUTIONS OF AUTHORS

All authors contributed to the Abstract, Background, Methods, Results, Discussion, and Authors' conclusions. Claudia Haupt, Alexia Kutschmar and Miriam Henke conducted the study selection.

DECLARATIONS OF INTEREST

Claudia Haupt declares no competing interest.

Miriam Henke declares no competing interest.

Alexia Kutschmar declares no competing interest.

Birgit Hauser (BH) declares no competing interest. BH is a clinical practitioner in private practice, who also prescribes hormone therapy.

Sandra Baldinger declares no competing interest.

Sarah Rafaela Saenz declares no competing interest.

Gerhard Schreiber declares no competing interest.

None of the review authors' incomes depends on the prescription of drugs. The review authors did not receive any financial support for this project, but paid for all related expenses themselves. They worked voluntarily and free of charge.

INDEX TERMS

Medical Subject Headings (MeSH)

Androgen Antagonists [*therapeutic use]; Drug Therapy, Combination [methods]; Estradiol [*therapeutic use]; Estrogens [*therapeutic use]; Placebos [therapeutic use]; Sex Reassignment Procedures [*methods]; *Transgender Persons

MeSH check words

Female; Humans; Male

- feminizing surgery in the Swedish National Treatment Recommendations. *Arch Sex Behav* 2016; 45:1879–1880
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41. Ring A, Malone M: Confounding effects on mental health observations after sex reassignment surgery. *Am J Psychiatry* 2020; 177:768–769
42. Bränström R, Pachankis JE: Toward rigorous methodologies for strengthening causal inference in the association between gender-affirming care and transgender individuals’ mental health. *Am J Psychiatry* 2020; 177:769–772

Correction to Bränström and Pachankis

After the article “Reduction in Mental Health Treatment Utilization Among Transgender Individuals After Gender-Affirming Surgeries: A Total Population Study” by Richard Bränström, Ph.D., and John E. Pachankis, Ph.D. (doi: 10.1176/appi.ajp.2019.19010080), was published online on October 4, 2019, some letters containing questions on the statistical methodology employed in the study led the *Journal* to seek statistical consultations. The results of these consultations were presented to the study authors, who concurred with many of the points raised. Upon request, the authors reanalyzed the data to compare outcomes between individuals diagnosed with gender incongruence who had received gender-affirming surgical treatments and those diagnosed with gender incongruence who had not. While this comparison was performed retrospectively and was not part of the original research question given that several other factors may differ between the groups, the results demonstrated no advantage of surgery in relation to subsequent mood or anxiety disorder-related health care visits or prescriptions or hospitalizations following suicide attempts in that comparison. Given that the study used neither a prospective cohort design nor a randomized controlled trial design, the conclusion that “the longitudinal association between gender-affirming surgery and lower use of mental health treatment lends support to the decision to provide gender-affirming surgeries to transgender individuals who seek them” is too strong. Finally, although the percentage of individuals with a gender incongruence diagnosis who had received gender-affirming surgical treatments during the follow-up period is correctly reported in Table 3 (37.9%), the text incorrectly refers to this percentage as 48%. The article was reposted on August 1, 2020, correcting this percentage and including an addendum referencing the postpublication discussion captured in the Letters to the Editor section of the August 2020 issue of the *Journal* (1).

1. Kalin NH: Reassessing mental health treatment utilization reduction in transgender individuals after gender-affirming surgeries: a comment by the editor on the process (letter). *Am J Psychiatry* 2020; 177:765



Letters to the Editor



Reassessing Mental Health Treatment Utilization Reduction in Transgender Individuals After Gender-Affirming Surgeries: A Comment by the Editor on the Process

On October 4, 2019, we published an article by Bränström and Pachankis in which it was reported that observed reductions in mental health treatment utilization lent support to the decision to provide gender-affirming surgeries to those who seek them (1). After this article's publication, we received several letters calling into question the statistical analyses employed and the conclusions drawn from said analyses. These letters follow this comment (2–8).

We enlisted the services of a statistical reviewer to look again at the article as well as the letters we received. We then sent the letters we received and the results of this statistical review, which called for a matched-pairs analysis, to the original authors. The study authors complied with the request to perform an additional analysis, as presented in their letter response (9).

We sent the original letters, statistical review, and author response to a second statistical reviewer. The response from this consultation convinced us that, given that the study used neither a prospective cohort design nor a randomized controlled trial design, the conclusion that “the longitudinal association between gender-affirming surgery and reduced likelihood of mental health treatment lends support to the decision to provide gender-affirming surgeries to transgender individuals who seek them” was too strong. In the August 2020 issue of the *Journal*, we are publishing a correction to this effect and including an addendum to the article pointing to this postpublication discussion and process, both of which were composed with contributions and approval from the original article authors.

We thank the letter writers, statistical reviewers, and the original study authors—as well as the editorialist we invited to place this study's findings in context (10)—for helping us to make clear to our readers and for the literature what the article shows and what still remains to be investigated in future research.

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Methodological Shortcomings Undercut Statement in Support of Gender-Affirming Surgery

TO THE EDITOR: The article by Bränström and Pachankis (1) has the stated aim “to ascertain the prevalence of mood and anxiety disorder health care visits and antidepressant and anxiolytic prescriptions in 2015 as a function of gender incongruence diagnosis and gender-affirming hormone and surgical treatment in the entire Swedish population.” The authors conclude that “the longitudinal association between gender-affirming surgery and reduced likelihood of mental health treatment lends support to the decision to provide gender-affirming surgeries to transgender individuals who seek them.” In support of this claim, the authors report that the time since “last gender-affirming surgery” (in 2005–2014) was associated with reduced “mental health treatment” (a combined variable of outpatient visits with a diagnosis of a mood or anxiety disorder and/or prescriptions for antidepressants or anxiolytics) during 2015 (adjusted odds ratio=0.92, 95% CI=0.87–0.98). The authors have also

shown that the group of people diagnosed with gender incongruence have a dramatically worse overall mental health outcome than the general population, which is, in fact, the answer to their stated aim and research question, but this finding is not even referred to in the title or in the Conclusions section of the article.

In view of the claim that surgery was shown to be an efficient treatment for gender incongruence, the following issues have to be raised:

1. Variables, hypotheses, and analytical strategies were not described pre hoc. Adequate power analyses and corrections for multiple comparisons were not provided.
2. The article is vague or noninformative with respect to key aspects. Biological sex ratios are not provided. Surgeries for complications or even unrelated surgeries (e.g., in the skin or the larynx) may have been included. Lithium and atypical antipsychotic medications were not included as treatments for mood disorders, while a histamine blocker such as hydroxyzine, which is mainly used for non-mental health problems, was. Outpatient visits for mood and anxiety disorders were included as “mental health treatment” but not care for sleeping disorders, substance-related disorders, major mental disorders, or any inpatient psychiatric treatment.
3. The nonnormal distribution of data, known secular changes, age effects, or people who left Sweden and moved abroad, died from suicide or other causes, or had surgery to desist were not considered in the interpretation of the analyses.

As the article stands, we actually have no way of knowing whether the four reported analyses of purported treatment effects (time elapsed since start of hormones OR since last surgery BY outpatient mental health treatment OR suicide attempt-related hospitalization), one of which was statistically significant by a small margin, were the first analyses made or the final setup chosen for publication after a “fishing expedition” in the database.

These methodological shortcomings preclude any statement on the suitability of early surgery in persons seeking treatment for gender noncongruence based on the results presented in this article.

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Gender-Affirmation Surgery Conclusion Lacks Evidence

TO THE EDITOR: We have concerns regarding severe shortcomings in the study by Bränström and Pachankis (1) that call into question the authors' conclusion that it “provides timely support for policies that ensure coverage of gender-affirming treatments.”

This study covered outcomes only for calendar year 2015 for all individuals living in Sweden on December 31, 2014. The retrospective metric of “time since last gender-affirming surgery” in Figure 1 in the article is easily misinterpreted as a prospective 10-year follow-up that did not occur and leaves open the question of number and type of prior surgeries.

The 2,679 individuals diagnosed with gender incongruence in Sweden is a full order of magnitude below prevalence expectations from DSM-5. Table 3 in the article indicates that 38% of these individuals had any kind of gender-affirming surgery, but only 53% of those had surgery of reproductive organs. Given that such treatment in Sweden is free, ample loss to follow-up is implied.

Measured outcomes were limited to “mood and anxiety disorder health care visits, antidepressant and anxiolytic prescriptions, and hospitalization after a suicide attempt.” This selection excludes completed suicides, suicide attempts without subsequent hospitalization, health care visits and hospitalizations for other medical or psychological issues still related to gender-affirming surgeries, individuals refusing treatment, and individuals choosing self-medication with alcohol or illicit substances. Again, significant loss to follow-up must be considered before declaring success.

Dhejne's cohort study of 324 persons in Sweden undergoing sex-reassignment surgery used 30 years of data, population controls, and matching by birth year, birth sex, and reassigned sex (2). Through the Hospital Discharge Register, the authors evaluated discharge diagnoses, external causes of morbidity and mortality, and surgical procedure codes. Compared with the general population, patients who had sex reassignment surgery had 19 times the rate of completed suicide, almost three times the rate of all-cause mortality, nearly three times the rate of inpatient psychiatric care, and close to five times the rate of suicide attempts.

These important findings could have been updated to the current period, given the sharp rise in adolescent case presentations, use of puberty blockers, and changes in cross-sex hormones from agents like ethinyl estradiol to 17 β -estradiol.

For those whose last surgery was 10 or more years earlier, how many completed suicide, died of other causes, or left Sweden prior to study initiation? A drop in hospitalizations for suicide attempts alone provides a very incomplete picture. When the data for such findings are accessible in the Swedish national registers, this omission is glaring.

The lack of control subjects, the limited 1-year time frame, and the avoidance of examining completed suicides and psychiatric hospitalizations are substantial study shortfalls.

The study supports only weak conclusions about psychiatric medication usage and nothing decisive about suicidality. In overlooking so much available data, this study lacks the evidence to support its progender-affirmation surgery conclusion.

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Study of Transgender Patients: Conclusions Are Not Supported by Findings

TO THE EDITOR: The study of transgender individuals by Bränström and Pachankis claims to demonstrate a reduction in mental health treatment utilization after gender-affirming surgery but, in fact, demonstrates no such thing (1).

The only result they present that they claim is statistically significant is that there is an association between years since last gender-affirming surgery and recent mental health treatment (adjusted odds ratio=0.92, 95% CI=0.87–0.98). This result makes no sense as it stands because analysis of a quantitative measure against an outcome does not produce an odds ratio. Presumably, the authors must mean that each year since surgery is associated with an odds ratio of 0.92. There are also discrepancies between the data discussed in the text and in the tables. For example, the authors quote the percentage of patients with gender incongruence who received no treatment as 29% in the text but 29.6% in Table 3 and, more importantly, the percentage of patients who received surgery as 48% in the text but only 38.0% in the table. However, the key statistical criticism is that they have failed to carry out standard corrections for multiple testing. As they tested two interventions, hormone treatment and surgery, against two outcomes, mental health treatment and suicide attempts, they performed four tests. Because the upper confidence interval that they quote is very close to 1, it is obvious that if appropriate correction for multiple testing had been applied, then none of the results would have been deemed significant.

When one views the data on which these analyses are based, as presented in Figure 1 in the article, some very clear features emerge. First, there is obviously no general correlation between the outcomes and time since surgery. Rather, a spike in suicide attempts is seen in the year after surgery (in 2.8% of the patients), which falls off over the next 1–2 years, and to a lesser extent, there is also a spike in the proportion of patients receiving mental health treatment in the first year, going up to 45.3%. There is also a low rate of mental health treatment among patients who received surgery 10 or more years earlier. This may reflect the fact that in the past, patients with mental health problems would have been less likely to be offered surgery.

The study confirms the strong association between psychiatric morbidity and the experience of incongruity between gender identity and biological sex. However, the study does not demonstrate that either hormonal treatment or surgery has any effect on this morbidity. It seems that the main message of this article is that the incidence of mental health problems and suicide attempts is especially high in the year after the completion of gender-affirming surgery and that increased support in this period might be indicated.

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Calling Into Question Whether Gender-Affirming Surgery Relieves Psychological Distress

TO THE EDITOR: The study by Bränström and Pachankis (1) shows a reduction in mental health treatments and hospitalization after suicide attempts with increased time after masculinizing or feminizing surgeries.

The data presented in Figure 1 in the article support findings from previous studies showing that transgender individuals have baseline mental health distress that is higher than that of the general population, but it is not possible to conclude from these data whether gender-affirming surgery relieves that distress.

According to the study, mental health utilization rates were highest in the perioperative period. However, the data also could be interpreted as showing that masculinizing or feminizing surgeries were the actual cause of increased mental health utilization. Surgery is a known risk factor for the development of depression (2) and may have caused a

deterioration in mental health in a population of individuals who already had more psychological distress, which abated with time since surgery. It is just as possible that mental health improved as individuals had fewer surgeries.

After the initial 11% drop in mental health visits in the first year after surgery, there was very little change in mental health visits (5.6% over 9 years), and there was a further 11% fall in the ≥ 10 -year group. It is not clear what caused the reduction in the two markers for mental health distress past the 10-year mark. Loss to follow-up, death from suicide of the most psychologically distressed individuals, or death from cardiovascular disease, all known to be increased in the transgender population, could have falsely skewed the ≥ 10 -year data. Comparisons with a control group would be best to answer these questions.

In addition, there are only 19 people in the ≥ 10 -year group who underwent gender-affirming surgery. A total of 21.1% of them received mental health treatment, which is only four people. This means that a single mental health utilization event in either direction would change the calculated rate of utilization by 5%. However, the assertion that gender-affirming surgeries reduce mental health visits by 8% is highly dependent upon this sudden drop in rates in the ≥ 10 -year group of only 19 people.

Finally, no information is given about the composition of the year 1 and ≥ 10 -year groups, but given the changing epidemiology of gender dysphoria in Sweden (3), the year 1 group likely included a higher percentage of younger natal females than the ≥ 10 -year group, which likely had more older natal males, making comparisons between the year 1 and ≥ 10 -year groups problematic.

Because of the limitations in the study design, it is not possible to determine the cause of the differences in mental health service utilization or whether true reductions in psychological distress actually occurred. Therefore, the authors' conclusion that the results of their study should be interpreted to support policies that provide gender-affirming surgeries cannot be supported.

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The Effect of Gender-Affirming Treatment on Psychiatric Morbidity Is Still Undecided

TO THE EDITOR: In this issue of the *Journal*, Bränström and Pachankis study mental health treatment and suicide attempts in persons diagnosed with gender dysphoria in Sweden (1). Their claim that the study shows that gender-affirming treatment reduces the risk of mental health treatment and suicide attempts is misleading because the study design is flawed.

The authors first found what was already known (2): the rate of psychiatric morbidity is much higher in persons with gender dysphoria compared with the general population. The authors then explored if the risk for mental health treatment changes as a function of years since starting hormonal treatment. They find no effect (odds ratio=1.0), but they do find a trend toward increased risk of suicide attempts as a function of years since starting hormonal treatment. In their key analysis, allegedly showing that gender-affirming surgery decreases risk for psychiatric treatment and suicide attempts, they relate these negative outcomes to the number of years since surgery. Contrary to what the authors repeatedly claim, they do not employ a longitudinal design but conduct a retrospective analysis unfit for their research question.

First, the authors include only persons who were alive in 2014. That means that those who died by suicide before 2014—and hence were at highest risk for suicide attempt—are excluded and confound the results. Second, any analysis starting with a negative event is bound to find a decreased risk for related negative outcomes with increasing time after the event. To exemplify this point, the rate of antidepressant treatment would decrease with time after a suicide attempt. This does not mean that suicide attempts cause a decrease in risk of antidepressant treatment; it is merely a case of regression toward the mean. Third, persons undergoing gender transition have, by definition, contact with mental health services in Sweden. After the transition, persons are followed up by endocrinologists and sometimes general practitioners; only those with persistent mental health issues are followed in psychiatric care. The authors' finding of lower rates of mental health treatment with increasing time after surgery is therefore not only a case of regression toward the mean, but it also follows from the standards of care and is not a proxy for improved mental health.

Because the authors do not present data prior to gender-affirming surgery, the study is uninformative with regard to the effects on psychiatric morbidity. Moreover, the authors miss the one conclusion that can be drawn: that the peri-operative transition period seems to be associated with high risk for suicide attempt. Future research should use properly designed observational studies to answer the important question as to whether gender-affirming treatment affects psychiatric outcomes.

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Gender-Corrective Surgery Promoting Mental Health in Persons With Gender Dysphoria Not Supported by Data Presented in Article

TO THE EDITOR: The article by Bränström and Pachankis (1) examines the psychiatric health of persons who have obtained a diagnosis of gender dysphoria between 2005 and 2015 compared with the general population. The variables examined were psychiatric diagnosis, prescription of psychiatric drugs (anxiolytics and antidepressants), and hospitalization for suicide attempt in 2015.

The results confirm what is already known, that is, that as a group, persons with gender dysphoria suffer from poorer psychiatric health than the general population.

However, the title of the article implies that gender-corrective surgery promotes mental health in this group, and the authors conclude in the Abstract section that the study “lends support to the decision to provide gender-affirming surgeries to transgender individuals who seek them.” In my opinion, this conclusion is not supported by the data presented in the article.

The most straightforward method to test whether surgery contributes to better psychological health would be to compare the health of those who underwent surgery with those who did not.

Of the persons diagnosed with gender dysphoria presented in the article, 1,018 had undergone surgery, while 1,661 had not. There were 22 individuals who were hospitalized in 2015 for a suicide attempt. The authors do not state how many of these individuals had received surgery, but this may be calculated by combining the data from Table 3 and Figure 1 in the article. Figure 1 shows the proportion of persons with gender dysphoria who were hospitalized for suicide attempt in 2015, grouped according to the time that had elapsed since the last gender-corrective surgery. Table 3 shows the number of individuals with gender dysphoria, grouped according to the time elapsed since last surgical operation (“Time since last gender-affirming surgical treatment”).

By combining these data, we can calculate that 10 of the suicide attempts (2.8% of 353) occurred during the same year that the last surgical correction was made (“perioperative” group in Figure 1). Two cases occurred 1 year after the last

surgical correction (0.9% of 221) and one case 2–3 years after the last surgical treatment (0.5% of 198), while none occurred more than 3 years after the last surgery. Thus, 13 individuals (10 plus two plus one) of the 22 persons who were hospitalized for a suicide attempt in 2015 had undergone gender-corrective surgery. Consequently, nine of them (22 minus 13) had not undergone any gender-affirmation surgery.

This corresponds to an odds ratio of 2.37 (95% CI=1.01–5.56, $p=0.047$). Hence, among the individuals examined in the study, the risk of being hospitalized for a suicide attempt was 2.4 times higher if they had undergone gender-corrective surgery than if they had not. Whether this is a causal relation (i.e., that surgery actually worsens the poor mental health in individuals with gender dysphoria) cannot be determined. Nevertheless, the data presented in the article do not support the conclusion that surgery is beneficial to mental health in individuals with gender dysphoria.

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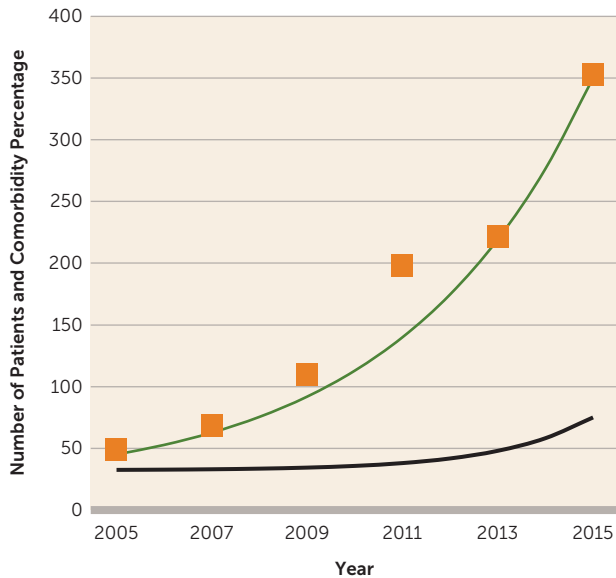
Confounding Effects on Mental Health Observations After Sex Reassignment Surgery

TO THE EDITOR: Bränström and Pachankis (1) report that Swedes with gender dysphoria who had undergone sex reassignment surgery in the decade to 2015 had a declining need for mental health treatment (as shown in Figure 1 in the article), leading them to consider that sex reassignment surgery improves mental health. However, the same data may be modeled in a way that leads to the opposite conclusion.

Except for a reduction after the perioperative year, Bränström and Pachankis found no further significant decrease in mental health treatment between the first and ninth years after surgery. They allowed for the increase in sex reassignment surgery from 2005 on but overlooked the increase in co-occurring mental health issues, which rose after 2005 but especially from about 2009 (2). A simple qualitative model illustrates how a dramatic change over time in mental health issues will affect the number of individuals accessing mental health treatment in 2015. In our Figure 1, the upper line depicts the rise in the number of sex reassignment surgeries, and the lower dark line depicts the rise in co-occurrence of mental health issues, assuming a final rise of 200% and a final co-occurrence of 75% (3).

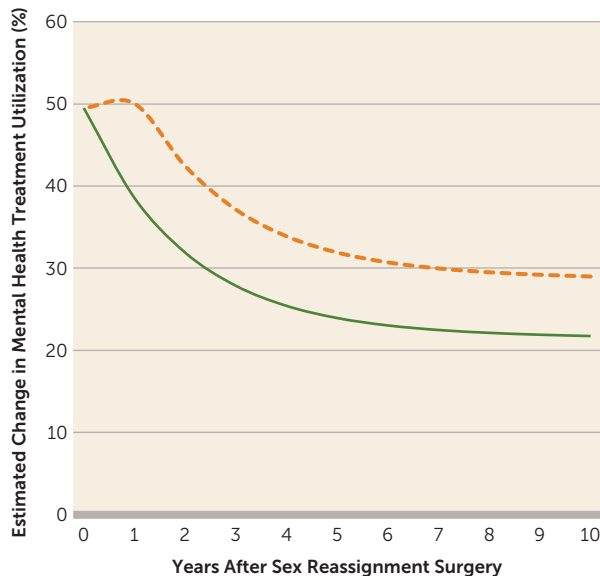
Because patients undergoing this surgery in the years closest to 2015 had higher rates of co-occurring mental health

FIGURE 1. Qualitative model of the number of sex reassignment surgeries and co-occurrence of mental health issues among individuals accessing mental health treatment^a



^a The orange boxes indicate the number of patients, the green line indicates the number of sex reassignment surgeries, and the dark line indicates the percentage of co-occurrence of mental health issues.

FIGURE 2. Estimation of mental health utilization by individuals in the years after sex reassignment surgery^a



^a The dotted line portrays projected mental health treatment utilization assuming aggravation of a mental health condition after sex reassignment surgery. The solid line portrays projected mental health treatment utilization assuming no aggravating effects after sex reassignment surgery.

issues than those whose surgery happened longer ago, we would expect the decline in mental health treatment to be pronounced (see the solid line in Figure 2), and with a beneficial effect of the surgery over time, the fall should be even more significant. Yet surprisingly, Bränström and Pachankis found only a very small decline over time.

However, if in fact this surgery aggravates a mental health condition by, say, 25%, then a more moderate fall in mental health utilization results (see the dashed line in Figure 2). The qualitative approximation of this curve with the reduction described by Bränström and Pachankis (in their Figure 1) is striking. Therefore, accounting for the increase in mental health issues from 2005, together with an assumption of increased mental health treatment due to this surgery, fits the data in the article and overturns the authors' conclusions, suggesting that sex reassignment surgery is in fact associated with increased mental health treatment.

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Toward Rigorous Methodologies for Strengthening Causal Inference in the Association Between Gender-Affirming Care and Transgender Individuals' Mental Health: Response to Letters

TO THE EDITOR: Increasing attention has been paid to identifying the best way to support transgender individuals seeking gender-affirming care. This attention springs from the increasing number of individuals seeking such care in many countries worldwide, coupled with a lack of sufficient knowledge to provide evidence-based treatment recommendations. This attention is also reflected in the letters to the editor (1–7) submitted in response to our article in this issue in which we describe mental health treatment utilization among transgender individuals seeking gender-affirming care in Sweden compared with the general population, and as a function of time since last gender-affirming surgery (8).

The letter writers question our conclusion that our study “lends support to the decision to provide gender-affirming surgeries to transgender individuals who seek them.” Their concerns about this conclusion can be summarized into three types:

Concern 1: The analysis focused on mental health treatment utilization during one specific year (i.e., 2015) rather than during a longer follow-up period, such as before and after provision of gender-affirming treatment.

Concern 2: The study did not employ an adequate comparison group.

Concern 3: The study did not sufficiently highlight the elevated mental health care needs of transgender individuals seeking gender-affirming care during the perioperative period.

Our study was motivated by two aims informed by the literature and the need for more knowledge in this field: first, to examine if transgender individuals seeking gender-affirming care have an increased risk of mental health treatment utilization compared with the general population; and second, to examine if mental health treatment utilization among transgender individuals who received gender-affirming care decreases as a function of number of years since receiving gender-affirming care.

In our article, we describe the background to our analytic decisions and discuss the limitations that our particular study design and analytic approach introduce. Many of the concerns raised by the letter writers are discussed at the conclusion of the article. In the article, we specifically call for further longitudinal studies that assess within-person changes in mental health treatment utilization before and after treatment. In the article, we also note that our approach was capable of ascertaining mental health only among those alive in 2015 and did not capture outcomes among the deceased. Several of the letter writers' concerns are drawn from assumptions about what our study methodology theoretically should have been or could have been but ultimately was not.

The letter writers suggest more ideal methodologies for identifying any causal impact of gender-affirming care on mental health treatment utilization, similar to what we wrote in our article. As outlined below, we join them in aspiring toward such methodologies capable of more rigorously establishing this impact. We also perform additional analyses permitted by our current data to start to move toward that goal.

Our Analytic Strategy

There is a great need for higher-quality studies using more representative samples of transgender individuals seeking gender-affirming care to better understand this population's mental and physical health care needs and the effects of gender-affirming care. Much current evidence derives primarily from small studies with cross-sectional designs, nonprobability samples, and self-reported treatment exposures and mental health outcomes. Our study does not. Although it is not capable of overcoming all threats to validity, our study design represents an improvement over much previous research.

Ours is an observational study based on registry data regarding mental health treatment utilization among individuals

with a gender incongruence diagnosis. We focus on mental health treatment utilization during one specific year (the latest for which we had data), and we used the total Swedish population as a comparison group. First, to answer whether transgender individuals seeking gender-affirming care have an increased risk of mental health treatment utilization compared with the general population, we compared the prevalence of treatment for mood and anxiety disorders among those with and without a gender incongruence diagnosis among all individuals living in Sweden. Second, to answer whether odds of mental health treatment utilization among transgender individuals who received gender-affirming care are lower as a function of number of years since receiving gender-affirming care, we evaluated mental health treatment utilization in 2015 among those with a gender incongruence diagnosis as a function of time since the initiation of gender-affirming hormone treatment and the last gender-affirming surgical treatment.

As outlined below, although this design is capable of ruling out certain threats to validity (e.g., confounding by secular trends), it is incapable of ruling out others (e.g., loss to mortality).

Responses to the Letters

Response to concern 1. The first concern is that our analysis focused on mental health treatment utilization during one specific year (i.e., 2015) rather than during a longer follow-up period, such as before and after provision of gender-affirming treatment. This decision was made to control for several important factors. First, the situation for transgender individuals has changed rapidly in the past 10–15 years. In Sweden, legislation affecting transgender individuals (e.g., removal of sterilization as a requirement for change of legal gender; increased protection of transgender individuals in hate-speech legislation) has improved at the same time that population attitudes have become more accepting (9, 10). Second, the proportion of individuals in the population treated for mental health problems has increased over time. Third, access to gender-affirming care has also increased over time. By restricting our outcome assessment period to one year, 2015, the most recent year for which we had data, we were able to remove the influence of these secular trends in transgender acceptance, visibility, and treatment utilization (both gender-affirming treatment and mental health treatment).

Although our chosen strategy addressed many of the problems of these secular effects, it has several drawbacks. Because we looked at mental health treatment utilization in one specific year, we could not follow individuals over time. Our analysis of time since last gender-affirming surgical treatment compared groups of individuals with varying lengths of time since their last treatment. It is possible that other factors, such as age and a changing proportion of individuals of different legal genders who have sought gender-affirming care over time, could influence these comparisons. Therefore, we controlled for those sociodemographic

factors in our analyses. Another drawback to using only one year of mental health treatment utilization data is that our analysis contains a very small number of suicide attempts and no information about previous attempts and completed suicides. Studies employing prospective cohort designs are needed to better understand suicidality within this group and its associations with gender-affirming care. Any conclusion regarding suicidality in our present study should be interpreted with this limitation in mind. This limitation is reported in our article.

Response to concern 2. The second concern is that our study design lacked an adequate comparison group. To answer whether transgender individuals seeking gender-affirming care have an increased risk of mental health treatment utilization compared with the general population, we used the total population without a gender incongruence diagnosis as a comparison group. Because the total population differs in significant ways from the group diagnosed with gender incongruence, we adjusted our analysis for all available sociodemographic variables (i.e., age, legal gender, education, income, urbanicity, and country of birth). An alternative way of testing this aim would be to create a comparison group matched on important demographic variables, which we have now done. Specifically, we now compare individuals diagnosed with gender incongruence with an equally sized group without such a diagnosis matched by age, legal gender, education, and country of birth. The results are presented in Tables S1 and S2 in the online supplement, and they indicate a similar pattern of results as reported in our article, with only a slightly reduced disparity in the odds of mental health treatment utilization when individuals diagnosed with gender incongruence are compared with matched control subjects (instead of with the full population without gender incongruence, as was done in the original analysis).

To determine if mental health treatment utilization among transgender individuals receiving gender-affirming care decreases as a function of number of years since receiving gender-affirming care, we did not use a comparison group but tested the association between both year since initiation of gender-affirming hormone treatment and year since last gender-affirming surgical treatment with mental health treatment utilization in 2015. As a reference, we included the proportion of the general population treated for mental health conditions in 2015 in Figure 1 of our article. We have added the proportion of the matched control subjects treated for mental health problems in 2015 to Figure S1 in the online supplement.

Like some of the letter writers suggest, we also considered using a stronger comparison group but found the options unsatisfactory, if not impossible. Perhaps the most obvious comparison would have been individuals with a gender incongruence diagnosis who had not received surgical treatment. This would be a strong comparison group if all individuals diagnosed with gender incongruence are, in fact, seeking gender-affirming surgical treatment. However, this is not the case. Some individuals diagnosed with gender

incongruence seek only gender-affirming hormonal treatment and not gender-affirming surgical treatment; others seek no treatment at all. The group diagnosed with gender incongruence not receiving surgery is a heterogeneous group, including those with no intention to seek surgery, that would be inappropriate as a comparison group for those receiving surgery. However, to be responsive to some of the letter writers' interest in comparing individuals with a gender incongruence diagnosis who received and did not receive gender-affirming surgery, we have created a matched group of individuals with a gender incongruence diagnosis who have not received surgery. These individuals were each matched to an individual with a gender incongruence diagnosis who had received gender-affirming surgery by age, legal gender, education, and country of birth. When comparing the mental health treatment outcomes between the two groups (Table 1), we found no significant difference in the prevalence of treatment for mood disorders and no significant difference in the prevalence of hospitalization after suicide attempt. However, individuals diagnosed with gender incongruence who had received gender-affirming surgery were more likely to be treated for anxiety disorders compared with individuals diagnosed with gender incongruence who had not received gender-affirming surgery. As reported in the article, the statistical test for hospitalization after suicide attempt must be interpreted with caution. As noted above, limited information can be drawn from this particular comparison.

Another comparison group could have involved individuals without a gender incongruence diagnosis undergoing a surgical treatment for which a thorough mental health assessment is required, as it is for gender-affirming surgery. However, we are unaware of any such surgical treatment. Such a comparison group would have, theoretically, enabled us to partially overcome two threats to the validity of our finding that odds of mental health treatment are lower as a function of time since final gender-affirming surgery. The first threat is that people are required to be screened for mental health problems before gender-affirming surgery and might therefore have particularly high odds of mental health treatment in the perioperative year because of their perhaps involuntary receipt of mental health services. These individuals might be less likely to voluntarily seek treatment for mental health problems with greater time since surgery. The second threat is that because we assessed only the mental health of individuals who were alive in 2015, individuals who died by suicide or migrated would not be included; greater time since last surgical treatment comes with greater time for suicide or migration to happen.

Response to concern 3. The third concern is that the study did not sufficiently highlight the elevated mental health care needs of transgender individuals seeking gender-affirming care during the perioperative period. The letter writers highlight this important finding of our study that we did not sufficiently emphasize originally. Specifically, regardless of the effect of gender-affirming care on mental health treatment

TABLE 1. Mood- and anxiety-related health care visits, antidepressant and anxiolytic prescriptions, and hospitalization after suicide attempt in 2015 among individuals diagnosed with gender incongruence in Sweden between 2005 and 2015, by gender-affirmative surgery status

2015 Treatment Outcome	Individuals Diagnosed With Gender Incongruence Who Have Received Gender-Affirmative Surgery (N=1,018)		Individuals Diagnosed With Gender Incongruence Who Have Not Received Gender-Affirmative Surgery (N=1,018) ^a		Analysis	
	N	%	N	%	Odds Ratio	95% CI
Psychiatric outpatient visits						
Any mood disorder	98	9.6	88	8.6	1.13	0.83–1.52
Any anxiety disorder	85	8.3	62	6.1	1.40	1.00–1.97
Prescribed medication						
Any antidepressant treatment	301	29.6	292	28.7	1.04	0.86–1.26
Any anxiolytic treatment	215	21.1	149	14.6	1.56	1.24–1.96
Inpatient visit (hospitalization after suicide attempt)	13	1.3	7	0.7	1.87	0.74–4.70

^a Control group matched by age, gender, education, and country of birth.

utilization, our results show that the mental health care needs of this population are substantial in the year surrounding the last gender-affirming surgery. These results highlight the need for further research and clinical attention to be paid to the stressors and needed supports of this period (11).

In sum, the letter writers point out that although our study design addressed some threats to validity (e.g., confounding by secular trends), it introduced others (e.g., loss to mortality). While the design clearly establishes that individuals diagnosed with gender incongruence utilized more mental health care than the general population in 2015, especially during the perioperative period, like most extant research on the topic, the design is incapable of establishing a causal effect of gender-affirming care on mental health treatment utilization.

Should the Concluding Message of Our Study Have Been More Moderate?

Our conclusion based on the findings at hand in the article, which used neither a prospective cohort design nor a randomized controlled trial design, was too strong. However, given the urgent need for more knowledge about the mental health of transgender individuals and the potential consequences of gender-affirming care, this large-scale observational study serves an important purpose and fills an important knowledge gap. Specifically, this study highlights the substantially increased risk of mental health problems among individuals diagnosed with gender incongruence, and in particular, among those in the process of receiving gender-affirming surgery. The study also lends support for expecting a reduction in mental health treatment as a function of time since completing such treatment, at least among those who are still living in Sweden.

We thank the letter writers for their attention to this important topic and, recognizing the importance of approaching this topic with triangulated, rigorous methodologies, look forward to further collaborative research using even higher-quality methodologies to move closer to establishing the causal impact of gender-affirming care on the well-being of the transgender population.

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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



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 unsuccessful³⁸ 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, Delemarre van 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% desistance 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 *avored 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 summarizes 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

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Appendix

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

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



A Follow-Up Study of Boys With Gender Identity Disorder

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This study reports follow-up data on the largest sample to date of boys clinic-referred for gender dysphoria ($n = 139$) with regard to gender identity and sexual orientation. In childhood, the boys were assessed at a mean age of 7.49 years (range, 3.33–12.99) at a mean year of 1989 and followed-up at a mean age of 20.58 years (range, 13.07–39.15) at a mean year of 2002. In childhood, 88 (63.3%) of the boys met the DSM-III, III-R, or IV criteria for gender identity disorder; the remaining 51 (36.7%) boys were subthreshold for the criteria. At follow-up, gender identity/dysphoria was assessed via multiple methods and the participants were classified as either persisters or desisters. Sexual orientation was ascertained for both fantasy and behavior and then dichotomized as either biphilic/androphilic or gynephilic. Of the 139 participants, 17 (12.2%) were classified as persisters and the remaining 122 (87.8%) were classified as desisters. Data on sexual orientation in fantasy were available for 129 participants: 82 (63.6%) were classified as biphilic/androphilic, 43 (33.3%) were classified as gynephilic, and 4 (3.1%) reported no sexual fantasies. For sexual orientation in behavior, data were available for 108 participants: 51 (47.2%) were classified as biphilic/androphilic, 29 (26.9%) were classified as gynephilic, and 28 (25.9%) reported no sexual behaviors. Multinomial logistic regression examined predictors of outcome for the biphilic/androphilic persisters and the gynephilic desisters, with the biphilic/androphilic desisters as the reference group. Compared to the reference group, the biphilic/androphilic persisters tended to be older at the time of the assessment in childhood, were from a lower social class background, and, on a dimensional composite of sex-typed behavior in childhood were more gender-variant. The biphilic/androphilic desisters were more gender-variant compared to the gynephilic desisters. Boys clinic-referred for gender identity concerns in childhood had a high rate of desistance and a high rate of a biphilic/androphilic sexual orientation. The implications of the data for current models of care for the treatment of gender dysphoria in children are discussed.

Keywords: gender dysphoria, gender identity disorder, gender non-conformity, sexual orientation, DSM-5



INTRODUCTION

Gender identity is considered to be, for most people, a central aspect of one's sense of self (1–6).¹ By around 3 years of age, if not earlier, most children can self-label themselves as either a boy or a girl (11–14) although cognitive-developmental gender theory suggests that the understanding of gender as an “invariant” aspect of the self does not occur until early to middle childhood, with the achievement of concrete operational thought (12, 15, 16). Gender differences in the adoption of gender role behavior, i.e., behavior associated with cultural definitions of masculinity and femininity, also emerge during the preschool years, if not earlier. These behaviors span various domains, including peer, toy, role play, and activity preferences [e.g., (3, 17, 18)]. Normative developmental research has long documented that, on average, both gender identity and gender role behaviors show significant and substantial between-sex differences (19–21). Later in development, sexual orientation also shows a substantial between-sex difference, i.e., most males are sexually attracted to females and most females are sexually attracted to males (19, 22).

In the 1950s and 1960s, a small clinical literature began to describe the phenomenology of children who displayed marked gender-variant behavior, including the strong desire to be of the other gender [e.g., (23–27)]. Subsequent volumes by Stoller (28) and Green (29) provided more comprehensive descriptions of such children. These early works were the sequel to the introduction of the diagnostic term Gender Identity Disorder (GID) of Childhood to the psychiatric nomenclature in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* [DSM-III; (30)], currently termed Gender Dysphoria (GD) in the DSM-5 (31). Since 1980, empirical research has examined a number of parameters pertaining to GID/GD: epidemiology, diagnostic and assessment methods, associated psychopathology, causal mechanisms, and therapeutic approaches [for reviews, see, e.g., (32–39)].

An additional parameter (the focus of the present study) pertains to the developmental course of GID in children. In the early literature, it was posited by some that pervasive gender-variant behavior in children might be a predictor of GID in adulthood (termed Transsexualism in the DSM-III) [e.g., (26, 40)]. At the same time, it was also recognized that gender-variant behavior in childhood was associated with sexual orientation (in males, androphilia, i.e., sexual attraction to men; in females, gynephilia, i.e., sexual attraction to women), but without co-occurring gender dysphoria [see, e.g., (41, 42); for a meta-analytic review, see (43)].

To date, there have been at least 10 follow-up studies of children whose behavior was consistent with the DSM diagnosis

of GID (or GD per DSM-5) (44–53). Across these studies, the year at the time of first evaluation in childhood ranged from 1952 (49) to 2008 (51). For the 9 studies that included boys, the sample sizes (excluding those lost to follow-up) ranged from 6 to 79 (Mean age, 26 years). Most of these studies also provided the age at the time of first evaluation in childhood, which ranged from a mean of 7 years (47) to a mean of 9 years (48), with an age range from 4 to 12 years.

At the time of follow-up, using different metrics (e.g., clinical interview, maternal report, dimensional measurement of gender dysphoria, a DSM diagnosis of GID, etc.), these studies provided information on the percentage of boys who continued to have gender dysphoria (herein termed “persisters”) and the percentage of boys who did not (herein termed “desisters”).² Of the 53 boys culled from the relatively small sample size studies (Bakwin, Davenport, Kosky, Lebovitz, Money and Russo, Zuger), the percentage classified as persisters was 9.4% (age range at follow-up, 13–30 years). In Green (47), the percentage of persisters was 2% (total $n = 44$; Mean age at follow-up, 19 years; range, 14–24); in Wallien and Cohen-Kettenis (52), the percentage of persisters was 20.3% (total $n = 59$; Mean age at follow-up, 19.4 years; range, 16–28); and in Steensma et al. (51), the percentage of persisters was 29.1% (total $n = 79$; Mean age at follow-up, 16.1 years; range, 15–19). Across all studies, the percentage of persisters was 17.4% (total $N = 235$), with a range from 0 to 29.1%.³

These studies also provided information on the sexual orientation of the boys at the time of follow-up. In the early studies, sexual orientation was ascertained from various sources (e.g., open-ended interviews with the patient, parent-report, chart information, etc.). In the more recent studies, sexual orientation was assessed in a more systematic manner, such as the use of a structured interview to assign a Kinsey-based rating of sexual orientation in fantasy and a rating of sexual orientation in behavior, dummy coded where a 0 = gynephilia and a 6 = androphilia [e.g., (47)].

Of the 53 boys culled from the relatively small sample size studies (op. cit.), 13 (34.2%) of the patients were classified as gynephilic and 25 (65.8%) were classified as biphilic/androphilic.⁴ In the remaining 15 patients (28.3% of the combined samples), their sexual orientation was either uncertain or unknown.

²The terms persistence and desistance have been used for a long time in clinical developmental psychiatry and psychology [e.g., (54)]. Zucker (55) was the first to apply these terms to describe the developmental psychosexual trajectories of children diagnosed with GID.

³The percentages provided here differ somewhat from other summary reviews [(39), pp. 285–286, (56, 57)] because we have excluded patients who were seen for the first time in adolescence [for this reason, data from Zuger (58) are also not included]. One other follow-up study was conducted by Nakamura (59). Unfortunately, this dissertation is not available for purchase at ProQuest (Ann Arbor, MI) and is only available for loan at the University of Essex library. Due to COVID-19 restrictions, it is currently inaccessible (K. Clarke, personal communication to G. Rieger, June 15, 2020). The director of the clinic at the time when the data were collected does not have a copy of the dissertation (D. Di Ceglie, personal communication, June 15, 2020).

⁴As pointed out by Reviewer 1, biphilic is a dubious neologism, combining Latin and Greek derivatives. Diphilic would be the more accurate derivative. However, introducing this term would probably confuse many readers, so we have retained the term biphilic (see https://en.wikipedia.org/wiki/Androphilia_and_gynephilia).

¹In one study, Turner and Brown (7) found that school-age children rarely mentioned their gender when providing open-ended self-descriptions; the most frequent descriptor pertained to activities and preferences. Turner and Brown suggested that it might be the case that gender is so central to one's self-concept that it “goes without saying” (p. 709). In contemporary times in the West, a very small number of parents choose to not “gender” their children (“theybies”) by not referring to them as boys or girls (and, at times, not even announcing to others the child's biological sex), dressing them in gender-neutral ways, etc. Little is known about the gender identity and gender role patterns of these children (8–10).

In Green's (47) study, 11 (25%) of the boys were classified as gynephilic (Kinsey ratings of 0–1) and 33 (75%) were classified as biphilic/androphilic in fantasy (Kinsey ratings of 2–6). For behavior, 6 (20%) were classified as gynephilic and 24 (80.0%) were classified as biphilic/androphilic. The remaining 14 boys (31.8% of the total sample) could not be classified with regard to behavior because they had had no interpersonal sexual experiences. In Green's study, the sexual orientation of a comparison group of boys, who had been recruited from the community, was also assessed: 100% of these boys ($n = 35$) were classified as gynephilic in fantasy and 96% ($n = 25$) were classified as gynephilic in behavior.

In the Wallien and Cohen-Kettenis (52) study, sexual orientation was assessed for attraction (2 items), fantasy (2 items), behavior (4 items), and sexual identity (1 item) using a self-developed Sexual Orientation Questionnaire. As in Green, Kinsey-type ratings were used in the analysis. Depending on the metric, data on sexual orientation were not available for anywhere between 22 and 40 (27.2–67.7%) patients. For attraction, 32% were classified as gynephilic and 68% were classified as androphilic (total $N = 37$); for fantasy, 19% were classified as gynephilic, 19% were classified as biphilic, and 62% were classified as androphilic (total $N = 21$); for behavior, 21% were classified as gynephilic, 16% were classified as biphilic, and 63% were classified as androphilic (total $N = 19$); lastly, for sexual identity, 19% were classified as gynephilic ("heterosexual"), 19% were classified as biphilic ("bisexual"), and 62% were classified as androphilic ("homosexual") (total $N = 27$). Steensma et al. (51) used the same metrics as Wallien and Cohen-Kettenis. Depending on the metric, data on sexual orientation were not available for anywhere between 25 and 40 (31.6%–50.6%) patients. For attraction, 19.2% were classified as gynephilic, 15.4% were classified as biphilic, and 65.4% were classified as androphilic (total $N = 52$); for fantasy, 14% were classified as gynephilic, 22% were classified as biphilic, and 64% were classified as androphilic (total $N = 50$); for behavior, 35.9% were classified as gynephilic, 12.8% were classified as biphilic, and 51.3% were classified as androphilic (total $N = 39$); lastly, for sexual identity, 13% were classified as gynephilic ("heterosexual"), 27.8% were classified as biphilic ("bisexual"), and 59.3% were classified as androphilic ("homosexual") (total $N = 54$).

In recent years, there have been various criticisms of these follow-up studies [see, e.g., (60–63); for a rebuttal, see (64)], particularly with regard to the putatively high percentage of desistance. It has been questioned, for example, to what extent the patients in these studies truly had GID/GD. For example, in the early studies, prior to the publication of DSM-III, one could reasonably argue that the diagnostic status of the patients was unclear because there were no formal diagnostic criteria to rely upon. However, one could argue in return that the behavior of these boys was phenomenologically consistent with the subsequent DSM criteria.

Consider, for example, the systematic study by Green [(47), Figure 1.2]. Green reported that 15% of the feminine boys, per parent-report, had "never" expressed the desire to be a girl or a woman at the time of the baseline assessment, 60% "occasionally" had such a desire, and only 25% had such a desire

"frequently." Thus, a conservative critic might argue that only the last group would have met one of the key indicators for the GID/GD diagnosis in the DSM.⁵ On the other hand, suppose a boy "occasionally" voiced the desire to be a girl over a period of several years. One might want to make the case that this would be consistent with the DSM descriptors of "persistently" or "repeatedly," etc. Of course, one could debate what would genuinely count as "occasionally" (in Green's trichotomous metric, it would be anything more than "never" and less than "frequently"). In any case, it is probably reasonable to argue that, in Green's study, some boys were threshold and some boys were subthreshold for the equivalent of a DSM diagnosis. Given that in Green's study only one boy persisted with gender dysphoria at the time of follow-up, the threshold-subthreshold distinction would not really matter.

Studies that employed DSM criteria for GID/GD allow for a more formal examination of the "No True Scotsman" argument (https://en.wikipedia.org/wiki/No_true_Scotsman).

In the Wallien and Cohen-Kettenis (52) study, the DSM-III-R criteria were used to diagnose GID. Of the 12 persisters, all met the criteria for GID at the time of the baseline assessment; in contrast, only 68% of the 47 desisters met the criteria for GID; the remainder were deemed subthreshold for the diagnosis. Thus, in their study, the threshold-subthreshold distinction appears to have been an important one in predicting outcome; nonetheless, it should be noted that 68% of the desisters had been threshold for the diagnosis in childhood—perhaps a strong rebuttal to the No True Scotsman argument. In Steensma et al. (51), the DSM-IV-TR criteria were used. Of the 23 persisters, 21 (91.3%) met the criteria for GID; in contrast, only 22 (39.3%) of the 56 desisters were threshold for the diagnosis, suggesting an even more substantial difference in the threshold-subthreshold distinction than was found in Wallien and Cohen-Kettenis. Although the latter percentage was lower than what was found in Wallien and Cohen-Kettenis, that almost 40% of the desisters met the criteria for GID in childhood still argues in favor that the children were desisting from something.⁶

From Wallien and Cohen-Kettenis (52) and Steensma et al. (51), one predictor of outcome, therefore, was the distinction between being threshold or subthreshold for the GID diagnosis in childhood. Dimensional measures of gender-variant behavior have also proven useful. In both Wallien and Cohen-Kettenis and Steensma et al., dimensional measures of sex-typed behavior in childhood also significantly discriminated between the persisters and desisters, with the former group having, on average, more severe gender-variant behavior at the time of the childhood

⁵The situation is compounded even further because in the DSM-IV, unlike in the DSM-III and DSM-III-R (65), the stated desire to be of the other gender was not a necessary criterion for the diagnosis [for the rationale, see (66), pp. 483–486]. In DSM-5, the desire to be of the other gender does not require explicit verbalization; the clinician is allowed leeway in drawing inferences based on other sources of information [see (67), pp. 904–905].

⁶In the follow-up study by Drummond et al. (46) of 25 girls from our clinic, the desistance rate was 88%. Of the 22 desisters, 13 (59.0%) met the DSM-III, III-R or IV criteria for GID. In Wallien and Cohen-Kettenis (52), of the 9 girls who desisted, 55.5% met the DSM-III-R criteria for GID. In Steensma et al. (51), of the 24 girls who desisted, 58.3% met the DSM-IV criteria for GID.

assessment. Steensma et al. found two other predictors of persistence: boys who were assessed at an older age and boys who had made either a partial or complete gender “social transition” [see (68–70)]. Of the 12 boys who had partially or completely transitioned prior to puberty, 10 (83.3%) were classified as persisters. In contrast, of the 67 boys who had not socially transitioned, only 13 (19.4%) were classified as persisters.

In the present study, we provide follow-up data with regard to both gender identity (persistence vs. desistance) and sexual orientation (gynephilia vs. biphilia/androphilia) on the largest sample of boys studied to date. Apart from providing percentage data on these two variables, which will be discussed in a comparative perspective in relation to the prior studies and the epidemiological literature, we also examine the predictors of outcome in relation to both demographic and sex-typed behavior measures (including whether or not the boys were threshold or subthreshold for GID) collected at the time of the baseline assessment in childhood.

METHOD

Participants

The participants were 139 boys (“birth-assigned males”)⁷ who, in childhood, had been referred to and then assessed in the Gender Identity Service, Child, Youth, and Family Program at the Centre for Addiction and Mental Health (CAMH) in Toronto, Ontario between 1975 and 2009 (Mean year of assessment, 1989.36) and were adolescents or adults at follow-up (Mean year at follow-up, 2002.35).⁸

Participants entered the follow-up study through two methods of recruitment. The majority of participants (77%) were recruited for research follow-up. There were two main waves of participant recruitment through research contact, from 1986 to 1993 ($n = 32$) and then from 2009 to 2011 ($n = 71$). During the period of data collection, 32 patients re-contacted the service for clinical reasons (eight for gender dysphoria, six for sexual orientation, and 18 for heterogeneous concerns) [for details, see (77), Appendix E]. They were informed about the opportunity to participate in the follow-up study and subsequently completed the study protocol. The majority of the patient-initiated participants had contacted the clinic between the two main waves of research recruitment. Thus, from 1994 to 2008, the participants who entered the study were primarily those who had contacted the service for clinical reasons.

In the early wave of follow-up, a lower-bound age for participation was set at 14 years, but by the mid-1990s this was

changed to a lower-bound age of 16 years. In total, 110 (79.1%) participants were at least 16 years of age and 29 (20.9%) were younger than 16. Across the entire period of data collection, eligible participants, after review of the medical chart, were contacted at random (other than the participants who had returned to the service for clinical reasons). Due to lack of study resources and time constraints, contact with 162 other eligible participants was not attempted.

In total, 145 patients were approached about the follow-up study, either through research contact ($n = 113$) or following their clinical involvement with the Gender Identity Service ($n = 32$). Six patients declined, which yielded a participation rate of 95.9%. For those recruited for research purposes, initial contact, by telephone, letter or email, was first made with the parents because the patients were minors at the time of the childhood assessment and may have had no recollection of their clinic attendance. A total of 19 (14.3%) potential participants could not be reached/traced through previous addresses, registrars, and personal contacts.

Of the 139 participants, 110 were seen for a face-to-face assessment. For various reasons, the remaining 29 patients could not be seen for the face-to-face assessment (e.g., lived in another province or country, “too busy,” severe mental health issues). For some patients, they provided some information over the phone or information was provided by the parents; thus, for these patients, it was possible to obtain some follow-up data about their gender identity and sexual orientation.

The demographic characteristics of the participants, including their age at assessment in childhood and at the time of follow-up, are shown in **Table 1**. The GID diagnosis in childhood was based on the DSM-III ($n = 53$), DSM-III-R ($n = 46$), or DSM-IV ($n = 40$) criteria applicable at the time of assessment.⁹ A total of 88 (63.3%) boys met complete DSM criteria for GID in childhood. The remaining 51 (36.7%) boys were subthreshold for a DSM diagnosis, but all had some indicators of GID, and, based on the historical information provided during the assessment, some would have met the complete DSM criteria at some point in their lives prior to their assessment in childhood.¹⁰ The percentage who met the complete DSM criteria for GID did not differ significantly as a function of DSM edition, $\chi^2_{(2)} < 1$.

Procedure

The majority of participants who completed the face-to-face assessment were evaluated on a single day. Three participants were seen twice. In these instances, the participants completed the self-report measures during their second visit as the complexity of their clinical presentation extended the duration of the assessment. Participants were provided a stipend for their participation in the follow-up assessment and reimbursement for travel expenses. For participants followed-up prior to 2009 ($n = 68$), the data were collected by the third author; for those followed-up between 2009 and 2011, the data were collected

⁷Two reviewers asked why we chose to use the noun “boys” instead of the noun “males.” In our view, the question was reasonable but also a matter of semantics and taste. The third edition of *The Oxford Dictionary of Current English* (71) defines boy as “a male child...” Thus, we believe that the two words can be used synonymously. Males can refer to any age in the life-span whereas boys connote childhood. The participants in our study were coded as male at the time of their birth in the hospital delivery record, of which we had the actual birth records for the majority of the participants in the current study (72). As per Bouman et al. (73), one would say that the participants were “assigned male at birth” and then declared socially to be “boys” (74).

⁸The clinic was established in 1975 at the Clarke Institute of Psychiatry (75, 76), which became part of the CAMH in 1998.

⁹For boys seen prior to the publication of DSM-III in 1980, the draft criteria were used.

¹⁰In DSM-III, termed Atypical Gender Identity Disorder; in DSM-III-R and DSM-IV, termed Gender Identity Disorder Not Otherwise Specified.

TABLE 1 | Demographic characteristics ($N = 139$).

Characteristic	<i>M</i>	<i>SD</i>	Range	%
From childhood				
Age (in years)	7.49	2.66	3.33–12.99	
Year of birth	1981.87	7.50	1966–1996	
Year of assessment	1989.36	7.50	1975–2004	
IQ ^a	105.93	15.47	69–138	
Social class ^b	40.74	15.15	8.0–66.0	
Marital status ^c				
Two-parent family				64.7
Other				35.3
Caucasian				84.9
At follow-up				
Age (in years)	20.58	5.22	13.07–39.15	
Year of follow-up	2002.35	9.08	1986–2011	
Follow-up interval (in years) ^d	12.88	6.07	2.77–29.29	
IQ ^{e,f}	105.88	16.03	65–138	

^aFull-Scale IQ was obtained with age-appropriate Wechsler intelligence scales.

^bHollingshead's (78) Four Factor Index of Social Status (absolute range, 8–66).

^cOther included the following family constellations: single parent, separated, divorced, living with relatives, or in the care of a child protection agency.

^dInterval denotes the time between childhood assessment and follow-up assessment.

^eFull Scale IQ estimated using four subtests: Vocabulary, Comprehension, Block Design, and Object Assembly.

^fAn IQ score was available only for participants who completed the face-to-face assessment. Of these, scores were not available for one participant.

by the first author ($n = 71$). The study was approved by the Institutional Review Boards at the Clarke Institute of Psychiatry (subsequently the Centre for Addiction and Mental Health; Protocol #198/2008–2011) and the University of Toronto.

Measures

Below, we describe the measures from assessment and follow-up of relevance for this article. A list of all measures used in the follow-up study can be found in Singh [(77), Table 4].

Childhood Assessment

Cognitive Functioning

Based on the child's age at the time of assessment, the appropriate version of the Wechsler Intelligence Scale for Children was administered (WPPSI-R or the WISC-R/WISC-III/WISC-IV). Full scale IQ scores were used to characterize level of cognitive functioning.

Behavioral and Emotional Problems

Parents completed the Child Behavior Checklist (CBCL), a measure of behavioral and emotional problems (79). Although not the focus of the present study, it is noted here because we used three CBCL indices (sum of all behavior problems and Internalizing and Externalizing *T* scores) as part of an internal validity analysis when comparing participants vs. non-participants (see Results).

Sex-Typed Behavior

Five child informant and two parent informant measures were used to assess the participants' sex-typed behavior in childhood: (1) Draw-a-Person [DAP] test (80); (2) a free-play task (81); (3) the Playmate and Playstyle Preferences Structured Interview (PPPSI) (82, 83); (4) sex-typed responses on the Rorschach test (84); (5) the Gender Identity Interview for Children (GIIC) (85–87); (6) the Gender Identity Questionnaire for Children (GIQC) (88–90); and (7) a measure of activity level/extraversion [(39); see also (91)]. These child and parent informant measures all have established discriminant validity, that is, they significantly differentiated the boys clinic-referred for gender identity concerns from control boys [for reviews, see (18, 92)]. A Childhood Sex-Typed Behavior Composite was subsequently computed for each participant (see below).

Follow-Up Assessment

Cognitive Functioning

Four subtests from the age-appropriate version of the Wechsler Intelligence Scales were administered (Vocabulary, Comprehension, Block Design, and Object Assembly). The standard scores from the subtests were averaged to form a prorated IQ score for cognitive functioning (93).

Concurrent Gender Identity

Concurrent gender identity was evaluated using a semi-structured interview and self-report questionnaires. During an audiotaped interview, each participant was asked to describe their current feelings about being a biological male. They were also asked to describe positive and negative aspects about their gender identity. For example, participants who reported a "male" gender identity were asked to describe positive and negative aspects of being male. The semi-structured interview also included questions based on the adolescent and adult GID criteria outlined in the DSM-III-R or DSM-IV (65, 94). Participants were asked to respond to these questions according to the last 12 months with *No*, *Sometimes*, or *Yes* [for details, see (77), Appendix G].

Two self-report measures were also used to assess current gender identity and gender dysphoria: (1) The Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults (GIDYQ-AA) (95–97) or (2) the Gender Dysphoria/Identification questionnaire (GDIQ) (98). The GDIQ was developed prior to the GIDYQ-AA. As such, the GIDYQ-AA was introduced to the protocol subsequent to the GDIQ and, as a result, the more recent participants completed the GIDYQ-AA while earlier participants completed the GDIQ.

The male version of the GIDYQ-AA was completed. This 27-item questionnaire measures gender identity and gender dysphoria in adolescents or adults; participants over the age of 17 completed the adult version and younger participants completed the adolescent version. The adolescent and adult versions are identical except that, in the adult version, the words "man" and "woman" are used instead of "boy" and "girl." Each item was rated on a 1–5 point response scale with verbal anchor points ranging from *Never* to *Always* based on a time frame of the past 12 months. Coding was such that a "lower" score signified more gender dysphoria. Item examples include the following:

"In the past 12 months, have you felt unhappy about being a man?" and "In the past 12 months, have you had the wish or desire to be a woman?" Principal axis factor analysis identified a one-factor solution that accounted for 61.3% of the variance. All factor loadings were ≥ 0.30 (median, 0.86; range, 0.34–0.96). The GIDYQ-AA has strong evidence for discriminant validity and a high threshold for specificity (i.e., low false positive rate for non-GID individuals) [see (95, 96, 99–102)].

The GDIQ (98) contains 8 items pertaining to gender identity and gender dysphoria. Factor analysis identified two factors, accounting for 31.4 and 12.5% of the variance, respectively (all factor loadings ≥ 0.45). Factor 1 consisted of five items pertaining to gender dysphoria and Factor 2 consisted of three items pertaining to gender role identification. For the present study, only the questions for Factor 1 were used. Each item was rated on a 3-point or 5-point scale for the past 12 months (see **Appendix 1** in **Supplementary Material**).

Participants were classified as having persistent gender dysphoria if their mean score on the GIDYQ-AA was ≤ 3.00 , in line with sensitivity and specificity analyses from other data sets (95, 96). For participants who did not complete the GIDYQ-AA, the GDIQ was used. A participant was classified as a persister if two or more of the following five items on the GDIQ were endorsed: wish to have been born a girl (Item 1), wish to have surgery to change body (Item 2), feel more like a girl than a boy (Item 3), wonder if would be happier as a girl (Item 4), and somewhat or very dissatisfied with being a boy (Item 5).

Information regarding participants' gender identity/gender dysphoria was also obtained during the semi-structured clinical interview and, therefore, allowed for cross-validation of these questionnaire data. For those participants who did not complete the face-to-face interview, clinical information regarding gender identity/gender dysphoria was obtained through self- or parent-report or chart review. Across the entire sample, the GIDYQ-AA was used to classify persistence or desistence for 64 participants, the GDIQ for 42 participants, and interview/chart data/parent report for 33 cases.

Sexual Orientation

Sexual orientation in fantasy was assessed with specific questions from an audiotaped face-to-face interview and the self-report Erotic Response and Orientation Scale (EROS) (103).

The interview asked about four types of sexual fantasy over the past 12 months: (1) crushes on other people; (2) sexual arousal to visual stimuli (e.g., acquaintances, partners, and individuals from movies, television, etc.); (3) sexual content of night dreams; and (4) sexual content of masturbation fantasies. During the interview, participants were not asked directly about the gender of the person or persons who elicited sexual arousal, thus allowing time for the participant to provide this information spontaneously. Directed questions about the gender of the person(s) who elicited sexual arousal were asked only if the participant did not volunteer specific information about whether their arousal was directed to same-sex or opposite-sex individuals, or both. By the end of the interview, each participant provided information about sexual arousal to both same-sex and opposite-sex individuals. Using the Kinsey scale criteria

(104), the interviewer assigned Kinsey ratings that ranged from 0 (exclusively gynephilic in fantasy) to 6 (exclusively androphilic in fantasy) for each question. A dummy score of 7 denoted that the participant did not experience or report any fantasies. A global fantasy score was also derived based on ratings from the four questions. Kinsey ratings for sexual orientation in fantasy were available for 129 participants.

Inter-rater reliability on Kinsey ratings for sexual orientation in fantasy was examined for 29 participants, selected at random. The second scorer listened to the audio recordings of the semi-structured interview, with specific attention to the information collected on sexual orientation. The inter-rater agreement on the Kinsey global fantasy rating was very good ($\kappa = 0.95$) and the kappa values for the four specific components ranged from 0.81 to 1.00.

The EROS is a 16-item self-report measure assessing sexual orientation in fantasy over the past 12 months. Half of the questions pertained to gynephilic fantasy (e.g., "How often have you noticed that you had sexual feelings [even the slightest] while looking at a woman?") and the other half pertained to androphilic fantasy (e.g., "How often have you noticed that you had sexual feelings [even the slightest] while looking at a man?"). Participants who were 18 years and older completed the adult version and younger participants completed the adolescent version. The adolescent and adult versions are identical except that, in the adult version, the words "man" and "woman" were used instead of "boy" and "girl." Each item was rated on a 5-point scale for frequency of occurrence, ranging from 1 ("none") to 5 ("almost every day"). Mean androphilic and gynephilic fantasy scores were derived for each participant. In the present study, we calculated a difference score between the participants' mean androphilic and gynephilic scores. Previous use of the EROS has shown good evidence of discriminant validity (98, 101).

Sexual orientation in behavior was assessed with specific questions during the face-to-face interview and with a modified version of the Sexual History Questionnaire (SHQ) (105). In the interview, questions asked about five types of sexual behavior: (1) dating; (2) holding hands in a romantic manner; (3) kissing; (4) genital fondling or touching a woman on the breasts, and (5) intercourse (penile-vaginal and anal). Kinsey ratings for behavior in the past 12 months were made in the same manner as fantasy ratings. Kinsey ratings for sexual orientation in behavior were available for 108 participants. Inter-rater reliability on Kinsey ratings for sexual orientation in behavior was examined for the same 29 participants. There was perfect inter-rater agreement on the Kinsey global behavior rating ($\kappa = 1.0$) and the kappa values for the five specific components ranged from 0.91 to 1.00.

The modified SHQ consists of 20 questions. Ten questions pertained to gynephilic experiences (e.g., "How many women have you kissed on the lips in a romantic way?") and 10 questions pertained to androphilic experiences (e.g., "How many men have you kissed on the lips in a romantic way?"). Participants who were 18 years and older completed the adult version and younger participants completed the adolescent version. The adolescent and adult versions are identical except that, in the adult version, the words "man" and "woman" were used instead of "boy" and "girl." Each item was rated on a 5-point scale for frequency

of occurrence, ranging from 1 (“none”) to 5 (“11 or more”), based on a time frame of the past 12 months. Mean total scores for gynephilic and androphilic experiences were derived. In the present study, we calculated a difference score between the participants’ mean androphilic and gynephilic scores.

On the basis of Kinsey ratings, participants who completed the face-to-face interview were classified, similar to Green (47), into the following three sexual orientation groups for both fantasy and behavior: (1) gynephilic (Kinsey global ratings of 0–1); (2) biphilic/androphilic (Kinsey global ratings of 2–6), and (3) no sexual fantasy or behavior.

Social Desirability

Social desirability refers to the desire to cast a favorable impression on others. It can threaten the validity of self-report scales if in answering questions respondents seek social approval or try to represent themselves in a favorable manner (106). People scoring high on social desirability tend to provide socially acceptable answers regardless if their response accurately describes them. Participants 18 years and older completed the Marlow-Crowne Social Desirability Scale (M-CSDS) (107), which consists of 33 true-false items. The scale contains 18 culturally acceptable but unlikely statements keyed in the true direction and 15 socially undesirable but probable statements keyed in the false direction for a maximum possible score of 33. Participants 17 years and under were given a shorter version of the M-CSDS (108), containing 20 items that consist of 12 culturally acceptable but improbable statements keyed in the true direction and eight socially undesirable but probable statements keyed in the false direction for a maximum possible score of 20. For the present study, the percentage of endorsed socially desirable items was calculated for each participant. In order to integrate the data from both versions of the M-CSDS, participants’ percentage score on each measure was converted to a proportion score which ranged from 0 to 1, which was used in all analyses. A higher proportion score indicates a greater propensity to give socially desirable responses. Several studies have found that the M-CSDS is a reliable and valid measure of social desirability (107, 109, 110).

RESULTS

Preliminary Analyses

Participants vs. Non-participants

Given that not all eligible participants were seen for follow-up, it is important to see to what extent the participants vs. non-participants were similar with regard to baseline characteristics, in part to gauge the internal validity of the sample (111).

The non-participants consisted of three subgroups: (1) patients who were eligible to participate in the study but were not contacted ($n = 163$), (2) patients who declined to participate ($n = 6$), and (3) patients who were not successfully traced ($n = 19$). Two sets of analyses were conducted to compare study participants vs. non-participants. First, the participants were compared to the patients who were eligible but not contacted. Second, the participants were compared to those who declined to participate and to those where contact was attempted but not successfully traced. Group comparisons were conducted on

five demographic variables (age at assessment in childhood, IQ, ethnicity, and parents’ marital status and social class), parent-report of behavior problems on the CBCL (three indices), and nine measures of childhood sex-typed behavior.

Of these 17 variables, there was only one significant difference between the 139 boys in the study compared to the 163 boys who were eligible to participate but were not contacted: participants had a higher IQ than non-participants, $t_{(289)} = 2.01$, $p = 0.046$.¹¹ The effect size for this comparison was small (unpooled $d = 0.22$) [for details, see (77), Tables 5, 6]. When compared to the six cases where participation in the study was declined and to the 19 cases where the families could not be traced, there was also only one significant difference: parent’s marital status, $\chi^2_{(2)} = 9.02$, $p = 0.011$. The participants did not differ significantly from the non-participants who refused; however, they differed significantly from the cases that could not be traced, $\chi^2_{(1)} = 6.39$, $p = 0.012$. The participants were more likely to have originated within a two-parent household than those who could not be traced. The comparison between the non-participants who refused and those who could not be traced approached significance ($p = 0.056$, Fisher’s exact test). Again, the non-participants who could not be traced were more likely to have come from a family composition that was not two-parent. A further summary of comparisons between the participants and those who declined or could not be traced can be found in the **Supplementary Material**.

Participants: Method of Recruitment

Using t -tests or chi-square tests, the 107 participants who entered the study through research contact were compared to the 32 participants who were recruited into the study after they had re-contacted the clinic for clinical reasons on the demographic variables, CBCL behavior problems in childhood, and the measures of childhood sex-typed behavior. There were no significant differences between the two groups on the demographic variables of age at assessment, ethnicity or parents’ social class and marital status ($ps > 0.05$). The comparison on childhood IQ approached significance, $t_{(137)} = 1.97$, $p = 0.051$, with the research entry participants having, on average, a higher IQ than the clinical entry participants. On the CBCL, there was a significant difference on Internalizing problems only, $t_{(137)} = -2.02$, $p = 0.046$, with the clinical entry participants rated by their parents as having more internalizing problems compared to the research entry participants. Of the nine measures of childhood sex-typed behavior, the two groups differed significantly on three: (1) free play, $t_{(119)} = -2.11$, $p = 0.037$, (2) the Gender Identity Interview for Children, $t_{(83)} = -2.09$, $p = 0.04$, and (3) the Gender Identity Questionnaire for Children, $t_{(95)} = 2.39$, $p = 0.019$, with the clinical entry participants having, on average, more childhood cross-gender behavior than the research entry participants. The percentage of clinical entry participants who were threshold for the diagnosis of GID in childhood did not differ significantly from the research entry participants (75.8 vs. 59.8%), $\chi^2_{(1)} = 1.83$. Of the 32 clinical entry participants, 8 had re-contacted the clinic because

¹¹IQ data were not available for 11 of the 163 boys who were eligible for the study but were not contacted.

of gender dysphoria. The above-described comparisons were repeated to compare the research and clinical entry participants but with these 8 participants excluded. With the eight participants who contacted the clinic for gender dysphoria removed, there were no significant group differences on demographic variables, CBCL behavior problems, and measures of childhood sex-typed behavior (all p s > 0.05).

Gender Identity at Follow-Up

Appendix 2 in Supplementary Material shows the follow-up data for gender identity and sexual orientation for each participant. Of the 139 participants, 17 (12%) were classified as persisters and the remaining 122 (88%) were classified as desisters. The age at the time of follow-up did not differ significantly between the persisters (Mean, 20.12 years; SD = 5.54) and desisters (Mean, 20.64 years; SD = 5.19), $t_{(137)} < 1$. Of the 107 participants who, for research purposes only, were contacted for the follow-up study, 10 (9%) were classified as persisters; of the 32 participants who were recruited into the study after they were seen for some type of clinical concern, 7 (22%) were classified as persisters. The difference in persistence rate as a function of recruitment entry type was not significant, $\chi^2_{(1)} = 2.53$, $p = 0.112$. The difference in persistence rate between those patients seen for the face-to-face assessment vs. those who were not (14.5 vs. 3.4%) was also not significant, $\chi^2_{(1)} = 1.70$, $p = 0.192$. **Supplementary Table 1** summarizes information on some domains of gender role outcome for the 17 participants classified as having persistent gender dysphoria.

For the 42 participants where the GDIQ was used to determine gender identity status at follow-up, four were classified as persisters and 38 were classified as desisters. Of the 38 desisters, three endorsed one item and the remainder endorsed none of the items.¹² The four participants classified as persisters endorsed between three and five items.

For the 64 participants where the GIDYQ-AA was used to determine gender identity status at follow-up, 12 were classified as persisters and 52 were classified as desisters. All 52 desisters had a mean score >3.00 on the GIDYQ-AA. Of the 12 persisters, 10 had a mean score ≤3.00 and two had mean scores that were >3.00. In spite of having mean scores on the GIDYQ-AA that were above the recommended cutoff for caseness (95), these two participants were considered persisters because their clinical interview data indicated that they were experiencing significant gender dysphoria. Thus, clinical judgment was used to make the final classification for these two participants.

For the remaining 33 participants, clinical interview, parent-report or chart data were used to classify the percentage who were persisters ($n = 1$; 3%) or desisters ($n = 32$; 97%).

The persistence rate of gender dysphoria was examined as a function of participants' GID diagnostic status in childhood (threshold vs. subthreshold). Of the 88 participants who met the full diagnostic criteria for GID in childhood, 12 (13.6%) were classified as persisters and the remaining 76 (86.4%) were

not. Of the 51 participants who were subthreshold for the GID diagnosis in childhood, 5 (9.8%) were classified as persisters and the remaining 46 (90.2%) were not. A chi-square analysis indicated that the rate of persistence did not differ significantly between the threshold and subthreshold groups, $\chi^2_{(1)} < 1$.

Over the years, prevalence rates for gender dysphoria in adults have varied considerably. The variation is likely a function of many factors, including definition, time period, and source of ascertainment. For example, in the Standards of Care of the World Professional Association for Transgender Health (112), probably relying on an estimate given in the DSM-IV-TR, the prevalence of gender dysphoria in adult males was estimated to be 1 in 30,000. In the meta-analysis by Arcelus et al. (113), the prevalence in adult males was estimated at 1 in 14,705. Lastly, Zhang et al.'s (114) review of recent population-based surveys estimated the prevalence of a self-reported transgender identity in adults to range between 0.33 and 0.53% (males and females combined). Regardless of which base rate figure one might choose to use as a point of comparison, the persistence rate of 12% (while low in an absolute sense) would be considerably higher than what one would detect in the general population.

Sexual Orientation at Follow-Up

Table 2 shows the Kinsey ratings for sexual orientation in fantasy. Data were not available for 10 participants, all of whom were desisters with regard to gender dysphoria. Based on the global rating for sexual orientation in fantasy, 43 (33.3%) participants were classified as gynephilic in fantasy and 82 (63.6%) were classified as biphilic/androphilic in fantasy. In the remaining four (3.1%) cases, the participants were classified as having no sexual fantasies and, therefore, a Kinsey rating could not be assigned.¹³ In all four cases, the participants were desisters. Of the 17 participants classified as persisters, 1 (5.9%) was gynephilic in fantasy and 16 (94.1%) were biphilic/androphilic in fantasy. For participants assigned a Kinsey rating between 0 and 6 in fantasy, we correlated the interviewer's Kinsey rating with the participants' responses on the EROS in which their mean gynephilic score was subtracted from their mean androphilic score. This yielded an $r(101) = 0.86$, $p < 0.001$.

Table 2 also shows the Kinsey ratings for sexual orientation in behavior. Data were available for 108 participants. Based on the global rating for sexual orientation in behavior, 29 (26.9%) participants were classified as gynephilic and 51 (47.2%) were classified as biphilic/androphilic. The remaining 28 (25.9%) participants did not report any sexual behaviors in the 12 months preceding the follow-up assessment. For participants assigned a Kinsey rating between 0 and 6 in behavior, we correlated the

¹²By "endorsed," we mean that the participants answered other than "never" on Items 1–4 or response options d–e for Item 5 (see **Appendix 1** in Supplementary Material).

¹³For 104 participants, the Kinsey rating in fantasy was based on the information provided in the face-to-face interview. For 21 other participants, the Kinsey rating in fantasy was based on self-report (by telephone), information available in the participant's health record, or parent-report. Participants were assigned a Kinsey rating of 6 if the participant self-identified as "gay" or if the health record indicated that the patient was "homosexual" or gay, etc. Participants were assigned a Kinsey rating of 0 if the patient self-identified as "straight" or "heterosexual," etc. A chi-square test showed that the percentage of participants who were classified as Kinsey 0–1 vs. 2–6 did not differ significantly as a function sexual orientation ascertainment method, $\chi^2_{(1)} = 1.49$.

TABLE 2 | Kinsey ratings for sexual orientation in fantasy and behavior.

Variable	Kinsey rating (fantasy) ^a															
	0		1		2		3		4		5		6		No fantasy	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Crush	36	36.7	0	0	2	2.0	4	4.1	2	2.0	11	11.2	29	29.6	14	14.3
Visual	31	31.6	1	1.0	2	2.0	10	10.2	3	3.1	12	12.2	29	29.6	10	10.2
Dreams	13	13.3	1	1.0	1	1.0	4	4.1	3	3.1	3	3.1	27	27.6	46	46.9
Masturbation	21	21.9	2	2.1	3	3.1	6	6.3	2	2.1	7	7.3	33	34.4	22	22.9
Global fantasy rating	40	31.0	3	2.3	3	2.3	8	6.2	2	1.6	14	10.9	55	42.6	4	3.1
	Kinsey rating (behavior) ^a															
	0		1		2		3		4		5		6		No sexual behavior	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Holding hands	26	26.3	0	0	0	0	5	5.1	1	1.0	1	1.0	35	35.4	31	31.3
Kissing	21	21.2	0	0	0	0	6	6.1	2	2.0	2	2.0	34	24.3	34	34.3
Genital/breast contact	13	13.1	0	0	0	0	3	3.0	2	2.0	1	1.0	35	35.4	45	45.5
Intercourse	8	8.2	0	0	0	0	3	3.1	2	2.0	0	0	27	27.6	58	59.2
Global behavior rating	28	25.9	1	0.9	0	0	4	3.7	3	2.8	1	0.9	43	39.8	28	25.9

^a0 = Exclusively gynephilic to 6 = Exclusively androphilic.

interviewer's Kinsey rating with the participants' responses on the SHQ in which their mean gynephilic score was subtracted from their mean androphilic score. This yielded an $r(75) = 0.79$, $p < 0.001$.

For those participants who could be assigned a Kinsey rating (i.e., excluding those participants who did not report any sexual fantasies or behavior or for whom data were not available), the correlation between Kinsey global fantasy and global behavior ratings was very strong, $r(78) = 0.92$, $p < 0.001$.

Group Classification as a Function of Gender Identity and Sexual Orientation in Fantasy at Follow-Up¹⁴

Combining gender identity (i.e., persister or desister) and sexual orientation in fantasy (i.e., gynephilic or biphilic/androphilic) at follow-up, the participants were classified into one of four outcome groups (for which we had all of the relevant data): (1) persistence of gender dysphoria with a biphilic/androphilic sexual orientation ($n = 16$); (2) desistance of gender dysphoria with a biphilic/androphilic sexual orientation ($n = 66$); (3) desistance of gender dysphoria with a gynephilic sexual orientation ($n = 42$); and (4) persistence of gender dysphoria with a gynephilic sexual orientation ($n = 1$). The participants who reported no sexual fantasies ($n = 4$) could not be included in this outcome classification. Given that only one participant was classified as gender dysphoric with a co-occurring gynephilic sexual orientation (Group 4), this category was excluded from subsequent analyses that compared these outcome groups.

¹⁴Given the strong correlation between Kinsey fantasy and behavior ratings and that there were fewer missing data on the Kinsey fantasy variable, participants were classified into one of the four outcome groups based on their fantasy ratings.

Demographic Characteristics in Childhood as a Function of Gender Identity and Sexual Orientation in Fantasy

Table 3 shows the demographic variables in childhood as a function of group. One-way ANOVAs and chi-square were conducted to evaluate whether the outcome groups differed on these variables. The groups differed significantly on four of the five childhood demographic variables. Duncan's multiple range test for unequal Ns showed that the biphilic/androphilic persisters were, on average, significantly older at the time of the childhood assessment than both the gynephilic desisters and the biphilic/androphilic desisters, who did not differ significantly from each other. The biphilic/androphilic desisters had, on average, a higher IQ than the biphilic/androphilic persisters but did not differ significantly from the gynephilic desisters. There was no significant difference in childhood IQ score between biphilic/androphilic persisters and gynephilic desisters. The biphilic/androphilic persisters were significantly more likely to come from a lower social class background compared to the gynephilic desisters and the biphilic/androphilic desisters, who did not differ significantly from each other (see also Figure 1). The biphilic/androphilic desisters were more likely to be living with both parents compared to the biphilic/androphilic persisters. There was no significant difference on marital status between the two desister groups.

The demographic variables from childhood on which the three groups differed—age at assessment, IQ, social class, and marital status—were significantly correlated (r s ranged from $|0.32-0.58|$) [see Table 12 in (77)]. To evaluate the predictive status of these variables on group outcome at follow-up, a multinomial logistic regression was performed. Table 4 shows the results. For these analyses, the biphilic/androphilic desisters served as the reference

TABLE 3 | Demographic characteristics as a function of group.

Variable		Group			<i>F</i> or χ^2	<i>p</i>	η^2 or Cramer's <i>V</i>
		Persisters Biphilic/ Androphilic (<i>n</i> = 16)	Desisters Biphilic/ Androphilic (<i>n</i> = 66)	Desisters Gynephilic (<i>n</i> = 42)			
Childhood							
Age (in years)	<i>M</i>	8.85	6.96	7.49	3.57	0.031	0.06
	<i>SD</i>	1.67	2.69	2.62			
IQ ^a	<i>M</i>	101.63	110.20	103.18	3.77	0.026	0.06
	<i>SD</i>	14.81	14.56	15.16			
Social class ^b	<i>M</i>	23.76	44.97	39.44	15.30	<0.001	0.20
	<i>SD</i>	10.22	13.64	15.91			
Marital status ^c							
Two-parent	<i>N</i> (%)	7 (43.8)	49 (74.2)	24 (57.1)	6.74	0.034	0.23
Other	<i>N</i> (%)	9 (56.3)	17 (25.8)	18 (42.9)			
Ethnicity							
Caucasian	<i>N</i> (%)	14 (87.5)	58 (87.9)	32 (76.2)	2.77	0.250	0.14
Other	<i>N</i> (%)	2 (12.5)	8 (12.1)	10 (23.8)			
Follow-up							
Age at follow-up (in years) ^d	<i>M</i>	20.32	22.13	17.85	10.41	<0.001	0.15
	<i>SD</i>	5.67	4.97	3.95			
IQ at follow-up ^{a,e,f}	<i>M</i>	99.07	110.47	104.19	3.82	0.025	0.07
	<i>SD</i>	16.29	13.54	17.50			
Follow-up interval (in years)	<i>M</i>	11.47	15.17	10.36	9.63	<0.001	0.04
	<i>SD</i>	6.77	6.03	4.85			
Social desirability ^g	<i>M</i>	0.44	0.43	0.52	3.07	0.051	0.07
	<i>SD</i>	0.17	0.18	0.19			

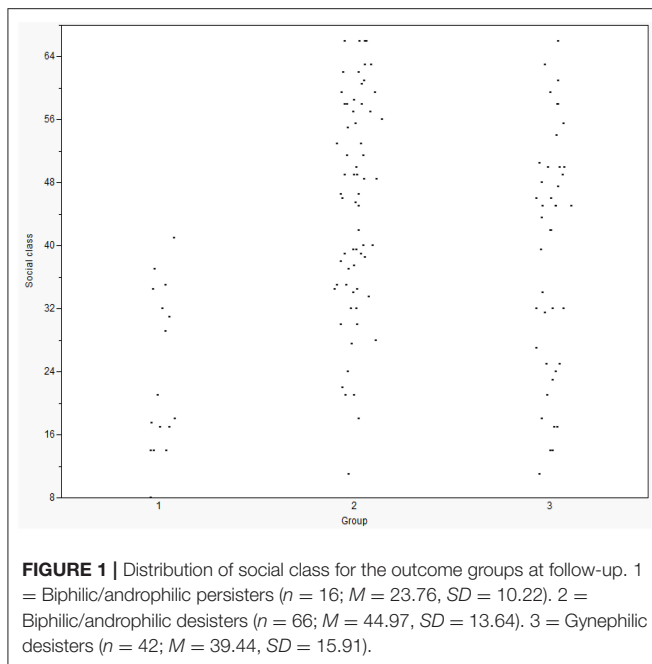
^aFull-Scale IQ was obtained with age-appropriate Wechsler intelligence scales.^bHollingshead's (78) Four Factor Index of Social Status (absolute range, 8–66).^cOther included the following family constellations: single parent, separated, divorced, living with relatives, or in the care of a child protection agency.^dInterval denotes the time between childhood assessment and follow-up assessment.^eFull Scale IQ was estimated using four subtests: Vocabulary, Comprehension, Block Design, and Object Assembly.^fAn IQ score was available only for participants who completed the face-to-face assessment.^gAbsolute range, 0.00–1.00. Higher score indicates a greater propensity to give socially desirable responses. Age at follow-up, IQ at follow-up, social class, and parent's marital status were co-varied.

group. Each coefficient, *B*, represents the change in the log odds for Group for a 1-unit increase in the corresponding predictor, controlling for all other predictors in the model. The next column presents the standard error (SE) for each *B*. The Wald statistic was the quantity used to determine the significance level of each predictor variable. The quantity, e^B , is the multiplicative change in the odds of being classified as a biphilic/androphilic persister (Model 1) or a gynephilic desister (Model 2) for a 1-unit increase in the corresponding predictor, and thus $100 \times (e^B - 1)$ represents the percentage change in the odds ratio for a 1-unit increase in that predictor (115).

It can be seen from **Table 4** that only social class had a significant contribution to the prediction of group outcome at follow-up (see also **Figure 1**). The biphilic/androphilic persisters had a 13% increase in odds of coming from a lower social class background compared to the biphilic/androphilic desisters.

However, social class did not predict outcome when the two desister groups were compared.

Table 3 also shows the variables of age, IQ, and social desirability scores at follow-up as a function of group. One-way ANOVAs revealed that both age and IQ differed significantly among the three groups ($ps < 0.01$), but social desirability scores did not. Duncan's multiple range test for unequal *N*s showed that the gynephilic desisters were, on average, younger than both the biphilic/androphilic persisters and the biphilic/androphilic desisters (both $ps < 0.05$), who did not differ significantly from each other. Regarding IQ at follow-up, the results were similar to those for IQ in childhood. The biphilic/androphilic desisters had, on average, a higher IQ than the biphilic/androphilic persisters ($p < 0.05$) but did not differ significantly from the gynephilic desisters. There was no significant difference in IQ between the biphilic/androphilic persisters and the gynephilic desisters.



Childhood Sex-Typed Behavior as a Function of Gender Identity and Sexual Orientation at Follow-Up
Supplementary Table 2 shows the means or percentage scores (for dichotomous measures) of the nine sex-typed measures obtained at the assessment in childhood as a function of the three outcome groups. ANCOVAs (with age at assessment, IQ, social class, and marital status covaried) or chi-square were used to examine whether the groups differed on any of these variables.¹⁵ There was a significant difference between the groups on four child-report measures (first drawn person on the Draw-a-Person, free play, Gender Identity Interview, and cross-sex peer preference on the Playmate and Play Style Preferences Structured Interview, and one parent-report measure (Gender Identity Questionnaire for Children). A statistical summary of these individual measures can be found in the **Supplementary Text** and the data are shown in **Supplementary Table 2**.

The childhood sex-typed behavior measures on which the groups differed were all significantly correlated (r s ranged from $|0.30-0.76|$) [reported in (77), Table 15].¹⁶ From these six measures (first drawn person on the Draw-a-Person, free play, Gender Identity Interview, cross-sex peer preference on the Playmate and Play Style Preferences Structured Interview, cross-sex toy preference on the Playmate and Play Style Preferences Structured Interview, and the Gender Identity Questionnaire for Children), a composite score of childhood sex-typed behavior was derived for each participant by taking the average of the

six variables (each expressed as z -scores).¹⁷ A higher composite z -score indicates more cross-gender behavior at the assessment in childhood.

To evaluate the influence of childhood sex-typed behavior and demographic variables on group outcome at follow-up, a multinomial logistic regression was performed using the composite score and the demographic variables on which the groups differed—age at assessment, IQ, and social class—as predictor variables. It can be seen from **Table 5** that both social class and the composite score of childhood sex-typed behavior were significant predictors of group outcome at follow-up in the first model, which compared the biphilic/androphilic persisters to the biphilic/androphilic desisters.

The biphilic/androphilic persisters had a 274% increase in odds of having a higher composite score (i.e., more childhood cross-gender behavior) and an 11% reduction in the odds of coming from a higher social class compared to the biphilic/androphilic desisters. Age at childhood assessment and IQ did not have a significant effect on group outcome (both p s > 0.05). In the second model, which compared the gynephilic desisters to the biphilic/androphilic desisters, the only significant predictor of group outcome was the composite measures of sex-typed behavior. The biphilic/androphilic desisters had a 48% increase in odds of having a higher composite score compared to the gynephilic desisters.

DISCUSSION

Methodological Issues

We were not able to recruit into the study all eligible patients; however, our analyses which compared the participants vs. the non-participants did not show any substantive or pervasive differences with regard to the baseline assessment characteristics, suggesting that the internal validity of the sample was not grossly compromised (111). The majority of follow-up participants were recruited for research purposes; however, a minority entered the study after having been seen in adolescence for some clinical issue. There was some evidence that the patients who were enrolled in the study after recontacting the clinic were, on average, more extreme in their gender-variant behavior in childhood; however, the percentage who were threshold for the GID diagnosis in childhood did not differ significantly between the two subgroups. Although the percentage of persisters was higher in the subgroup that had recontacted the clinic than the subgroup recruited for research purposes only (22% vs. 9%), the difference was also not statistically significant. If anything, the direction of the difference would suggest that the overall rate of persistence may have been slightly overestimated had we relied entirely on a “research-only” follow-up sample.

Another methodological issue is that we relied on different metrics to assess gender identity and gender dysphoria at follow-up. For example, we replaced the GDIQ with the GIDYQ-AA as we viewed the latter as a better measure; in some instances,

¹⁵The ANCOVA model was adjusted to accommodate a categorical covariate.

¹⁶Although the groups did not differ significantly on cross-sex toy preference on the PPPSI, this measure is included here because there was a trend in the direction of a significant group difference.

¹⁷For some participants, data were not available on all six measures. In these cases, the composite score was the average of the number of variables for which there were data.

TABLE 4 | Multinomial logistic regression of group outcome at follow-up.

Predictor	Biphilic/Androphilic persisters					Gynephilic desisters				
	<i>B</i>	<i>SE</i>	<i>Wald</i>	<i>p</i>	<i>e^B</i>	<i>B</i>	<i>SE</i>	<i>Wald</i>	<i>p</i>	<i>e^B</i>
Age at assessment	0.11	0.14	0.62	0.433	1.12	−0.02	0.09	0.03	0.856	0.98
IQ	0.02	0.03	0.85	0.358	1.02	−0.02	0.02	1.91	0.167	0.98
Social class	−0.14	0.04	13.66	<0.001	0.87	−0.01	0.02	0.13	0.716	0.99
Marital status	0.76	0.80	0.88	0.349	0.47	−0.43	0.52	0.70	0.402	1.54

Reference group is the Biphilic/Androphilic Desisters. This group was chosen as the reference because it had the largest group size.

TABLE 5 | Multinomial logistic regression predicting group outcome at follow-up.

Predictor	Biphilic/Androphilic persisters					Gynephilic desisters				
	<i>B</i>	<i>SE</i>	<i>Wald</i>	<i>p</i>	<i>e^B</i>	<i>B</i>	<i>SE</i>	<i>Wald</i>	<i>p</i>	<i>e^B</i>
Age at assessment	0.26	0.16	2.90	0.09	1.30	−0.14	0.11	1.55	0.21	0.87
IQ	0.02	0.03	0.58	0.45	1.02	−0.03	0.01	2.77	0.10	0.97
Social class	−0.12	0.03	12.28	<0.001	0.89	−0.01	0.01	0.51	0.47	0.99
Composite z-score	1.32	0.55	5.82	0.02	3.74	−0.66	0.31	4.38	0.04	0.52

Reference group is the Biphilic/Androphilic Desisters. This group was chosen as the reference because it had the largest group size. A preliminary analysis with marital status included as a predictor variable showed that it did not have a significant effect and was, therefore, excluded in the final regression model. As suggested by Reviewer 3, per Benjamin et al. (116), for the “discovery of new effects,” *p*-values between 0.05 and 0.005 should be viewed as “suggestive” (i.e., informative, but cautiously interpreted), and *p*-values < 0.005 as “significant” (i.e., stronger evidence for the implausibility of a difference merely by chance).

we relied solely on interview data or information available in the patient’s medical chart. However, we did not detect any substantive difference in the percentage of persisters across these different sources of information and thus do not believe that such method variance challenges the validity of the findings.

Although a minority of participants were seen on more than one occasion for follow-up, the majority were not. Thus, our results and interpretation of the follow-up data are largely limited to one “moment in time,” at a mean age of 20.58 years. It would, of course, be of value to have additional follow-up of the patients as they move further into adulthood in order to assess the stability (or lack thereof) of the data with regard to both gender identity and sexual orientation. In our own clinical experience, for example, we have observed that some of the patients seen during adolescence “fluctuated” between self-identifying as transgender and self-identifying as gay. Others have noted that a small number of apparent or presumed desisters during adolescence subsequently identified as transgender when seen at a later point in time (117).

Summary of Key Findings

The present study provided follow-up data with regard to gender identity and sexual orientation in boys referred clinically for gender dysphoria. There were three key findings: (1) the persistence of gender dysphoria was relatively low (at 12%), but obviously higher than what one would expect from base rates in the general population; (2) the percentage who had a biphilic/androphilic sexual orientation was very high (in fantasy: 65.6% after excluding those who did not report any sexual fantasies; in behavior: 63.7% after excluding those who did not have any interpersonal sexual experiences), markedly higher than what one would expect from base rates in the general

population; (3) we identified some predictors (from childhood) of long-term outcome when contrasting the persisters with a biphilic/androphilic sexual orientation with the desisters with a biphilic/androphilic sexual orientation and when contrasting the desisters with a biphilic/androphilic sexual orientation and the desisters with a gynephilic sexual orientation.

The 12% persistence rate was somewhat lower than the overall persistence rate of 17.4% from the prior follow-up studies of boys combined. When compared to the three most methodologically sound follow-up studies, the persistence rate was higher than the 2.2% rate found by Green (47), but lower than the 20.3% rate found by Wallien and Cohen-Kettenis (52) and the 29.1% rate found by Steensma et al. (51). There is one methodological caveat regarding the Steensma et al. study that is worth noting. In their study, the mean interval between assessment and follow-up was relatively short (7.21 years). The patients were eligible for follow-up if they were at least 15 years of age. Given the relatively short interval between the assessment in childhood and the follow-up assessment in adolescence, this meant that patients who had been assessed at younger ages in childhood would not have been old enough to participate in the follow-up assessment. Given that Steensma et al. found that (older) age at the time of the assessment in childhood was a significant predictor of persistence, it is conceivable that their persistence rate was an overestimate. Nonetheless, in the broadest sense, our data were quite consistent with the general finding from the prior follow-up studies that desistance from gender dysphoria is by far the more common outcome.

In our study, we did not find that persistence was more common among boys who were threshold for the diagnosis of GID when compared to the boys who were subthreshold (13.6% vs. 9.8%) although the pattern was in the same direction

as that found by Wallien and Cohen-Kettenis (52) and Steensma et al. (51). We would, therefore, argue that the threshold-subthreshold distinction should not be abandoned in future follow-up studies although such studies might profit from using a symptom count of DSM indicators in addition to the dichotomous coding of the diagnosis as threshold vs. subthreshold. Consistent with both Wallien and Cohen-Kettenis and Steensma et al., our composite measure of sex-typed behavior in childhood was a significant predictor of outcome in that the patients classified as persisters with a biphilic/androphilic sexual orientation had more severe gender-variant behavior than the patients classified as desisters with a biphilic/androphilic sexual orientation; in addition, desisters with a biphilic/androphilic sexual orientation had more gender-variant behavior than the desisters with a gynephilic sexual orientation. Thus, dimensional measurement of gender identity and gender role behaviors from childhood provides added nuance in characterizing longer term trajectories with regard to both gender identity and sexual orientation.

With regard to sexual orientation at follow-up, the percentage of patients with a biphilic/androphilic sexual orientation in either fantasy or behavior was reasonably similar to those reported on in the prior follow-up studies which included standardized assessment measures (47, 51, 52). This finding also converges with three representative, general population prospective studies (118–120) and many retrospective studies (43) which document a significant association between patterns of gender-typed behavior in childhood and later sexual orientation.

The multinomial logistic regression analysis (**Table 4**) also showed a trend for the persisters with a biphilic/androphilic sexual orientation to be older at the time of the assessment in childhood compared to the desisters with a biphilic/androphilic sexual orientation; however, when the composite measure of sex-typed behavior in childhood was added to the equation (**Table 5**), age at assessment in childhood no longer showed such a trend [cf. Steensma et al. (51)]. In our smaller study of girls with GID (46), the persisters were, on average, 2.5 years older than the desisters at the time of the assessment in childhood (11.08 vs. 8.59 years) although the difference was not significant. It is our view that age at the time of a childhood assessment in relation to long-term outcome should continue to be examined in future follow-up studies.

Social class was a significant predictor of outcome: the persisters with a biphilic/androphilic sexual orientation were from a lower social class background compared to the desisters with a biphilic/androphilic sexual orientation (even after controlling for the other demographic variables). Why might this be the case? Because we had not made formal *a priori* predictions of outcome regarding any of our demographic variables, it is, of course, important to see whether or not it will be replicated in new follow-up studies. At present, our interpretation of the social class effect reflects on its relationship to other literatures.

One possibility pertains to the notion that acceptance of a gay or homosexual sexual identity is less in “working class” subculture (121). If this is, in fact, the case, it has been argued that transitioning from male to female—the so-called “homophobic” hypothesis with regard to gender dysphoria in adults (122)—would allow an androphilic sexual orientation to be more

acceptable. Future studies would need to systematically examine whether boys with persistent GID first attempt to live as gay men before transitioning to the female gender role and whether or not this temporal sequence, when it occurs, is related to social class background.

In the present study, it could be hypothesized that the parents of persisters held less favorable views of androphilia (homosexuality) compared to the desisters and thus predisposed to persistence in order to “normalize” one’s sexual orientation. However, this is simply a conjecture as parental attitudes toward homosexuality were not measured in the study sample. Indeed, none of the follow-up studies to date on boys with gender dysphoria have specifically examined attitudes toward homosexuality as a predictor of outcome.

Social class could also be a proxy for other explanatory factors. For example, in the present study, a lower social class background was significantly correlated with age at assessment in childhood ($r = 0.44$) and families where there had been a separation/divorce, etc. ($r = 0.58$). If one wanted to make the case that a later age at assessment might be associated with persistence (for a variety of reasons), perhaps social class is associated with a “delay” in seeking out an assessment and possible treatment (e.g., family stress, various other mental health challenges in the child and/or the family, etc.). In one study comparing the demographic characteristics of children vs. adolescents clinic-referred for gender dysphoria, it was found that the adolescents were more likely than the children to come from a lower social class background and from families in which there had been a separation/divorce, etc. (123).

Clinical Implications

What clinical implications might be drawn from our data on the persistence and desistance rates of gender dysphoria in children? First, it should be recognized that the boys in the current study were seen during a period of time when treatment recommendations, if such were made, often aimed to reduce the gender dysphoria between the child’s felt gender identity and biological sex. If one peruses the treatment literature, such recommendations were carried out using many therapeutic modalities: psychotherapy or psychoanalysis, behavior therapy, group therapy, parent-counseling, and interventions in the naturalistic environment, such as encouragement of same-sex peer relations [see, e.g., (124–126); for reviews, see (127, 128)].¹⁸

¹⁸This “broad stroke” summary of therapeutic goals is not meant to minimize the complexity of ethical issues regarding how treatment has been conceptualized over the years [see, e.g., (129–133)]. In the early years, treatment recommendations included other goals: for example, Bakwin (44) wrote that “Suggestions for management...[were]...designed to encourage gender appropriate behavior and to prevent homosexuality” [p. 620, emphasis added; see also (134)]. Rekers (135) was subsequently quite transparent regarding the influence of his own religious beliefs in formulating treatment goals, sometimes congruent with parents’ religious beliefs (see p. 131). Prayer appears to have guided Rekers’ selection of behavior therapy as a treatment modality for the treatment of his patients with childhood GID (p. 131). Money and Russo (50) wondered what the course of psychosexual differentiation might be if “a group of boys with discordance of gender identity/role [were] transferred from the home of origin to, say, a children’s recovery center or foster home...as happens in the case of child-abuse dwarfism...” (p. 40). In our own clinic, although some parents might have desired or requested that treatment be designed in order to prevent homosexuality, this was a goal that we never endorsed [see (136), pp. 391–393]. Over the years, many secular-minded

In our own sample, the kinds of treatments that the boys received, if any, were quite variable but it is beyond the scope of this article to describe them in general [however, for examples, see (136, 140, 141)]. It can, however, be said with certainty that the vast majority of boys were seen during a particular period of time when the therapeutic approach of recommending or supporting a gender social transition prior to puberty was not made. Indeed, in the current study, there was only one patient who had socially transitioned prior to puberty (at the suggestion and support of the professionals involved in this individual's care) and this particular patient was one of the persisters with a biphilic/androphilic sexual orientation. Second, it should also be recognized that, for the boys seen in the current study, none who were in late childhood and had (likely) entered puberty (Tanner Stage 2) had received puberty-blocking hormone treatment (GnRH analogs) to suppress somatic masculinization (142, 143) until sometime during adolescence.

In contrast, in recent years, it has become more common for some clinicians to recommend a gender social transition prior to puberty [e.g., (69, 144–147); for discussion, see (148–150)]. It has also become more common for parents to have already implemented a gender social transition on their own, without any formal input from a health professional (151). As argued by Zucker (64, 152), this is a very different type of psychosocial treatment designed to reduce gender dysphoria when compared to the other kinds of treatments noted above that have been recommended over the years.

The study by Steensma et al. (51), which found the highest rate of persistence, included some patients who had made a partial or complete gender social transition prior to puberty and this variable proved to be a unique predictor of persistence (see the Introduction). Rae et al. (153) recruited from a variety of community groups a sample of 85 markedly gender non-conforming children (Mean age, 7.5 years), none of whom had socially transitioned at a baseline assessment. At the time of follow-up, at a mean of 2.1 years later, 36 (42.3%) had socially transitioned and 49 (57.6%) had not. Using a composite of various metrics of gender identity and gender role behaviors, Rae et al. found that those who subsequently socially transitioned had more extreme gender-variant behavior at baseline than those who had not. Thus, this short-term follow-up study was consistent

with the longer-term findings reported on by Wallien and Cohen-Kettenis (52), Steensma et al. (51), and the present study.

To date, however, there are no long-term follow-up studies of clinic-referred samples of children who had all socially transitioned prior to puberty. Future follow-up studies should be able to capture a much larger subgroup of such children and compared to those who have not with regard to long-term outcome with regard to persistence and desistance [e.g., (154)]. The persistence-desistance rates found in this study and the ones preceding it can be used as a comparative benchmark for samples in which a social transition took place prior to puberty.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The research protocol was reviewed and approved by Clarke Institute of Psychiatry (subsequently the Centre for Addiction and Mental Health) and the University of Toronto. All participants who completed the face-to-face assessment gave written informed consent.

AUTHOR CONTRIBUTIONS

DS contributed to the conceptualization, data collection, data analysis, interpretation, and writing of the paper. SB contributed to the conceptualization and interpretation of the study. KZ contributed to the conceptualization, data collection, data analysis, interpretation, and writing of the paper. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpsy.2021.632784/full#supplementary-material>

clinicians—although clearly opposed to any type of preventive efforts with regard to sexual orientation—argued in favor of reducing gender dysphoria vis-à-vis natal sex, if that was feasible. Meyer-Bahlburg (125), for example, wrote: "...we cannot rule out the possibility that early successful treatment of childhood GID will diminish the role of a continuation of GID into adulthood. If so, successful treatment would also reduce the need for the long and difficult process of sex reassignment which includes hormonal and surgical procedures with substantial medical risks and complications" (p. 362). Along similar lines, Cohen-Kettenis and Pfäfflin (33) remarked: "Relatively little dispute exists regarding the prevention of transsexualism, though evidence about the effectiveness of treatment in preventing adult transsexualism is also virtually nonexistent" (p. 120). In more recent years, what the best-practice should be for the treatment of gender dysphoria in children has been widely discussed and debated, which highlight the various limitations of treatment effectiveness studies (137–139).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer RB declared a past co-authorship with one of the authors KZ to the handling Editor.

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Part 1: Scrutinizing the Evidence

2 March 2019



In 2010, Tavistock and Portman NHS Trust's Gender Identity Development Service (GIDS) launched a trial of [puberty blockers](#) for children in their early teens with gender dysphoria. This was—and remains—an experimental treatment. These drugs, Gonadotropin-Releasing Hormone agonists (GnRHa), have not been certified as a safe or effective treatment for gender dysphoria by their manufacturers, nor by the National Institute for Clinical Excellence.

The Director of GIDS, Polly Carmichael, was keenly aware of the controversy over these drugs. 'The question is, if you halt your own sex hormones so that your brain is not experiencing puberty, are you in some way altering the course of nature?' ([Guardian, 14 August 2008](#)). '[T]he debate revolves around

the reversibility of this intervention—physical and also psychological, in terms of the possible influence of sex hormones on brain and identity development' ([Carmichael and Davidson 2009](#)). Before 2010, GIDS administered blockers to children only when they reached 16; this is the age at which young people have the presumptive capacity to [consent](#) to medical treatment.

This cautious approach was vociferously opposed by two organizations devoted to transgendering of children, [Mermaids](#) and the [Gender Identity Research and Education Society](#). As Carmichael later recounted: 'There was a lot of pressure coming from certain group [sic] to introduce it—families were travelling abroad because they knew it was available in Holland and America. As a service, we didn't have the evidence one way or the other, so the best way to do it was as part of a research study' ([Vice, 16 November 2016](#)).

Tavistock Trust announced the study on its website in [April 2011](#). It stated that GnRHa treatment 'is deemed reversible'. This assertion contradicted the study's own research protocol (which I obtained under Freedom of Information from the NHS Health Research Authority). '*It is not clear* [my emphasis] what the long term effects of early suppression may be on bone development, height, sex organ development, and body shape and their reversibility if treatment is stopped during pubertal development' (Early Pubertal Suppression in a Carefully Selected Group of Adolescents with Gender Identity Disorder, 4 November 2010, Research Ethics Committee number 10/H0713/79). A paediatrician on the study team, Russell Viner, frankly acknowledged the risks. 'If you suppress puberty for three years the bones do not get any stronger at a time when they should be, and we really don't know what suppressing puberty does to your brain development. We are dealing with unknowns' ([Daily Mail, 25 February 2012](#)).

The study received considerable publicity, being reported in the *Mirror*, the *Daily Telegraph*, and the *Times*. As Carmichael observed, 'as professionals we need to be looking at the long term and making sure this treatment is safe' ([Daily Telegraph](#), 15 April 2011). The bare outlines of the study can be gleaned from a conference presentation and a half-page published abstract ([Gunn et al. 2015a](#); [Gunn et al. 2015b](#)). From 2010 to 2014, 61 children aged between 12 and 15 were recruited; puberty blockers were administered to 44 of them.

Even before the final patient was enrolled, Carmichael announced success to the tabloid press. 'Now we've done the study and the results thus far have been positive we've decided to continue with it' ([Daily Mail](#), 17 May 2014). In fact the decision had already been made, at least six months earlier ([Daily Mail](#), 17 November 2013). Tavistock Trust then embraced the drug regime with enthusiasm. Three years later, GIDS (and its satellite operation in Leeds) had prescribed puberty blockers for a total of 800 adolescents under 18, including 230 children under 14 ([Daily Mail](#), 30 July 2017). By 2018, new prescriptions were running at 300 per year ([BBC News](#), 2 July 2018). Freedom of Information requests have failed to elicit more recent figures because GIDS does not collate basic data on this experimental treatment—and neither does the University College London Hospitals NHS Foundation Trust, which provides its endocrinology services.

Over a thousand adolescents have been given puberty blockers on the basis that the 2010–14 study yielded 'positive' results. Tavistock is surprisingly reticent to share these results with the scientific community. GIDS has a webpage on the [evidence base](#) for puberty blockers. It notes that 'research evidence for the effectiveness of any particular treatment offered is still limited.' There is no mention of its own study; it cites only research from the Netherlands. The former director of GIDS stated last year that the 'project is ongoing and the results are yet to be published' ([De Ceglie 2018](#)).

Diligent searching does, however, uncover some unpublished results. Most revealing is an appendix within a report to Tavistock's Board of Directors ([Carmichael 2015](#)). It tracks the

first 30 children on GnRHa, measuring changes after one year of the drug regime. The text is sometimes internally inconsistent and occasionally contradicts the tabulated figures, suggesting that it was prepared in haste. But we can summarize those changes that were reported as statistically significant (p -value < .05). Only one change was positive: 'according to their parents, the young people experience less internalizing behavioural problems' (as measured by the Child Behavior Checklist). There were three negative changes. 'Natal girls showed a significant increase in behavioural and emotional problems', according to their parents (also from the Child Behavior Checklist, contradicting the only positive result). One dimension of the Health Related Quality of Life scale, completed by parents, 'showed a significant decrease in Physical well-being of their child'. What is most disturbing is that after a year on blockers, 'a significant increase was found in the first item "I deliberately try to hurt or kill self"' (in the Youth Self Report questionnaire). Astonishingly, the increased risk of self-harm attracted no comment in Carmichael's report. Given that puberty blockers are prescribed to treat gender dysphoria, it is paradoxical that 'the suppression of puberty does not impact positively on the experience of gender dysphoria' (measured by the Body Image Scale). When differentiated by sex, the impact was positive for boys on one aspect of body image, but negative for girls on two aspects.

Preliminary results (44 children after one year on GnRHa) were also presented at a symposium at the World Professional Association for Transgender Health ([Carmichael et al. 2016](#)). Only the abstract is available. 'For the children who commenced the blocker, feeling happier and more confident with their gender identity was a dominant theme that emerged during the semi-structured interviews at 6 months. However, the quantitative outcomes for these children at 1 years time suggest that they also continue to report an *increase in internalising problems and body dissatisfaction* [my emphasis], especially natal girls.' Why were these negative results never published?

The study apparently contributed data on outcomes to one publication, coauthored by Carmichael ([Costa et al. 2015](#)). The abstract proclaims that 'adolescents receiving also

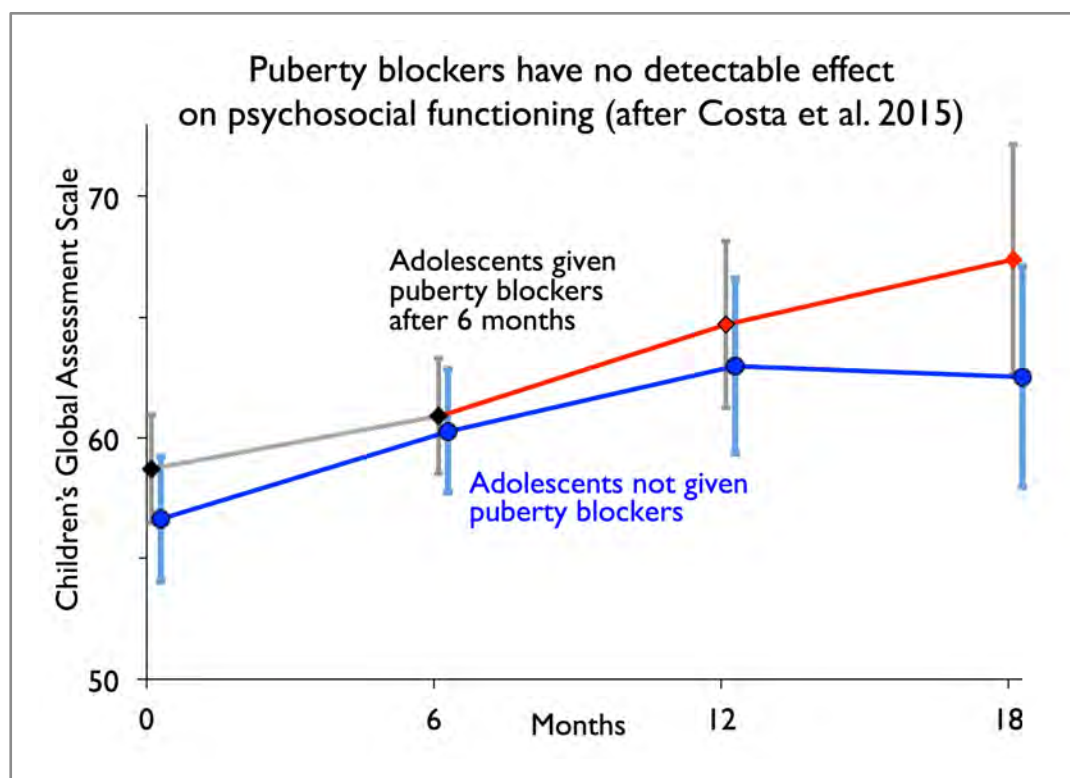
puberty suppression had significantly better psychosocial functioning after 12 months of GnRHa ... compared with when they had received only psychological support'. The article is treated in the literature (e.g. [Heneghan and Jefferson 2019](#)) as providing evidence in favour of puberty blockers. But the abstract is misleading: the analysis actually *failed to detect any difference* between children who were given blockers and those who were not. To understand this, we need to scrutinize the article in detail. (Statistically minded readers will recognize the fallacy described by [Gelman and Stern 2006](#).)

The analysis starts with 201 adolescents diagnosed with gender dysphoria. The children were divided into two groups: those deemed eligible for puberty blockers immediately, and those who needed more time due to 'comorbid psychiatric problems and/or psychological difficulties'. This second group did not receive any physical intervention during the time of this analysis, and so serves as a control group. Both groups received psychological support. The article chooses one outcome, psychosocial functioning as measured by the Children's Global Assessment Scale (CGAS). This scale was administered at the outset, and then after six, twelve, and

eighteen months. It is intriguing that the article omits the outcomes that were negative in the preliminary results: the Child Behavior Checklist, the Youth Self Report Questionnaire, the Health Related Quality of Life scale, and the Body Image Scale.

The authors graph the CGAS results, but without confidence intervals—which indicate the extent of random statistical variation or noise. The smaller the sample, the greater this noise. These samples shrank over time: after eighteen months, the group getting puberty blockers numbered only 35, and the control group 36. The article does not explain why two thirds of the subjects disappeared. Presumably they did not stop the medication, because all 44 children given blockers in the 2010–14 study continued the drug regime for two years ([Gunn et al. 2015b](#)).

My graph plots the results with standard 95% confidence intervals. The group given puberty blockers from six months onwards showed improvement at eighteenth months: the average CGAS score had increased from 61 to 67 (coloured red on the graph). This improvement is statistically significant, and it is the one that the authors chose to highlight.



However, these children also received psychological support, and so attributing this improvement to medical intervention is unjustified. The crucial comparison is between the group receiving blockers and the control group. The latter's average CGAS score (coloured blue) after eighteen months was lower, 63 compared to 67. But this difference is *not statistically significant*; the 95% confidence intervals substantially overlap. (For statistically minded readers, a two-tailed *t*-test for the difference between group means yields a *p*-value of .14, far beyond the conventional .05 threshold.) In other words, the samples were so small, and there was such wide variation in scores within each group, that we can draw *no conclusions*. There is no evidence that puberty blockers improve psychosocial functioning. Presumably this is why GIDS omits the article from its own [evidence base](#).

The abstract describing the baseline characteristics of the children in the 2010–14 study concluded: 'Assessment of growth, bone health and psychological outcomes *will* [my emphasis] be important to assess the medium and long-term safety and effectiveness of early intervention' ([Gunn et al. 2015b](#)). However, GIDS apparently failed to collect any data on its experimental subjects after they turned 18. In a startling admission, Carmichael and coauthors blame 'the frequent change in nominal and legal identity, including NHS number in those referred on to adult services'—'to date they have not been able to be followed up' ([Butler et al. 2018](#)). (Transgender activists successfully lobbied the NHS to provide new numbers to patients as well as to change the 'gender' on their medical records.)

To summarize, GIDS launched a study to administer experimental drugs to children suffering from gender dysphoria. Between 2010 and 2014, puberty blockers were given to 44 children. This study yielded only one published scientific article on outcomes. It showed no evidence for the effectiveness of GnRHa: there was no statistically significant difference in psychosocial functioning between the group given blockers and the group given only psychological support. In addition, there is unpublished evidence that after a year on GnRHa children reported greater self-harm, and that girls experienced more behavioural and emotional problems and expressed greater dissatisfaction with their body—so puberty blockers exacerbated gender dysphoria. Yet the study has been used

to justify rolling out this drug regime to several hundred children aged under 16. Almost five years after the last patient was enrolled in the experiment, there is no evidence to substantiate Carmichael's claim 'that the results thus far have been positive'.

The Director of GIDS needs to answer these questions about the 2010–14 experimentation with puberty blockers:

- *On what evidence did you claim in 2014 that 'the results thus far have been positive'?*
- *When preliminary results in 2015 showed that children after a year on blockers showed a statistically significant increase in reported self-harm, was this ever investigated?*
- *Why did you never publish the negative results reported to Tavistock's Board of Directors in 2015 and to WPATH in 2016?*
- *Why did your only published article (Costa et al. 2015) using data from the study omit all the outcomes that were negative in the preliminary results (Child Behavior Checklist, Youth Self Report questionnaire, Health Related Quality of Life scale, and Body Image Scale)?*
- *In your article, why did the abstract and conclusion not report the finding that there was no statistically significant difference between the group given GnRHa and the control group?*
- *In your article, what accounts for the reduction in the number of subjects from 201 to 71 over eighteen months?*
- *What steps have you taken to monitor the 'long-term safety and effectiveness of early intervention', as these experimental subjects become adults?*

Note

How many subjects from the 2010–14 study are included in Costa et al. (2015) is unclear. The 2010–14 study gave GnRHa to 44 adolescents, referred at ages from 10 to 15. ([Gunn et al. 2015a, 2015b](#)). One would expect all of them to be included in the 'immediately eligible' group in Costa et al. (2015), along with some older adolescents to boost the sample size. The article counts 101 children in this group at 6 months when GnRHa commenced (Table 2), starting at ages from 13 to 17 (Table 1). The age range indicates the exclusion of some children from the 2010–14 study: those who commenced GnRHa from ages 10 to 12. Why? Another puzzle is worth noting. When I requested the Research Ethics Committee number from Tavistock and

Portland NHS Trust under Freedom of Information, it provided the number 10/H0718/62. According to the NHS Health Research Authority, however, this number refers to a study that was given an 'unfavourable opinion' and therefore could not proceed.

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Part 2: An Update

22 July 2019

Tavistock and Portman NHS Trust started an experiment in 2011, using Gonadotropin-Releasing Hormone agonist (GnRHa) to block puberty in children suffering gender dysphoria. [My original investigation for Transgender Trend](#) (posted on 5 March 2019) raised serious questions about this experiment. The outcomes were never published in a scientific journal. And I discovered unpublished evidence that initial results, after the drugs had been administered for one year, were predominantly negative.

My research was reported by the [Daily Telegraph](#). It is elaborated in a chapter in [Inventing Transgender Children and Young People](#), edited by Michele Moore and Heather Brunsell-Evans. It has just [featured on BBC Newsnight](#), broadcast on 22 July.



Following my original investigation, I wrote to Professor Russell Viner at University College London (UCL), the experiment's principal investigator, and Dr Polly Carmichael, Director of the Tavistock's Gender Identity

Development Service (GIDS), asking why they failed to publish results. I also contacted the Research Ethics Committee which originally granted permission, pointing out that the researchers consistently failed to provide annual progress reports. Another researcher working with Transgender Trend submitted a [Freedom of Information request](#) for further details of the experiment, and this apparently prompted GIDS to post a [webpage](#) entitled 'A statement and update on the Early Intervention Study by the Tavistock and Portman NHS Foundation Trust' at the end of June. The statement first came to notice in the [Sunday Times](#) on 7 July.

The statement runs to more than 4,600 words. The first 3,600 detail the origins of the experiment, emphasizing two points. First, in the years before 2011, families and transgendering organizations like Mermaids lobbied vigorously to lower the age at which GnRHa drugs were administered to children, and the Tavistock could not resist this pressure. Second, the researchers could not employ the standard randomized trial to assess the effects of blocking puberty. Both points have some justification, but one

wonders why such a lengthy apologia would be necessary if the experiment's outcomes have been favourable.

The Tavistock now claims 'The study concluded in February 2019 when the last cohort member began the next stage of therapy (cross-sex hormones) at age 17 years'. When the [Daily Telegraph](#) asked GIDS to respond to my questions

(before publication on 6 March), its spokesman did not mention that the study had just concluded. Similarly, on 26 March, Viner replied to my letter, stating 'The early intervention study cohort *remain under study*

as some of the last recruited young people have still not completed the treatment pathway' (italics added). Carmichael's reply on the same date also said nothing about the study having been concluded in February. The webpage on GIDS' [research](#) still describes it as 'a study that is currently underway'.

When [Lord Lucas](#) kindly followed my suggestion to ask a parliamentary question, he was told on 22 May that the Tavistock 'plans to publish the data once all of the young people in the study have reached the stage when a clinical decision is made about moving from pubertal suppressants to cross-sex hormones, which the Trust expects to occur in the next 12 months'. Did the Tavistock mislead the Parliamentary Under-Secretary for the Department of Health and Social Care, who answered the question? The earliest indication that the experiment had terminated came from the NHS Research Ethics Committee, which informed me on 25 June that a final report is now being drafted by the chief investigator, Viner. One suspects that this precipitous ending – which has apparently been backdated to February – was forced by Transgender Trend's scrutiny.

Whenever the study formally ended, the researchers have been collecting data for eight years. The first subject consented to GnRHa drugs in June 2011. All 44 subjects enrolled in the experiment had completed one year on the drugs by mid 2015, two years by mid 2016, and three years by mid 2017. The results should have been closely monitored and the outcomes published in a scientific journal. After all, GnRHa has never been licensed for treating gender dysphoria, not just in the United Kingdom but anywhere in the world.

Five years ago, in 2014, Carmichael told the [Mail on Sunday](#) that the study demonstrated favourable outcomes: 'Now we've *done* the study and the results thus far have been *positive* we've decided to continue with it' (italics added). She even appeared in a BBC television programme – 'I Am Leo', aimed at audiences aged 6 to 12 – to promote the benefits of GnRHa drugs. ([See our analysis of the programme here](#)).

[A video clip can be found here](#)



Credit: [@STILLtish](#)

The Tavistock's statement says remarkably little about the experiment's outcomes. It cites Carmichael and Viner's presentation to the 2014 World Professional Association for Transgender Health (WPATH) conference showing 'there was *no overall improvement* in mood or psychological wellbeing using standardized psychological measures' (italics added). This finding was presented in February 2014, but just four months later Carmichael claimed 'the results thus far have been positive'. I cannot find slides from this 2014 presentation, but Carmichael's [presentation](#) to the 2016 WPATH conference apparently recycles the same finding. It also acknowledges that 'Natal girls showed an *increase in internalising problems* from t0 to t1 [after 12 months on GnRHa] as reported by their parents' (italics added). This negative outcome is omitted from the Tavistock's statement.

The statement also omits two other statistically significant negative outcomes that I discovered buried in an [appendix](#) submitted to the Tavistock's Board of Directors in 2015. Most seriously, after a year on GnRHa, 'a significant increase was found in the first item "I deliberately try to hurt or kill self"'. Evidence that an experimental treatment raised the risk of self-harm should be a major concern, but GIDS have never addressed this finding.

There is a backhanded admission in a [presentation](#) given by the GIDS endocrinologist, Professor Gary Butler, to the 2016 WPATH conference (only the abstract is available). 'Partial suppression [of sex hormones by GnRHa] may produce more side effects due to hormone swings, and also a lowering in mood leading to clinical depression. Expectations of improvement in functioning and relief of the dysphoria are not as extensive as anticipated, and psychometric indices do not always improve nor does the prevalence of measures of disturbance such as deliberate self harm improve.' Butler's presentation is, curiously enough, not cited in the Tavistock's statement.

The Tavistock's statement also fails to mention an article coauthored by Carmichael ([Costa et al. 2016](#)), which includes data from some subjects in the Early Intervention Study. This article purported to show beneficial outcomes from GnRHa, but I have [demonstrated](#) that the authors made an elementary statistical error. The analysis actually failed to detect any difference between children who were administered GnRHa and those who were not.

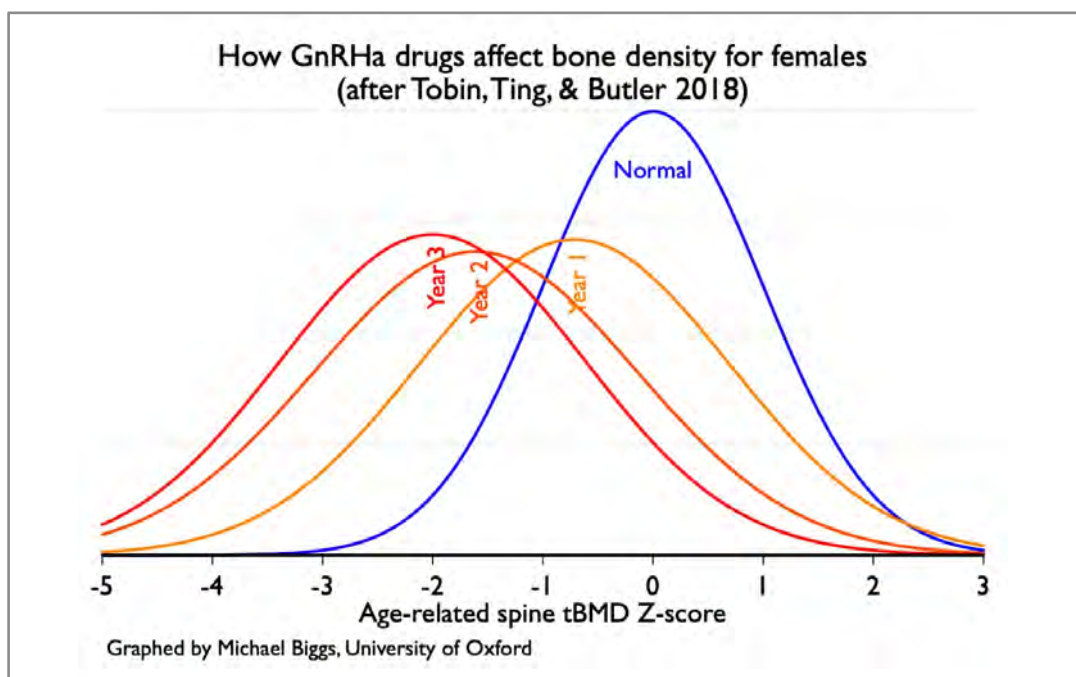
Finally, the Tavistock's statement cites a recent article on bone density, coauthored by Butler ([Tobin, Ting, and Butler 2018](#)). The article – a one-page abstract – emphasizes that bone density did not decline, in absolute terms, after GnRHa was administered. This is extremely misleading, as pointed out by [Dr Michael Laidlaw](#) and reiterated by [Dr William J. Malone](#), both endocrinologists.

Growing children need bone density to *increase*. The article admits that the children did experience a decline relative to the normal standard for their age group, and this decline was especially marked for girls. My graph shows the distributions implied by the article's figures.

It is obvious that a substantial minority of the girls on GnRHa suffered from abnormally low bone density.

In sum, the Tavistock's statement continues the sorry record of prevarication and obfuscation that has dogged the experiment for several years. GIDS is clearly incapable of undertaking rigorous scientific research, perhaps because it has been swamped by exponentially increasing caseloads. There is no such excuse for the failure of UCL's Institute of Child Health, the experiment's lead sponsor. Neither organization can be trusted to objectively analyze the 2011 experiment.

We demand that a team of independent researchers be given access to all the data from the experiment. They will need expertise in statistics, psychiatry, and endocrinology; most importantly, they must have no vested interests in the promotion of GnRHa drugs. Given that this experiment has been used since 2014 to justify the provision of these drugs to children under the NHS, the outcomes of this experiment – on all the physical, psychological, and behavioural measures that were collected – must be published urgently.



Part 3: The Health Research Authority report

17 October 2019



The Health Research Authority (HRA) has just published its [investigation into the 2010 experiment with puberty blockers](#), or more precisely its role in giving ethical approval and oversight. The investigation was prompted by research published on [Transgender Trend](#) in March 2019, with an update in July (the full paper is [here](#)). The HRA report's conclusions are predictably bland. Firstly, 'the research team involved in the design and delivery of the study ...

worked in accordance with recognised practice for health research, and in some areas such as patient involvement and transparency were ahead of normal practice at the time' (p. 11). Secondly, 'The HRA has acted within its Standard Operating Procedures and its normal practice in relation to this study' (p. 10).

On close reading, however, the report contains an astonishing admission. The paragraph deserves to be quoted in full:

It would have reduced confusion if the purpose of the treatment had been described as being offered specifically to children demonstrating a strong and persistent gender identity dysphoria at an early stage in puberty, such that the suppression of puberty **would allow subsequent cross-sex hormone treatment** without the need to surgically reverse or otherwise mask the unwanted physical effects of puberty in the birth gender. The present study was **not designed to investigate the implications on persistence or desistence of offering puberty suppression** to a wider range of patients, it was limited to a group that had already demonstrated persistence and were actively requesting puberty blockers.

(p.5, my own emphasis added in bold).

In fact the 2010 research protocol declared that one of its three aims was '[t]o evaluate persistence and desistence of the gender identity disorder and the continued wish for gender reassignment' (Early pubertal suppression in a carefully selected group of adolescents with gender identity disorder, proposal submitted to Central London REC 2, November 2010, obtained under Freedom of Information from the HRA; italics added). History is being rewritten to alter the rationale

for the experiment. It is not clear whether this revisionist history originates with the HRA, or whether the HRA is conveying the current views of the experiment's chief investigator, Professor Russell Viner (Professor in Adolescent Health at University College London) or his co-investigator, Dr Polly Carmichael (Director of the Gender Identity Development Service, GIDS).

Whatever the source, this is a clear admission that puberty blockers were the first stage on the predestined path to cross-sex hormones. After four assessment interviews, a child of 12 would be consenting in effect to a lifetime of drug dependence and the loss of fertility and the probable loss of sexual functioning. Because the "treatment" was intended to enhance the child's desire to change sex, it naturally exacerbated her or his gender dysphoria. 'Worsening behavioural and emotional symptoms of dysphoria', the HRA notes cheerily, 'would therefore not in itself be unexpected' (p. 6).

While the HRA is quite clear that puberty blockers were supposed to set the child on a course for full medical transition, it ignores one gruesome irony. For a boy who wishes to resemble a woman, puberty blockers will indeed prevent 'the unwanted physical effects of puberty' such as voice deepening. But they also leave the adolescent with the genitalia of a prepubescent boy. If he subsequently chooses (after the age of 18) to undergo genital surgery, there is insufficient for a vaginoplasty and so a piece of his bowel will have to be used. This point was underlined at a conference organized by the [Gender Identity Research and Education Society](#) in 2005:

'Although there are surgical means to deal [with] this difficulty, the patient and her parents or guardians should be fully informed about its implications.'

The conference was attended by Viner and Carmichael. Unaccountably they forgot to mention these implications on the Patient Information Sheet they gave to children and carers in their experiment.

Following from the HRA's admission that puberty blockers are really the start of irreversible physical transition, it makes one valuable recommendation. 'Researchers and

clinical staff should consider carefully the terms that they use in describing treatments e.g. avoid referring to puberty suppression as providing a "breathing space", to avoid risk of misunderstanding.'

That phrase is common. According to Dr Gordon [Wilkinson](#) at the Young People's Gender Clinic in Glasgow—the Scottish equivalent of GIDS—GnRHa drugs 'provide breathing space to explore options'. [Gendered Intelligence](#), a charity which trains staff in many universities, describes puberty blockers as giving 'young trans people appropriate time and breathing space to ensure that they are sure about the permanent effects of cross-sex hormones, without the adverse effects of an incorrect [sic] puberty'. (The phrase is also widely used in the [USA](#) and [New Zealand](#).)

It is not the only misleading phrase. Carmichael went on [BBC children's television](#) in 2014 to tell one of the children in the experiment and the audience (aged 6 to 12) that puberty blockers merely pressed a pause button. We can only hope that the HRA's report will stop clinicians and charities from misleading the public—and more importantly the children and carers who are making life-changing decisions.

The HRA's investigation repeats a familiar misconception: because Gonadotropin-Releasing Hormone agonist (GnRHa) drugs are licensed for the postponement of [central precocious puberty](#), therefore 'the treatment was licensed for the purpose of blocking progression of puberty' (p. 4). In the case of precocious puberty, a child starts to go through puberty at an abnormally young age—a girl starts menstruating at five, for example. This condition has an objective physical diagnosis. GnRHa drugs are then prescribed in order to *postpone* puberty until the normal age of puberty is reached, when the drugs are stopped and puberty resumes normally. There is no similarity at all for the case of a child with gender dysphoria. This condition has no objective physical diagnosis. GnRHa drugs are prescribed in order to prevent the child from ever experiencing puberty. The adolescent never develops the ability to conceive a baby and might never develop the capacity to [orgasm](#).

When it comes to the HRA's own ethical

procedures, its investigation throws some intriguing findings. The experiment was first rejected by one Research Ethics Committee (REC 1), and was then submitted to another Committee (REC 2). 'A number of members' on the latter 'had connections with University College London', which by coincidence was Viner's own institution. The committee also co-opted a member who had co-authored with Viner. 'It is not clear whether the potential conflict of interest was declared, whether this committee discussed this potential conflict of interests and agreed that it was not a concern, or whether the other members agreed that the individual concerned could contribute but that they would ensure that it did not influence their decision-making' (p. 9). It is unfortunate that the minutes provide no information.

The Research Ethics Committee made the submission of annual progress reports 'a condition of the favourable ethical opinion', as it stressed in its letters (e.g. letter of 29 April 2013, obtained under Freedom of Information from the HRA). Viner failed to submit such reports in 2013, 2014, and 2015. The HRA reassures us that 'it is common for researchers not to supply annual progress reports' (p. 10). Rules, after all, are made to be broken.

After 2015, the Research Ethics Committee forgot about the experiment, as apparently did Viner and Carmichael. It had served its purpose, for what had been 'research' now became policy at GIDS: puberty blockers are routinely given to children from the age of 12, and in some cases as to children as young as 10.

Let us leave the last word to Viner, who spoke with remarkable candour in 2012:

If you suppress puberty for three years the bones do not get any stronger at a time when they should be, and we really don't know what suppressing puberty does to your brain development. We are dealing with unknowns. ([Daily Mail](#), 25 February 2012)

We know no more now than we did then.

The HRA should review how effectively declarations of interest by REC members are managed, and seen to be managed.

The Tavistock and Portman NHS Trust should provide greater clarity both internally and externally about the boundaries between research and clinical service.

Researchers and clinical staff working in gender identity development should consider carefully the terms that they use in describing treatments e.g. avoid referring to puberty suppression as providing a 'breathing space', to avoid risk of misunderstanding.

UCL should ensure it has mechanisms to oversee version labeling of documents used in research.

NHS England should provide guidance to NHS organisations on appropriate and transparent oversight and governance of innovative practice undertaken outside research.

From: Investigation into the study 'Early pubertal suppression in a carefully selected group of adolescents with gender identity disorders'



Part 4: The Judicial Review

3 December 2020

Keira Bell's and Mrs A's claim against the Tavistock and Portman NHS Foundation Trust led to a momentous [judgment](#) on 1 December 2020. The judgment places significant constraints on the use of GnRHa (Gonadotropin-Releasing Hormone agonist) to suppress puberty in children suffering from gender dysphoria, as adopted by the Tavistock's Gender Identity Development Service (GIDS) in 2011.

1. Puberty suppression is an experimental treatment

The judgment is unequivocal that puberty suppression for gender dysphoria is an experiment: 'it is right to call the treatment experimental or innovative in the sense that there are currently limited studies/evidence of the efficacy or long-term effects of the treatment' (para 148). This finding should finally dispose of the claim—frequently made by the GIDS—that the treatment is not experimental because GnRHa drugs are licensed for precocious puberty. Treating a

child whose puberty arrives abnormally early (under the age of 8) so that he or she can experience puberty at a normal age cannot be compared to stopping puberty at the normal age so that a child can proceed to cross-sex hormones at the age of 16.

Puberty suppression is an experiment whose aims are ambiguous. The judgment highlights the 'lack of clarity over the purpose of the treatment: in particular, whether it provides a "pause to think" in a "hormone neutral" state or is a treatment to limit the effects of puberty, and thus the need for greater surgical and chemical intervention later' (para 134).

2. GIDS fails to collect basic data and to report outcomes

At several points the judges express surprise at the failure of the GIDS to provide data to the court. The GIDS could not provide comprehensive figures on the ages at which children have been prescribed GnRHa (para 28). It had no information on how many were diagnosed with Autism Spectrum Disorder (para 35). It could not say how many proceeded from GnRHa to cross-sex hormones (paras 59). This failure—or perhaps reluctance—to collect basic data has been highlighted by [Transgender Trend](#).

(1) QUINCY BELL (2) MRS A
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THE TAVISTOCK AND PORTMAN NHS FOUNDATION TRUST

it is right to call the treatment experimental or innovative in the sense that there are, at present, limited studies/evidence of the efficacy or long-term effects of the treatment

Judges' Statement



During the proceedings, the judges asked the GIDS to produce results from their initial experiment with puberty blockers on 44 children from 2011 to 2014. This initial experiment had been conveniently forgotten by GIDS—and even by the Principal Investigator, Professor Russell Viner—until it was brought to light by [Transgender Trend](#) in March 2019. We called then for the outcomes of the treatment on all 44 subjects to be published immediately.

When the judges asked for these results during the hearing, the GIDS refused. As the judges explain, ‘we note that though this research study was commenced some 9 years ago, at the time of the hearing before us the results of this research had yet to be published. Dr Carmichael says in her witness statement dated 2 February 2020 that a paper is now being finalised for publication. At the hearing we were told that that this paper had been submitted for peer-review but that Professor Viner, one of the authors of it, had yet to respond to issues raised by the reviewers, as he has been otherwise engaged in working on issues relating to the coronavirus pandemic’ (para 24).

Using the pandemic as an excuse is not plausible given that Professor Viner and Dr Carmichael promised (in their protocol given ethical approval in 2010) to provide outcomes after the patients had been on GnRHa for two years, which would have been in 2016. (The only peer-reviewed publication on the experiment’s outcomes for psychological functioning and gender dysphoria is my letter in [Archives of Sexual Behavior](#).) If the longer-term outcomes of the 2011-14 experiment were positive, why would Dr Carmichael and Professor Viner refuse to produce this evidence for the judges?

The failure to publish cannot be blamed on lack of resources. In 2019 the GIDS won a £1.3 million grant to research outcomes for children treated for gender dysphoria.

3. Puberty suppression inexorably leads to cross-sex hormones

The judgment should finally dispose of the illusion that puberty suppression simply provides a “breathing space” or pushes a

“pause” button (as Dr Carmichael claimed on BBC Children’s Television in 2014). As I have said, it is more like pressing [fast forward](#) into cross-sex hormones and ultimately surgery. The [Health Research Authority](#) has acknowledged that the rationale for puberty suppression is lifelong physical transition. The judges emphasized that ‘the vast majority of children who take PBs [puberty blockers] move on to take cross-sex hormones, that Stages 1 and 2 are two stages of one clinical pathway and once on that pathway it is extremely rare for a child to get off it’ (para 136).

Therefore for a child to actually consent, he or she ‘would have to understand, retain and weigh up’ the following information: ‘(i) the immediate consequences of the treatment in physical and psychological terms; (ii) the fact that the vast majority of patients taking PBs go on to CSH [cross-sex hormones] and therefore that s/he is on a pathway to much greater medical interventions; (iii) the relationship between taking CSH and subsequent surgery, with the implications of such surgery; (iv) the fact that CSH may well lead to a loss of fertility; (v) the impact of CSH on sexual function; (vi) the impact that taking this step on this treatment pathway may have on future and life-long relationships; (vii) the unknown physical consequences of taking PBs; and (viii) the fact that the evidence base for this treatment is as yet highly uncertain’ (para 138).

4. Can children consent to sterility and potentially losing sexual function?

The judges remarked on the curious fact that the GIDS could not recall any child ever being considered to lack “Gillick competence” to consent to GnRHa drugs (para 44). Gillick competence requires the child to have ‘sufficient maturity and intelligence to understand the nature and implications of the proposed treatment’ (para 105). Even when treating children as young as 10, the GIDS invariably assessed them as having the ability to consent, ‘on the assumption that if they give enough information and discuss it sufficiently often with the children, they will be able to achieve Gillick competency’. The judges concluded laconically, ‘we do not think that this assumption is correct’ (para 150).

One of the GIDS' witnesses, "J" embarked on puberty suppression at the age of 12. According to J's recollection of the consent process: "We discussed sex and I told them the idea of it disgusted me. I knew I would be unable to consider having a sexual relationship as an adult with my body so wrongly formed" (para 86). Such testimony heightened the judges' concerns about consent. 'Some of the children and young people who have been treated at GIDS say in their witness statements that the thought of sex disgusted them, or they did not really think about fertility. These normal reactions do not detract from the difficulties surrounding consent and treatment with PBs. That adolescents find it difficult to contemplate or comprehend what their life will be like as adults and that they do not always consider the longer-term consequences of their actions is perhaps a statement of the obvious.' (para 141).

Remarkably little is known about the effect of puberty suppression on the development of sexual desire and the capacity to orgasm. This was revealed in the proceedings, when the judges asked for evidence that the development of sexuality was unimpaired by GnRHa. The question stumped the barrister for University College London Hospitals NHS Foundation Trust, which prescribes the drugs on behalf of the GIDS. One clue is that GnRHa

is prescribed to chemically castrate sex offenders in Broadmoor—a use for which it is licensed, unlike for gender dysphoria. It seems implausible that an adolescent's sexuality would be unaffected by several years of chemical castration.

5. Who can consent to puberty suppression?

The judges concluded by emphasizing the 'enormous difficulties in a child under 16 understanding and weighing up this information and deciding whether to consent to the use of puberty blocking medication' (para 150). Therefore GIDS—and private clinicians who wish to prescribe GnRHa for treating gender dysphoria—will have to seek a court order for each individual patient. The judgment sets a high bar for meeting Gillick competence: for a child aged 13 or under, this would be 'highly unlikely'; for a child aged 14 or 15, it would be 'very doubtful'. Even for a child aged 16 or 17, for whom there is a presumption of consent, the judges recommend that clinicians 'may well regard these as cases where the authorisation of the court should be sought' (para 151). The judgment closes the era of unconstrained experimentation on children suffering from gender dysphoria, when the GIDS could flout ethical rules and ignore scientific principles.



Part 5: The belated results

18 December 2020

The Tavistock's Gender Identity Development Service (GIDS) and University College London have finally released the results of their experiment on puberty blockers, albeit not in a scientific journal. The timing is curious. The paper's first author, Dr Polly Carmichael (Director of GIDS) refused to provide it to the judicial review brought by Keira Bell and Mrs A, on a flimsy pretext. On the day after the judgement was handed down, the paper appeared on a preprint server, medRxiv (Carmichael et al., 2020). It was not discovered for some days because the authors were too modest to seek publicity. The event has not been mentioned on the website of the Tavistock and Portman NHS Foundation Trust, which had originally announced the experiment in 2011 with some fanfare: 'It is hoped that the results of this study will contribute to improving the standards of care offered to this group of young people and their families.'

The fact that the Carmichael et al. have only now published results that were available in 2016—for outcomes after one year—and in 2017—after two years—shows their lack of concern for the standards of care offered to this group of young people. Indeed, it is almost certain that the experiment would have been conveniently forgotten without Transgender Trend's sustained scrutiny. This website first called on the Tavistock to publish the results of its 'Early Intervention Study' in March 2019. I made a formal complaint to the Health Research Authority, which oversees the

Research Ethics Committee that had approved this experiment. The report of its investigation was sent to me (embargoed before publication) on 11 October 2019. Carmichael et al.'s statistical analysis plan was 'lodged with the Research Ethics Committee of the Health Research Authority on 9 October 2019' (Appendix S2, p. 1).

The long-delayed paper provides results for 44 subjects—aged 12 to 15—who were prescribed Gonadotropin-releasing Hormone agonist (GnRHa). They were followed up at three time points: after one year, two years, and three years. Because the subjects could progress to cross-sex hormones soon after their sixteenth birthday, only 24 remained on GnRHa after two years, and only 14 at three years.

Managing expectations

The authors' statistical analysis plan, written in 2019 after they had come under scrutiny from Transgender Trend, is remarkable for its low expectations. It is far more pessimistic than the original research protocol from 2010.

- 2010: 'Going through puberty in what is perceived to be the wrong body can be very distressing and in some cases contribute to self-harm and suicide attempts It is important to evaluate whether intervention early in puberty reduces self harm and suicide attempts' (Viner et al., 2010, p. 15).
- 2019: 'We hypothesise no change in self-harm across the study' (Carmichael et al., 2020, S2, p. 9).
- 2010: 'Early intervention is also associated with a reduction in the gender dysphoria experienced by these adolescents ...' (Viner et al., 2010, p. 15).
- 2019: 'It is therefore unlikely that GnRHa treatment will result in significant reduction in body dissatisfaction' (Carmichael et al., 2020, S2, pp. 12-13).

The authors have provided a perfect illustration of what psychologists call ‘HARKing’: hypothesizing after the results are known (Kerr, 1998). Aside from this being a questionable research practice, one wonders how it could be ethical to give an experimental treatment to children if the experimenters themselves expect the treatment not to lead to any improvement.

Psychological functioning does not change

The paper’s headline finding is that ‘GnRHa treatment brought no measurable benefit nor harm to psychological function in these young people with GD [gender dysphoria]’ (p. 45). This seems reassuring given that the first 30 subjects enrolled in the GIDS experiment reported more negative than positive effects after one year (GIDS, 2015; Biggs, 2020).

The paper’s findings might partly reflect the authors’ choice to present results only for girls and boys combined, and to test sex differences (Table 6) for only 2 measures out of 26. ‘Our statistical analysis plan restricted testing all outcomes for differences by sex due to the type 1 error risk’, they explain (p. 46). This risk is a legitimate concern, which will be discussed below. There is no justification, however, for not tabulating the results disaggregated by sex, as done by the landmark Dutch study on which the Tavistock’s experiment was modelled (de Vries et al., 2011), and by Carmichael’s presentation of the preliminary results (GIDS, 2015). My article (Biggs, 2020) shows that the measures for boys and for girls are uncorrelated, in the preliminary GIDS results and likewise in the Dutch study. In both data sets, to take the clearest example, girls’ body image worsened following GnRHa, while boys’ body image improved. By combining both sexes, the authors make it impossible to discern such patterns.

The authors also provide frustratingly little information on self-harm. There are two indexes, one created from the child’s answers and one from the parent’s. Each index sums two questions, each scored as 0, 1, or 2. The authors report only the median and the interquartile range (Table 4). The median is always 0 because most children do not harm themselves. The lower quartile is 0, of course;

the upper quartile is 1 in every measure except the index for Youth Self Report after twelve months, when it is 2. (The difference between this measure at baseline and at one year is apparently not statistically significant; $p = .4$.) Why not report the mean, as they had previously (GIDS, 2015)? Or tabulate the frequency? Disaggregating by sex would also be informative, because their own preliminary results for the first 30 subjects showed that the increase in self-harm—on the question ‘I deliberately try to hurt or kill myself’—was greater for girls than for boys (the sex difference was statistically significant, $p = .014$).

The lack of discernible improvement is quite surprising because children and their parents must have been enthusiastic about puberty blockers and would have considered themselves fortunate to be in the first group of British adolescents to receive them. After all, this treatment had been demanded for years by Mermaids and GRES, as a lifesaving elixir for children who identify as transgender (Biggs, 2019). This context should have created a powerful placebo response, even if the specific physical effects of GnRHa were minimal. We know that almost all or all the benefit of anti-depressants comes from placebo response (Kirsch, 2019).

The sample is too small

The authors are right to be wary of conducting too many statistical tests on a small sample, comprising only 44 individuals. I will try to explain this simply. Let us say we find a sample statistic—like the average change in one measure after these particular patients have been treated for a year—to be statistically significant at the .05 level. This means that if the population parameter were truly zero—if there were really no effect—we would then have only a 5% probability of getting a statistic of that magnitude in a sample of that size, simply due to random variability. In other words, the probability of a ‘Type I error’ is 5%. The more measures we test, however, the greater the probability of finding one to be statistically significant. If we were to carry out 20 statistical tests on completely random variables, on average 1 in 20 would be statistically significant at the .05 level.

The authors point out that my analysis (Biggs, 2020) of their preliminary results does not adjust for the number of statistical tests. I replicated the procedure used in the Dutch article (de Vries et al., 2011) which provides the only significant evidence for the benefits of puberty blockers. The authors' critique therefore applies equally to that article, whose sample was almost as small, ranging from 41 to 57 (depending on the measure). Statistical tests were conducted on 14 measures. Applying the Bonferroni correction, as the authors advocate (Carmichael et al., 2020, p. 18), would also eliminate 3 out of 8 of the positive Dutch findings. Most importantly, the improvement in overall psychological functioning (captured the Children's Global Adjustment Scale) and the reduction in depression would no longer be statistically significant ($p > .05 / 14$).

The authors make a convincing argument that their sample was too small to really detect changes in so many measures. Why did they not realize this earlier? When the experiment was designed, the GIDS had a caseload of only 29 teenagers aged between 12 and 15 (Viner et al., 2010, pp. 8–9), and so they planned to enrol 30–45 patients over three years. Referrals subsequently grew exponentially, perhaps helped by Dr Carmichael's promotion of puberty blockers in newspaper interviews and on BBC Children's Television. In 2014/15, the final year of enrolment on to the experiment, the GIDS received referrals for 282 teenagers in the 12–15 age bracket. In other words, the *annual increase* was by then ten times greater than the *total* number of patients just four years earlier. After enrolment in the experiment finished, the GIDS recruited over 50 children aged 10–14 each year to its GnRHa programme. The GIDS therefore should now possess data on the effect of puberty suppression—after one year—on at least 250 more children (counting those referred to the endocrine clinic from January 2015 to December 2018). A sample size of around 300 would provide sufficient statistical power to really test whether adolescents undergoing puberty suppression improve or deteriorate. Unfortunately, the GIDS chose either not to collect or not to report these data, despite winning £1.3 million in research funding. Why?

No information on autism

In the case brought by Keira Bell and Mrs A, the judges asked for the number of children on the autism spectrum who were administered puberty blockers. They were told that these data could not be obtained. The judgment 'found this lack of data analysis—and the apparent lack of investigation of this issue—surprising' (para 35). The authors mention that they used the Social Responsiveness Scale to assess autism but simply promise that 'these data will be analysed in the future' (Carmichael et al., 2020, p. 17). We know only that out of the first 30 experimental subjects, 16 were in the normal range, 10 had 'mid to moderate' Autism Spectrum Disorder traits, and 5 had 'severe' traits as measured by SRS-2 (GIDS, 2015, p. 50).

Bone density

An American endocrinologist, Dr Michael Laidlaw, raised the alarm about the effects of GnRHa on bone density, which must accrue rapidly during puberty to avoid osteoporosis later in life. This paper confirms his fears. At baseline the subjects were already half a standard deviation below the norm for their age and sex (Table 3). After one year, they were one standard deviation below the norm; at two years, more than one standard deviation below. (The authors chose not to statistically test these changes in Z-scores, for reasons which are unclear.) The paper omits the range of bone density, which is crucial: given that after one year the *average* was a standard deviation below the norm, many of the subjects would fall more than two standard deviations below the norm—which is a warning sign 'that your bone density is lower than it should be for someone of your age' (NHS, 2020). In the overall population, only 2% of individuals will experience such low bone density to meet this warning threshold (Z-score < -2). After two years on GnRHa, perhaps 30% of those with puberty suppression could meet this threshold for spine bone density, even adjusting for height. (My calculation assumes the Normal distribution and necessarily estimates the standard deviation of the Z-score from the authors' confidence intervals.)

Whether the failure to accrue bone density increases the risk of fractures is unclear. The authors collected data on various 'adverse events', but these did not include broken bones.

Puberty blockers lead inexorably to cross-sex hormones

The most important outcome—but the least surprising—is that 43 out of 44 subjects continued to cross-sex hormones. Although puberty blockers are promoted as a diagnostic aid, since 2006 (if not before) we have known that in almost every case they lead to cross-sex hormones and eventually surgery. It is therefore astonishing that the authors continue to claim that 'pubertal suppression may be both a treatment in its own right and also an intermediate step' (p. 48).

Considered as a treatment in its own right, the suppression of puberty with GnRHa might be the only treatment provided by the NHS for which the costs clearly exceed the benefits. The sole justification for GnRHa is to prepare a child for lifelong medicalization with cross-sex hormones and surgeries, with irreversible consequences for sexuality and fertility. After all, the paper that introduced puberty suppression was entitled 'The Feasibility of Endocrine Interventions in Juvenile Transsexuals' (Gooren & Delemarre-van de Waal, 1996). The question is whether the GIDS has the moral authority and scientific expertise to designate children as young as 10 as juvenile transsexuals. As the judges ruled in the case of Keira Bell and Mrs A, 'Apart perhaps from life-saving treatment, there will be no more profound medical decisions for children than whether to start on this treatment pathway' (para 149).

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Apart perhaps from life-saving treatment, there will be no more profound medical decisions for children than whether to start on this treatment pathway. In those circumstances we consider that it is appropriate that the court should determine whether it is in the child's best interests to take PBs.

Judges' Statement



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Part 6: The effects on bone density

3 May 2021

Transgender Trend first examined the effects of Gonadotropin-Releasing Hormone agonist (GnRHa) on bone density in [2019](#). This was prompted by a study co-authored by Professor Gary Butler, the lead clinical endocrinologist for the Gender Identity Development Service (GIDS) at the Tavistock and Portman NHS Foundation Trust ([Joseph, Ting, and Butler 2018; Joseph, Ting, and Butler 2019](#)).

The authors emphasized that adolescents administered with GnRHa had not experienced any decline in absolute bone density. As endocrinologists Dr William J. Malone and Dr Michael Laidlaw pointed out on Twitter, however, adolescence is a period of increasing bone density—this is the developmental stage when an individual lays down the bone mass that will last them the rest of their life. What matters, then, is the individual's bone density relative to the norm for their age and sex, which is measured by the Z-score (standardized deviation from the population mean). The Z-scores of the patients at the GIDS had fallen significantly. Spurred by Laidlaw's and Malone's comments, I produced a graph to illustrate how these Z-scores had declined (the graph was crude because it had to be derived from the mean and standard deviation of Z-scores alone, because nothing more was reported by Butler's study). My conclusion: 'It is obvious that a substantial minority of the girls on GnRHa suffered from abnormally low bone density.'

This claim can be vindicated now that the Tavistock [finally released](#) a subset of data from their experiment with GnRHa on children aged 12 to 15. The data were released following Transgender Trend's lengthy [campaign](#) to disclose the outcomes of the experiment, which included a formal [complaint](#) to the

Health Research Authority. My reanalysis of these data is now published by the [Journal of Paediatric Endocrinology and Metabolism](#). I find that after two years on GnRHa, the Z-scores for up to a third of the children had declined to below -2. Only about 2% of the population fall below this threshold, and this is the threshold of clinical concern. Indeed, the Tavistock's 2011 experimental protocol initially excluded any child with a Z-score below -2. This restriction was subsequently relaxed, with the stipulation that the patient must understand the 'risks of later osteoporosis' (Amendment 1.2, 3 July 2012). The Patient Information Sheet, however, never mentioned osteoporosis; it stated merely 'We do not know how blocker treatment in early puberty will affect bone strength ...'. The experimental protocol provides evidence that Butler—one of the investigators in the project, led by Professor Russell Viner and Dr Polly Carmichael—understood that such low bone density indicates a risk of osteoporosis.

The graphs show my results in detail. The blue line shows the normal distribution of bone density in the population. For hip bone mineral density, the Z-scores of one third of the patients had fallen below -2. For spine bone mineral density, over a quarter of Z-scores had declined below this threshold. Some had even fallen below -3; such low bone density is extremely rare, found in only 0.13% of the population. Adjusting for height—bone mineral apparent density—does not attenuate the lowest values.

Does such abnormally low bone density increase the risk of bone fractures? One of the Tavistock's [patients](#) who started GnRHa at age 12 then experienced four broken bones by the age of 16. We have no idea whether this was unusual because Butler and the other researchers collected no data on fractures. Dutch studies show that the accrual of bone density recommences when cross-sex hormones are taken from age 16, and so Z-scores increase ([Klink et al 2015; Stoffers et al. 2019](#)).

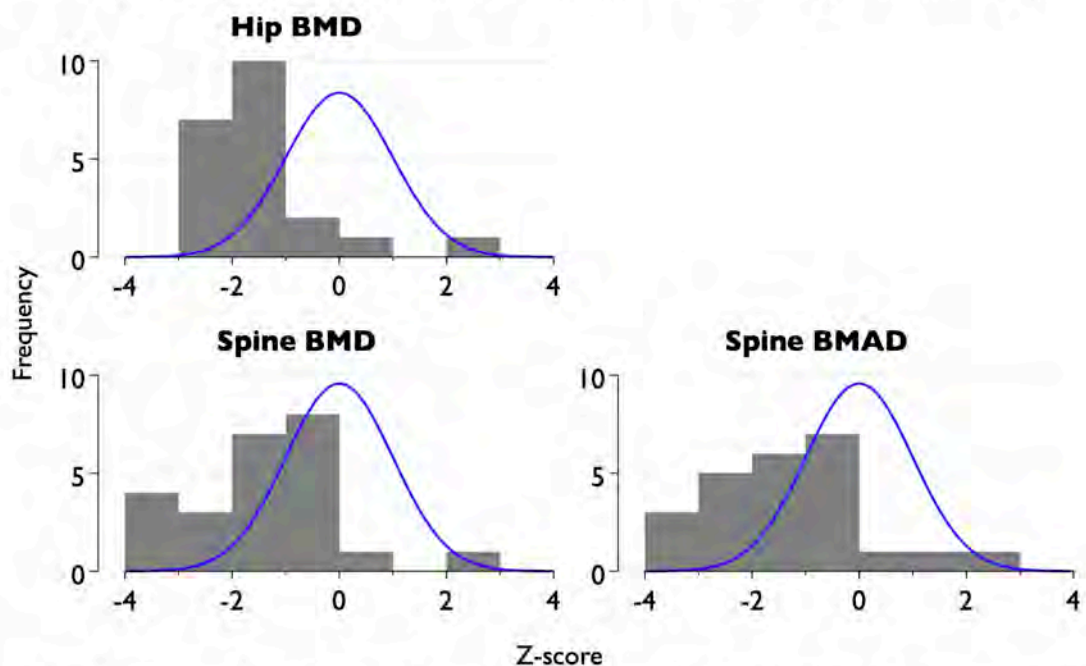
But in many cases the recovery is partial, and the Z-scores do not return to the level registered at the onset of GnRHa. The Tavistock has given GnRHa to a child as young as 10 years old, and so the failure to accrue bone mass could last up to five years. The Tavistock never follow up GIDS patients once they turn 18—not even those who graduate to the adult Gender Identity Clinic in the Tavistock Trust itself—and so there is no way of knowing whether patients who experience abnormally low Z-scores for years in adolescence have experienced osteoporosis as adults.

The fact that adolescents undergoing puberty suppression failed to accrue bone mass—to the point where a significant minority ended up with abnormally low bone density—inspired Butler and his coauthors to make two recommendations ([Joseph, Ting, and Butler 2019](#)). One is to reduce the monitoring of bone density, which has ‘significant financial implications for healthcare providers’. The other is to change the computation of Z-scores; ‘reference ranges may need to be re-defined for this select patient cohort’. When a measure provides inconvenient results, stop measuring or choose another scale: that is how transgender medicine is practiced at the Tavistock.

The Tavistock’s Dutch counterparts at least provide practical advice: ‘Adolescents should be counseled on the importance of weight-bearing exercise, an adequate dietary calcium intake, sufficient sunlight exposure to ensure adequate vitamin D levels, or vitamin D supplementation’ ([Schagen et al. 2020](#)). But the Dutch researchers also apparently omitted to collect data on fractures. Their latest article (which acknowledges a research grant from Ferring Pharmaceuticals, the manufacturer of the GnRHa drug used in the Netherlands and Britain) suggests that future studies should ‘investigate clinically important outcomes such as fracture risk’ ([Schagen et al. 2020](#)).

Fifteen years ago the exponents of the Dutch protocol for transgendering children admitted that their patients could ‘end with a decreased bone density, which is associated with a high risk of osteoporosis’ ([Delemarre-van de Waal & Cohen-Kettenis 2006](#)). It is remarkable that the proponents of puberty suppression are only now contemplating collecting evidence on this key clinical outcome at some future date.

Fig. 1. Bone density after 24 months of puberty suppression



N = 24 for spine, 21 for hip. BMD, bone mineral density; BMAD, bone mineral apparent density.

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The Tavistock's Experiment with Puberty Blockers^{*}

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(version 1.0.1, 29 July 2019)

In 1994 a 16-year-old girl who wished to be a boy, known to us as B, entered the Amsterdam Gender Clinic. She was unique for having her sexual development halted at the age of 13, after an adventurous paediatric endocrinologist gave her a Gonadotropin-Releasing Hormone agonist (GnRHa). Originally developed to treat prostate cancer, these drugs are also used to delay puberty when it develops abnormally early: in girls younger than 8, and boys younger than 9. The endocrinologist's innovation was to use the drug to stop normal puberty altogether, in order to prevent the development of unwanted secondary sexual characteristics—with the aim of administering cross-sex hormones in later adolescence. Dutch clinicians used B's case to create a new protocol for transgendering children, which enabled physical intervention at an age far below the normal age of consent (Cohen-Kettenis and Goozen 1998).

The Dutch protocol promised to create a more passable simulacrum of the opposite sex than could be achieved by physical intervention in adulthood. It was therefore embraced by trans-identified children and their parents, by older transgender activists, and by some clinicians specializing in gender dysphoria. The Gender Identity Development Service (GIDS), part of the Tavistock and Portman NHS Foundation Trust, treats children with gender dysphoria from England, Wales, and Northern Ireland. It launched an experimental study of “puberty blockers”—the more friendly term for GnRHa when administered to children with gender dysphoria—in 2011. The experiment gave triptorelin to 44 children, which in all or almost all cases led eventually to cross-sex hormones. This paper describes the origins and conduct of this study and scrutinizes the evidence on its outcomes. It draws on information obtained by requests under the Freedom of Information Act to the Tavistock, to the NHS Health Research Authority, and to University College London (UCL). I will argue that the experimental study did not properly inform children and their parents of the risks of triptorelin. I will also demonstrate that the study's preliminary results were more negative than positive, and that the single published scientific article using data from the study is fatally flawed by a statistical fallacy. My conclusion is that GIDS and their collaborators at UCL have either ignored or suppressed negative evidence. Therefore the NHS had no justification for introducing the Dutch protocol as general policy in 2014.

^{*} Some of this material was first posted on Transgender Trend (Biggs 2019a, 2019b); most will appear in an edited volume (Moore and Brunsell-Evans 2019). Earlier drafts were shared with reporters at *The Times* (including Lucy Bannerman) and BBC Newsnight (including Deborah Cohen). Special thanks are due to Stephanie Davies-Arai, Elin Lewis, Susan Matthews, and an anonymous former clinician at GIDS for sharing their extensive knowledge, and to Sherena Kranat for her steadfast support. Credit is due also to three woke students taking the Sociology MSc who exhorted me to educate myself on the subject of transgendered children.

Origins

GnRHa drugs have never been licensed for treating children suffering from gender dysphoria. The particular drug used in Britain, as in the Netherlands, is triptorelin, which is licensed to treat advanced prostate cancer and sexual deviance in men; endometriosis and uterine fibroids in women (for no longer than six months); and precocious puberty in children (Electronic Medicines Compendium 2019). Using GnRHa to treat gender dysphoria is “a momentous step in the dark”, for it is “presumptuous to extrapolate observations from an intervention that suppresses pathologically premature puberty to one that suppresses normal puberty” (Richards et al. 2018). Therefore the origins of the Tavistock’s experiment needs some explanation.

The Dutch protocol became well known in Britain before the first scientific article was published. A television documentary showed girls who wished to be boys travelling to meet their peers in the Netherlands, who were taking GnRHa as young as 13 (Channel 4 1996). This inspired Stephen Whittle—who led the transgender campaigning organization Press for Change—to argue for a legal right to access “pubertal suppression”; doctors who failed to provide drugs could be vulnerable to litigation (Downs and Whittle 2000; Wren 2000: 224). This argument was first advanced at a conference at Oxford in 1998, whose keynote speaker was the head of the Amsterdam Gender Clinic. There was little movement, however, over the next few years. Guidelines issued by the British Society for Paediatric Endocrinology and Diabetes (BSPED) in 2005 still insisted that children had to reach full sexual development (known as Tanner Stage 5)—around the age of 15—before being prescribed GnRHa drugs.

A crucial role was played by organizations that campaign for the transgenering of children: the Gender Identity Research and Education Society (GIREs) and Mermaids. GIREs organized a symposium in London in 2005 to develop “guidelines for endocrinological intervention”. Additional funding came from Mermaids, two medical charities—Nuffield Foundation and King’s Fund—and the Servite Sisters Charitable Trust Fund. This brought together the creators of the Dutch protocol, American clinicians like Norman Spack in Boston, and key British figures such as Domenico Di Ceglie, the Director of GIDS, and Polly Carmichael and Russell Viner, both at Great Ormond Street Hospital. (The latter two would lead the 2011 experiment.) Some of the participants vigorously lobbied for the Dutch protocol. Veronica Sharp from Mermaids “described users’ and parents’ views of the available treatments, and the anguish they may experience when hormone blocking is delayed” (GIREs 2005). The symposium ended with agreement to push for amendments to guidance from bodies like BSPED, and to conduct collaborative research between London, Amsterdam, and Boston. There was another meeting in Amsterdam in the following year, but the collaboration did not eventuate.

International developments did enable parents to circumvent the NHS. GIREs (2006) warned that “those who can in any way afford to do so have to consider taking their children to the USA”. The first was Susie Green, who later became the chief executive of Mermaids. In 2007 she took her son Jackie, aged 12, to Boston, to purchase a prescription for GnRHa from Spack; the drug was supplied by an online Canadian pharmacy (*Sun*, 19 October 2011). A presentation at Mermaids, presumably by Green, instructed parents in this medical tourism (Mermaids 2007). Spack treated a further seven British children over the next few years (*Times*, 22 January 2012).

By 2008, GIREs was more strident in criticizing British clinicians. One of its founders, Terry Reed, denounced them as “transphobic”:

They are hoping that during puberty the natural hormones themselves will act on the brain to ‘cure’ these trans teenagers. What we do know is what happens if you don’t offer hormone blockers. You are stuck with unwanted secondary sex characteristics in

the long term and in the short term these teenagers end up suicidal. (*Guardian*, 14 August 2008)

Reed was clearly drawing on the experience of her own child, who transitioned two decades before. This feature article in the *Guardian* signalled that the controversy was becoming newsworthy. GIRES objected to the fact that the Royal Society of Medicine had not invited many advocates for the Dutch protocol to its conference on gender dysphoria in adolescents. The conference was noteworthy as the occasion for a rare public protest by transgender activists (Brown 2018: 311). They targeted Kenneth Zucker from Toronto, a leading psychologist, who was denounced as a “transphobic doctor who supports repression and torture of gender-variant children” (Kennedy 2008). Criticism was not confined to activists. The psychiatrist Richard Green, formerly head of Britain’s Gender Identity Clinic for adults, arranged a rival conference:

Medical experts from the US, Canada and the Netherlands who treat young teenage transsexuals with puberty-blocking medications at the first signs of body change will discuss their programmes. Teenage Dutch transsexuals and their parents will discuss their positive experiences with blocking puberty. A UK family will report how their desperation led to them travelling to the US for treatment. (*Guardian*, 28 August 2008)

Contributors included a medical ethicist at the University of Manchester who denounced Viner’s caution about the risks of GnRHa, on the grounds that “anything is better than life in an alien body” (Giordano 2008: 583). As the decade drew to a close, the demand for puberty blockers was irresistible.

Experiment

Shortly after Carmichael became Director of GIDS in 2009, she decided to offer GnRHa to younger children as part of a research project (BBC News 2009). The chief investigator was Viner at UCL; co-investigators included Carmichael and Di Ceglie, who had moved to Director of Training, Development, and Research. The proposal—“Early pubertal suppression in a carefully selected group of adolescents with gender identity disorder”—was rejected by the NHS Research Ethics Committee, on the grounds that it was not a proper randomized trial and therefore could not yield valid results (GIDS 2019b). The revised proposal (Viner 2010) argued that a randomized trial was not practical. Just as importantly, perhaps, it was submitted to a different Research Ethics Committee. This Committee approved the experiment in February 2011. Aside from the absence of any control group, what is surprising is how the proposal failed to maximize information on the effects of GnRHa. Children were asked to consent to completing questionnaires only until they were 16. If they had been asked to give consent for the researchers to access their medical records in perpetuity, then GIDS would have been able to analyze effects of the drugs over the long term. Although the proposal called this a “study”, I prefer the word “experiment” (following Davies-Arai 2018) to underline the fact that it involved a drug regime that has never been licensed for this condition anywhere in the world.

The research proposal provided a comprehensive review of the potential benefits and risks of GnRHa. “It is not clear what the long term effects of early suppression may be on bone development, height, sex organ development, and body shape and their reversibility if treatment is stopped during pubertal development” (Viner 2010). Viner spoke frankly in a later newspaper interview:

If you suppress puberty for three years the bones do not get any stronger at a time when they should be, and we really don’t know what suppressing puberty does to your brain development. We are dealing with unknowns. (*Daily Mail*, 25 February 2012)

This caution echoed previous comments by Carmichael: “the debate revolves around the reversibility of this intervention—physical and also psychological, in terms of the possible influence of sex hormones on brain and identity development” (Carmichael and Davidson 2009: 917).

When the Tavistock announced the study, however, it claimed that GnRHa treatment “is deemed reversible” (Tavistock 2011). More disturbing is the fact that the Patient Information Sheet provided to children when they gave consent also minimized the risks acknowledged in the research proposal.¹ Although the sheet ran to four pages, it omitted the fact that GnRHa has never been certified as safe and effective for treating gender dysphoria. The words “experiment” or “trial” did not appear. Under “the possible benefits of taking part” came this astonishing statement:

If you decide to stop the hormone blockers early your physical development will return as usual in your biological gender [sic]. The hormone blockers will not harm your physical or psychological development.

This directly contradicted the chief investigator’s own statements.

As for side effects, there was a vague warning that the drug “could affect your memory, concentration and the way you feel”. The triptorelin formulations used by GIDS—Gonapeptyl® Depot and Decapeptyl® SR—carry detailed warnings of side effects. Depression is common, affecting between 1% and 10% of patients (Ferring Pharmaceuticals 2016), and “may be severe” (Ipsen 2017). Other side effects affecting up to 10% of children treated for precocious puberty include “pain in abdomen, pain bruising [sic], redness and swelling at injection site, headache, hot flushes, weight gain, acne, hypersensitivity reactions” (Ipsen 2017). None are mentioned in the Patient Information Sheet.

One further absence deserves emphasis. The 2005 Symposium had noted the paradox that blocking a boy’s puberty left him with stunted genitalia, which were then not sufficient to transform into a pseudo-vagina. “Although there are surgical means to deal this difficulty, the patient and her parents or guardians should be fully informed about its implications” (GIRES 2005). The Patient Information Sheet failed to mention this.

All these omissions might be explained by the input of parents who saw GnRHa as an elixir that would enable their child to change sex. “The wording ... was agreed with a number of families with whom the draft had been discussed” (Di Ceglie 2019: 149). Whatever the cause, GIDS and UCL gave children and parents incomplete and misleading information, which contradicted the research proposal. Whether they could provide informed consent, in such circumstances, is open to serious question.

The basic parameters of the experiment are not entirely clear. It is known that GnRHa was administered to 44 children, starting from June 2011 (Tavistock 2019b). A conference presentation and published abstract described “baseline characteristics of a UK cohort beginning early intervention” but rather confusingly these numbered 50 subjects (Gunn et al. 2015a; Gunn et al. 2015b). The additional six, “included to improve the sample size”, “were not eligible for this study due to being further developed in puberty and were treated at 15 years” (GIDS 2019b). Apparently the last child to enter the experiment was recruited in April 2014 (GIDS 2019b) and presumably some months elapsed before he or she was actually prescribed GnRHa.

There is contradictory information on the age of the subjects. GIDS recently stated that the youngest gave consent at the age of 12 years and one month (Tavistock 2019b). According to the initial presentation, however, the youngest child was 10.3 years “at hormone blockers” (Gunn et. al. 2015a: slide 17). The proposal approved by the Ethics Committee explicitly

¹ Version 1.0, 4 November 2010, obtained from UCL under the Freedom of Information Act. One portion is reproduced by Di Ceglie (2019: 149).

specified “age 12 and above” in the inclusion criteria (Viner 2010), and so the administration of drugs below this age would be a serious breach. Possibly the figure in the presentation was a typographical error, but another slide gives the age range at referral to the endocrine clinic as “10–15 years” (slide 14). A subsequent report gives the mean age at “start GnRHa” as 13.16, with a standard deviation of 1.06 (GIDS, 2015: 50). A Normal distribution with these parameters would have 14% of observations below 12; if you drew 44 observations from this distribution, the probability that none fell below 12 is only 0.2%. This is conjectural, of course, but it is difficult to reconcile these parameters with a minimum age of 12.

Results

Three years after the experiment began, Carmichael announced success to the tabloid press. “Now we’ve done the study and the results thus far have been positive we’ve decided to continue with it” (*Mail on Sunday*, 17 May 2014). Her statement was at best misleading. Six months earlier, she had already planned to continue the experiment indefinitely (*Sunday Times*, 17 November 2013). Then the sole justification was the large number of parents demanding drugs. At that point, the experiment had started only 23 children on triptorelin. These pronouncements make a mockery of Carmichael’s earlier bromide: “as professionals we need to be looking at the long term and making sure this treatment is safe” (*Daily Telegraph*, 15 April 2011). Given the uncertainty surrounding the minimum age, it is telling that when she announced the experiment’s success, she envisaged recruiting younger children. “Twelve is an arbitrary age. If they started puberty aged nine or ten instead of 12, as long as they’re monitored and the bone density doesn’t suffer, then it is right that the aim is to stop the development of secondary sex characteristics” (*Mail on Sunday*, 17 May 2014).

Where are these “positive” results described by Carmichael in 2014?² The current GIDS webpage on the evidence for puberty blockers states that “research evidence for the effectiveness of any particular treatment offered is still limited” (GIDS 2019a). There is no mention of its own experiment; it cites only research from the Netherlands. This is curious seeing that Carmichael told the World Professional Association for Transgender Health (WPATH) that “our results have been different to the Dutch” (Carmichael 2016). Di Ceglie stated last year that the “project is ongoing and the results are yet to be published” (Di Ceglie 2018: 14).

After my own investigation (Biggs 2019a; *Daily Telegraph*, 8 March 2019) pointed out the absence of published results, GIDS (2019b) posted a belated update on the experiment. It lists a total of two scientific publications; both are one-page abstracts on the physical effects of GnRHa. One describes the height of 14 of the subjects after they continued to cross-sex hormones (Catanzano and Butler 2018). Another reports bone density for children on GnRHa, some of whom were subjects in the experiment (Tobin, Ting, and Butler 2018). Density was measured over three years for 31 children.³ The authors state reassuringly that bone density did not decline in absolute terms. This is misleading, because growing children need density to *increase* (Laidlaw 2018). The abstract acknowledges that the children experienced a decline relative to the norm for their age group, and this decline was especially marked for girls. By year three, the average girl on GnRHa had lower bone density than 97.7% of the population in her age group. Surely this raises serious concerns?

² I emailed the address listed on the webpage announcing the study (communications@taviport.nhs.uk) on 1 February 2018, inquiring after the results. There was no reply.

³ It is not clear whether “year 1” refers to the baseline before GnRHa or to one year after GnRHa. My email of 11 July to the authors requesting clarification has not yet been answered.

Diligent searching has uncovered unpublished results on the psychological effects. Most revealing is an appendix to Carmichael's report to the Tavistock's Board of Directors (GIDS 2015).⁴ It tracks 30 of the children on triptorelin, measuring changes after one year of the drug regime; presumably the remaining 14 subjects had not completed their first year on the drug.⁵ The text is sometimes internally inconsistent and occasionally contradicts the tabulated figures, suggesting that the appendix was prepared in haste. But we can summarize those changes that were reported as statistically significant (p -value < .05). Only one change was positive: "according to their parents, the young people experience less internalizing behavioural problems" (as measured by the Child Behavior Checklist). There were three negative changes. "Natal girls showed a significant increase in behavioural and emotional problems", according to their parents (also from the Child Behavior Checklist, contradicting the only positive result). One dimension of the Health Related Quality of Life scale, completed by parents, "showed a significant decrease in Physical well-being of their child". What is most disturbing is that "a significant increase was found in the first item 'I deliberately try to hurt or kill self'" (in the Youth Self Report questionnaire). Astonishingly, the increased risk of self-harm attracted no comment in Carmichael's report. Given that puberty blockers are prescribed to treat gender dysphoria, it is paradoxical that "the suppression of puberty does not impact positively on the experience of gender dysphoria" (measured by the Body Image Scale). When differentiated by sex, the impact was positive for boys on one aspect of body image, but negative for girls on two aspects.

Results for the 44 children after one year on triptorelin were given in two presentations to WPATH in 2016. Unfortunately only the abstracts are obtainable.

For the children who commenced the blocker, feeling happier and more confident with their gender identity was a dominant theme that emerged during the semi-structured interviews at 6 months. However, the quantitative outcomes for these children at 1 years time suggest that they also continue to report an *increase in internalising problems and body dissatisfaction*, especially natal girls. (Carmichael et al. 2016, my emphasis)

Expectations of improvement in functioning and relief of the dysphoria are *not* as extensive as anticipated, and psychometric indices do *not* always improve *nor* does the prevalence of measures of disturbance such as deliberate self harm improve. (Butler 2016, my emphasis)

Where are the positive results announced by Carmichael in 2014? Curiously, both presentations are omitted from the recent list of publications on the experiment (GIDS 2019b).

In evaluating the psychometric evidence, we should remember that children and parents alike had a clear bias towards reporting favourable outcomes; after all, they had enrolled in the experiment because they wanted to take GnRHa. This positive bias increases the probative value of negative evidence. Why were these negative results never published?

There is one article on the outcome of puberty blockers, coauthored by Carmichael, which apparently includes some data from the experiment (Costa et al. 2015). The article discusses 101 children given GnRHa at GIDS, starting at ages ranging from 13 to 17. Given the date of publication, most or all of those children who started at ages 13 and 14 (and perhaps 15?) must have been part of the 2011 experiment. But the age range also indicates the exclusion of

⁴ My annotated version is available at http://users.ox.ac.uk/~sfos0060/Annotated_GIDS_results.pdf.

⁵ As the final subject was recruited in April 2014, it is surprising that so many had not completed a year on triptorelin by the time the report was issued in June 2015. I previously (Biggs 2019a) erred badly in describing these results as pertaining to 44 subjects, which is the number given on the first page (GIDS 2015: 50).

the experimental subjects who commenced GnRHa before the age of 13. Excluding some subjects without justification is poor practice, and raises suspicion of cherry picking. Nevertheless, we should consider this article as having some bearing on the 2011 experiment.

The abstract proclaims that “adolescents receiving also puberty suppression had significantly better psychosocial functioning after 12 months of GnRHa ... compared with when they had received only psychological support” (Costa et al. 2015: 2206). The literature treats this article as providing evidence in favour of puberty blockers (e.g. Butler et al. 2018; Heneghan and Jefferson 2019). But the abstract is misleading: the analysis actually *failed to detect any difference* between children who were given GnRHa and those who were not. To understand this, we need to scrutinize the article in detail. (Statistically minded readers will recognize the fallacy described by Gelman and Stern 2006.)

The analysis starts with 201 adolescents diagnosed with gender dysphoria. The children were divided into two groups: those deemed eligible for puberty blockers immediately, and those who needed more time due to “comorbid psychiatric problems and/or psychological difficulties”. This second group did not receive any physical intervention during the time of analysis, and so serves as a comparison group. Both groups received psychological support. The article chooses one outcome, psychosocial functioning as measured by the Children’s Global Assessment Scale (CGAS). This scale was administered at the outset, and then after six, twelve, and eighteen months. It is suspicious that the article omits all the outcomes that were negative in the preliminary results of the 2011 experiment (GIDS 2015): the Child Behavior Checklist, the Youth Self Report Questionnaire, the Health Related Quality of Life scale, and the Body Image Scale.

The authors graph the CGAS results, but without confidence intervals—which indicate the extent of random statistical variation or noise. (The graph is redrawn with confidence intervals in Biggs 2019a.) The smaller the sample, the greater this noise. These samples shrank over time: after eighteen months, the group getting drugs numbered only 35, and the comparison group 36. The article does not explain why two thirds of the subjects disappeared. Presumably they did not stop the medication, because none of the children in the 2011 experiment quit GnRHa in the first two years (Gunn et al. 2015b).

The group given puberty blockers from six months onwards showed improvement at eighteenth months: the average CGAS score had increased from 61 to 67. This improvement is statistically significant, and it is the one that the authors chose to highlight. However, these children also received psychological support, and so attributing this improvement to medical intervention is unjustified. The crucial comparison is between the group receiving GnRHa and the comparison group. The latter’s average CGAS score after eighteen months was lower, 63 compared to 67. This is hardly surprising because the comparison group was composed of children with more serious psychological problems. Anyway, this difference is *not statistically significant*: a two-tailed *t*-test for the difference between group means yields a *p*-value of .14, far beyond the conventional .05 threshold. In other words, the samples were so small, and there was such wide variation in scores within each group, that we can draw no conclusions. There is no evidence that puberty blockers improve psychosocial functioning. No wonder that GIDS’ own webpage on the evidence for medical intervention does not cite this article, nor does the recent update on the experiment (GIDS 2019a, 2019b).

The failure to fully publish the results of the experiment—for all 44 children given triptorelin, on all the outcomes that the study measured—suggests that it was a pretext to administer unlicensed drugs rather than an attempt to acquire scientific knowledge.

Consequences

The absence of comprehensive publications would be serious enough if the unlicensed use of triptorelin had been confined to the 44 experimental subjects. Sometime around 2013, however, the Director of GIDS transitioned from scientific caution to enthusiastic advocacy. Her new attitude was manifested in a BBC television documentary—aimed at children aged 6 to 12—broadcast in November 2014. It followed a 13-year-old girl who wished to be a boy, Leo, who was one of the experimental subjects. Carmichael appears on camera to reassure Leo:

The blocker is an injection that someone has every month which pauses the body and stops it from carrying on to grow up into a man or a woman. ... And the good thing about it is, if you stop the injections, it's like pressing a start button and the body just carries on developing as it would if you hadn't taken the injection. (BBC 2014)

To emphasize this point for the juvenile audience, the film superimposes a pause button on the screen. The clearest indictment of her statement to children comes from her own words a year later:

The blocker is said to be completely reversible, which is disingenuous because nothing's completely reversible. It might be that the introduction of natal hormones [those you are born with] at puberty has an impact on the trajectory of gender dysphoria. (*Guardian*, 12 September 2015)

By 2015, however, GIDS had embraced the Dutch protocol with enthusiasm. “The Early Intervention Clinic will continue to follow the Service’s 2011 research protocol, which *following evaluation*, has now become established practice, with the exception that hormone blockers will now be considered for any children under the age of 12 if they are in established puberty” (NHS England 2015: 26, my emphasis). By 2017, GIDS (including its satellite operation in Leeds) had prescribed GnRHa for a total of 800 adolescents under 18, including 230 children under 14 (*Mail on Sunday*, 30 July 2017). New prescriptions were running at 300 per year (BBC News, 2018). Freedom of Information requests submitted at the end of 2018 revealed that neither GIDS nor University College London Hospitals NHS Foundation Trust (which provides endocrinology services) kept precise records of the number of children given GnRHa; “work is currently in progress to manually enter all hormone blocker prescription data onto a database, pending future meetings with UCLH and LGI [Leeds General Infirmary] to ascertain who is collecting this info and how it is to be reported.”⁶ A subsequent request, however, revealed that 267 children under 15 were referred to the endocrine clinic and consented to puberty blockers from the beginning of 2012 to the end of 2018 (Tavistock 2019a). This figure includes most of the 44 experimental subjects, excepting perhaps half a dozen who started in 2011.

The abstract describing the baseline characteristics of the children in the experiment concluded: “Assessment of growth, bone health and psychological outcomes will be important to assess the medium and *long-term safety and effectiveness* of early intervention” (Gunn et al. 2015b: A198, my emphasis). This aspiration was never implemented. GIDS recently acknowledged that it loses track of its patients after they turn 18, blaming “the frequent change in nominal and legal identity, including NHS number in those referred on to adult services”—“to date they have not been able to be followed up” (Butler et al. 2018: 635).⁷ By contrast, the Amsterdam clinic does attempt to trace its patients over time. The

⁶ Internal Review (18-19312) of Susan Matthews’ Freedom of Information request to the Tavistock (18-19230), 24 February 2019.

⁷ Transgender activists successfully lobbied the NHS to provide new numbers to patients as well as to change the sex on their medical records (Birch 2014).

pioneer, B, has been followed to the age of 35. He did not regret transition, but scored high on the measure for depression. Owing to “shame about his genital appearance and his feelings of inadequacy in sexual matters”, he could not sustain a romantic relationship (Cohen-Kettenis et al. 2011: 845). To the clinicians, however, this case exemplifies the success of the Dutch protocol.

Conclusion

GIDS and UCL launched an experiment in 2011 to use GnRHa to stop puberty in children suffering from gender dysphoria. The impetus for this unlicensed treatment came from children and parents, along with transgender activists and some clinicians, who seized on the notion that blocking puberty was akin to alchemy—it would enable a child to change sex, as long as he or she started young. Given unrelenting pressure from Mermaids and GIRES, supported by the climate of opinion among the *Guardian*-reading classes, the Tavistock arguably had to concede to the demand for GnRHa below the age of 16. From the outset, however, the experiment was flawed. The Patient Information Sheet understated the risks of this unlicensed treatment, despite those risks being acknowledged explicitly in the research proposal. Worse was to come. Before the experiment had run its course, Carmichael claimed “that the results thus far have been positive” in order to justify what must have been a premeditated decision to incorporate the Dutch protocol into the policy of GIDS. She even appeared on children’s television to disingenuously promote GnRHa.

In fact, the initial results showed predominantly negative outcomes. The only tabulated data available, for 30 of the subjects after a year on triptorelin, showed that children reported greater self-harm; girls experienced more behavioural and emotional problems and expressed greater dissatisfaction with their body—so drugs exacerbated gender dysphoria (GIDS 2015). The fact that these outcomes have never been published is a serious indictment of Carmichael, Viner (now President of the Royal College of Paediatrics and Child Health), Di Ceglie, and the other scientists who proposed the research.⁸ The failure can be highlighted by comparing another use of triptorelin: the treatment of hypersexuality in men, for which it is licensed. The chemical castration of seven dangerous sex offenders in Broadmoor Hospital resulted in a report spanning two pages, which detailed the adverse side effects experienced by three patients (Ho et al. 2012). The use of triptorelin on 44 adolescents—off license—has produced only two single-page abstracts reporting outcomes for subsets of the subjects (Catanzano and Butler 2018; Tobin, Ting, and Butler 2018).

Some of the experimental subjects were apparently included with older adolescents from GIDS in one published article (Costa et al. 2015). It examines a single outcome measure—notably not one of the measures that yielded negative effects in the preliminary results. This article misrepresents its finding. Properly analyzed, it shows no evidence for the effectiveness of drugs: there was no statistically significant difference in psychosocial functioning between the group given triptorelin and the comparison group given only psychological support.

My critique has evaluated the Tavistock’s experiment in accord with its own aims, as laid out in the 2010 research proposal. For reasons of space, this paper has not discussed three additional serious problems attending the use of GnRHa to block puberty. The Dutch protocol was originally touted as diagnostic aid as well as treatment; it would give the child time to ponder her or his gender identity (Cohen-Kettenis and van Goozen 1998). In fact, however, children given GnRHa almost invariably progress to cross-sex hormones. The 2011 experiment was typical insofar as none of the children is known to have stopped the drug regime after one or two years (Gunn et al. 2015; Carmichael et. al 2016). (GIDS has never

⁸ Names were redacted in the copy obtained from the Health Research Authority.

revealed the proportion who went on to cross-sex hormones.) Before the introduction of puberty blockers, around four fifths of young children with gender dysphoria would grow out of it naturally, typically becoming gay, lesbian, or bisexual adults (e.g. Zucker 2019). Using GnRHa to block puberty does not mean pressing a pause button, as Carmichael asserted—it is more like pressing fast forward into cross-sex hormones and ultimately surgery.

The second problem is obvious. Blocking puberty effectively destroys the individual's ability to have children. If the adolescent stops taking GnRHa, fertility should recover, but as we have seen, stopping is exceptional. The third problem is rarely admitted. Blocking puberty impedes the development of sexual functioning; some children given GnRHa never develop the capacity for orgasm (Jontry 2018). There is a strong taboo against mentioning this. The word 'orgasm' did not appear in the proposal for the 2011 experiment, and never appears on the GIDS website. When the endocrinologist at GIDS, Gary Butler, was asked about the effect of GnRHa on the ability to orgasm, he refused to answer.⁹

Since my critique was initially posted in March (Biggs 2019a), GIDS has responded with prevarication and obfuscation. When a parliamentary question was asked on my behalf, the House of Lords was told on 22 May that the Tavistock “plans to publish the data once all of the young people in the study have reached the stage when a clinical decision is made about moving from pubertal suppressants to cross-sex hormones, which the Trust expects to occur in the next 12 months” (Blackwood 2019). Just over a month later, GIDS belatedly posted a webpage providing an update on the experiment. “The study concluded in February 2019 when the last cohort member began the next stage of therapy (cross-sex hormones) at age 17 years” (GIDS 2019b). How can these two statements be reconciled? If the study had really finished in February, coincidentally just before my critique appeared, why was Parliament told in May that it would finish in the next twelve months?

“Analysing and extrapolating from different data sets out of context can be misleading” states the Tavistock (*Daily Telegraph*, 8 March 2019), downplaying my revelation of negative results. My analysis was dictated by the fact that GIDS and UCL produced a congeries of inconsistent data. The number of subjects varies from 30 (GIDS 2015) to 31 (Tobin, Ting, and Butler 2018) to 44 (e.g. Carmichael et al. 2016) to 50 (e.g. Gunn et al. 2015a) to 101 (Costa et al. 2015). It has taken me—along with Elin Lewis, Susan Matthews, and two others who must remain anonymous—many months of painstaking effort to reconstruct the course and results of the experiment. To dispel this confusion, Viner and Carmichael could simply tabulate *all* the various outcomes for *all* 44 children given GnRHa in this experiment. If the results were really positive, why the secrecy? Even after the experiment has come under scrutiny, GIDS still seems to be concealing negative findings. “Outcomes and outputs from the study” (GIDS 2019b) notably omits unpublished sources that showed psychological outcomes to be disappointing (Butler 2016) or negative (GIDS 2015; Carmichael et al. 2016). The conference presentation disclosing that the youngest child given GnRHa was 10 (Gunn et al. 2015a) has now vanished from the website.

By now the experiment has been running for eight years. According to the original research proposal, “At the end of the *first three years* the data will be analysed and an interim report will be produced giving a provisional evaluation in line with the objectives of the study” (Viner 2010, my emphasis). That commitment to produce a report with evaluation in 2014 has never been met. Subsequently, Carmichael's keynote address to WPATH in 2016 promised that “we're about to publish” results of the early intervention research (Carmichael 2016). That was three years ago. The first child consented to GnRHa in June 2011; the final subject must have started on the drug by late 2014. Therefore the entire cohort must have

⁹ The question was posed by Susan Matthews after Butler's talk to the European Society for Paediatric Endocrinology's symposium on the Science of Gender, London, 19 October 2018.

completed three years of the drug regime by the end of 2017. The results should have been closely monitored and the outcomes published in scientific journals. The Tavistock has failed not just the scientific community, but more importantly the children in its care.

The Health Research Authority also emerges as negligent. After approving the research in 2011 (and an amendment in 2012 to enable children with very low bone density to take part), the Research Ethics Committee did nothing to ensure that the experimental findings were reported. From 2013 onwards, Viner as chief investigator did not submit the requisite annual progress report. The Committee posted occasional reminders, the final one in August 2015. It then seems to have forgotten the study.¹⁰

The Tavistock Trust now boasts of winning £1.3 million to conduct research (with UCL and two other universities) into the long-term outcomes for young children who use the service, “including both those who go on to use physical interventions such as hormone blockers and those who do not” (Tavistock 2019c). Given the failure of GIDS and UCL to publish the comprehensive data they have been gathering for eight years, why fund them to collect more? There is also a more insidious problem. Carmichael pronounced the results of the experiment to be “positive” back in 2014, and used this to justify a general policy of blocking puberty. Since then, GnRHa has been administered to more than 200 children under 15. How can GIDS and UCL now objectively analyze data from the experiment, when they naturally have a vested interest in justifying their longstanding policy of treating gender dysphoria with GnRHa?

What, then, is to be done? Richard Byng (2019) recently demanded a moratorium on the use of GnRHa for children suffering from gender dysphoria until there is robust evidence that this drug regime is safe and effective. A team of independent researchers must be given access to all the data from the 2011 experiment. They will need expertise in statistics, psychiatry, and endocrinology; most importantly, they must have no vested interests in the promotion of GnRHa. Given that this experiment has been used since 2014 to justify the provision of these drugs to children under the NHS, the outcomes of this experiment—on all the physical and psychological measures that were collected—must be published urgently.

¹⁰ I wrote to the Chair of the London-Bloomsbury Research Ethics Committee, James Linthicum, on 11 April 2019 to convey my serious concerns; he never replied.

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Clinical guidelines

Potential benefits, limitations, and harms of clinical guidelines

Steven H Woolf, Richard Grol, Allen Hutchinson, Martin Eccles, Jeremy Grimshaw

Over the past decade, clinical guidelines have increasingly become a familiar part of clinical practice. Every day, clinical decisions at the bedside, rules of operation at hospitals and clinics, and health spending by governments and insurers are being influenced by guidelines. As defined by the Institute of Medicine, clinical guidelines are "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances."¹ They may offer concise instructions on which diagnostic or screening tests to order, how to provide medical or surgical services, how long patients should stay in hospital, or other details of clinical practice.

The broad interest in clinical guidelines that is stretching across Europe, North America, Australia, New Zealand, and Africa (box) has its origin in issues that most healthcare systems face: rising healthcare costs, fueled by increased demand for care, more expensive technologies, and an ageing population; variations in service delivery among providers, hospitals, and geographical regions and the presumption that at least some of this variation stems from inappropriate care, either overuse or underuse of services; and the intrinsic desire of healthcare professionals to offer, and of patients to receive, the best care possible. Clinicians, policy makers, and payers see guidelines as a tool for making care more consistent and efficient and for closing the gap between what clinicians do and what scientific evidence supports.

As guidelines diffuse into medicine, there are important lessons to learn from the firsthand experience of those who develop, evaluate, and use them.³ This article, the first of a four part series to reflect on these lessons, examines the potential benefits, limitations, and harms of clinical guidelines. Future articles will review lessons learned about their development,⁴ legal and emotional ramifications,⁵ and finally their implementation.⁶

Potential benefits of clinical practice guidelines

The principal benefit of guidelines is to improve the quality of care received by patients. Although it has been shown in rigorous evaluations that clinical practice guidelines can improve the quality of care,^{7,8} whether they achieve this in daily practice is less clear. This is partly because patients, doctors, payers, and managers define quality differently and because current evidence about the effectiveness of guidelines is incomplete.

Potential benefits for patients

For patients (and almost everyone else in health care), the greatest benefit that could be achieved by guidelines is to improve health outcomes. Guidelines that promote interventions of proved benefit and

Summary points

Clinical guidelines are an increasingly familiar part of clinical practice

They have potential benefits and harms

Rigorously developed evidence based guidelines minimise the potential harms

Clinical guidelines are only one option for improving the quality of care

discourage ineffective ones have the potential to reduce morbidity and mortality and improve quality of life, at least for some conditions. Guidelines can also improve the consistency of care; studies around the world show that the frequency with which procedures are performed varies dramatically among doctors, specialties, and geographical regions, even after case mix is controlled for.⁹ Patients with identical clinical problems receive different care depending on their clinician, hospital, or location. Guidelines offer a remedy, making it more likely that patients will be cared for in the same manner regardless of where or by whom they are treated.

Clinical guidelines offer patients other benefits. Those accompanied by "consumer" versions (leaflets, audiotapes, or videos in lay language) or publicised in magazines, news reports, and internet sites inform patients and the public about what their clinicians should be doing. Increasingly, lay guidelines summarise the benefits and harms of available options, along with estimates of the probability or magnitude of potential outcomes.¹⁰ Such guidelines empower patients to make more informed healthcare choices and to consider their personal needs and preferences in selecting the best option. Indeed, clinicians may first learn about new guidelines (or be reminded of oversights) when patients ask about recommendations or treatment options.

Finally, clinical guidelines can help patients by influencing public policy. Guidelines call attention to underrecognised health problems, clinical services, and preventive interventions and to neglected patient populations and high risk groups. Services that were not previously offered to patients may be made available as a response to newly released guidelines. Clinical guidelines developed with attention to the public good can promote distributive justice, advocating better delivery of services to those in need. In a cash limited healthcare system, guidelines that improve the efficiency of health care free up resources needed for other (more equitably distributed) healthcare services.

This is the first in a series of four articles on issues in the development and use of clinical guidelines

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An additional article—an international overview—is available on our website, as is a longer version of this article

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Overview of international activity on guidelines

More details in the form of a full paper are available on the *BMJ's* website.

Europe

United Kingdom—Guidelines have existed in England for decades; recent years have heightened interest in guidelines as a tool for implementing health care based on proof of effectiveness. Professional bodies, encouraged by the NHS, are producing guidelines for use by providers to improve care and by purchasers to guide contracting and commissioning decisions. The NHS is now using a critical appraisal instrument to determine which guidelines to commend to health authorities. Although historically most British guidelines have derived from consensus conferences or expert opinion, there is growing interest in using explicit methods to develop evidence based guidelines. The Scottish Intercollegiate Guideline Network uses a systematic multidisciplinary approach to prepare evidence based guidelines. National guidelines are converted at the local level into formats that encourage adoption in practice.

The Netherlands—In the Netherlands, the Dutch College of General Practitioners has produced guidelines since 1987, issuing more than 70 guidelines at a rate of 8-10 topics per year. A rigorous procedure involves an analysis of the scientific literature, combined with consensus discussions among ordinary general practitioners and content experts. A systematic implementation programme follows guideline development. Updating of the guidelines has recently begun. Guidelines figure prominently in Dutch health policy.

Finland and Sweden—In Finland, national and local bodies have issued more than 700 guidelines since 1989. A programme for evidence based guideline development has been started recently. Guidelines in Sweden appear in reports by the Swedish Council on Technology Assessment in Health Care, an internationally consulted technology assessment agency, and in recommendations from other government bodies.

France—In France, the Agence Nationale de l'Accréditation et d'Évaluation en Santé has published over 100 guidelines based on consensus conferences or modified guidelines from other countries. It has also developed more than 140 références médicales, guidelines on procedural indications for use in setting coverage policy. The guidelines are disseminated through networks of general practitioners, and their effectiveness is evaluated through local audits.

Germany, Italy, and Spain—Guidelines are on the rise in Germany and Italy, where a guidelines database is being developed to support national healthcare reform. In Spain, the Catalan Agency for Health Technology Assessment has begun preparing guidelines and teaches methods of guideline development. Consensus guidelines figure prominently in Catalonian healthcare reform.

North America

Guidelines, protocols, and care pathways developed by professional societies and other groups are common in American hospitals and health plans, where they are used for quality improvement and cost control. Although some evidence based guidelines produced by government panels and medical societies have received prominent attention, many healthcare organisations purchase commercially produced guidelines that emphasise shortened lengths of stay and other resource savings. Canadian health care is largely state funded, but a similar proportion of organisations as in the United States use guidelines. The massive guideline industry in America has created special problems such as information overload. Directories and newsletters have become necessary to monitor the hundreds of guideline topics and sponsoring organisations. Americans have articulated evidence based methods in manuals and other reports. This expertise has not always found its way into actual guidelines—most of which remain rooted in consensus or opinion.

Australia and New Zealand

Guidelines in Australia date to the late 1970s, when the state health authority began endorsing guideline booklets,² and they continue on a large scale today. There is an increasing emphasis on the need for evidence based methods.

Guidelines in New Zealand emanate directly from national health policy. New Zealand's choosing to restrict services at the point of service through guidelines received international attention in debates about rationing. One guideline on hypertension and a subsequent cholesterol guideline from the New Zealand National Heart Foundation broke new ground methodologically by linking recommendations to patients' absolute risk probabilities rather than to generic treatment criteria.

Potential benefits for healthcare professionals

Clinical guidelines can improve the quality of clinical decisions. They offer explicit recommendations for clinicians who are uncertain about how to proceed, overturn the beliefs of doctors accustomed to outdated practices, improve the consistency of care, and provide authoritative recommendations that reassure practitioners about the appropriateness of their treatment policies. Guidelines based on a critical appraisal of scientific evidence (evidence based guidelines) clarify which interventions are of proved benefit and document the quality of the supporting data. They alert clinicians to interventions unsupported by good science, reinforce the importance and methods of critical appraisal, and call attention to ineffective, dangerous, and wasteful practices.

Clinical guidelines can support quality improvement activities. The first step in designing quality assessment tools (standing orders, reminder systems,

critical care pathways, algorithms, audits, etc) is to reach agreement on how patients should be treated, often by developing a guideline. Guidelines are a common point of reference for prospective and retrospective audits of clinicians' or hospitals' practices: the tests, treatments, and treatment goals recommended in guidelines provide ready process measures (review criteria) for rating compliance with best care practices.¹¹

Medical researchers benefit from the spotlight that evidence based guidelines shine on gaps in the evidence. The methods of guideline development that emphasise systematic reviews focus attention on key research questions that must be answered to establish the effectiveness of an intervention¹² and highlight gaps in the known literature. Critical appraisal of the evidence identifies design flaws in existing studies. Recognising the presence and absence of evidence can redirect the work of investigators and encourage funding agencies to support studies that fulfill this effectiveness based agenda.

Finally, some uses of clinical guidelines straddle the boundary between benefits and harms. Clinicians may seek secular (and even self serving) benefits from guidelines. In some healthcare systems, guidelines prompt government or private payers to provide coverage or to reimburse doctors for services. Specialties engaged in “turf wars” to gain ownership over specific procedures or treatments may publish a guideline to affirm their role. Clinicians may turn to guidelines for medicolegal protection or to reinforce their position in dealing with administrators who disagree with their practice policies.

Potential benefits for healthcare systems

Healthcare systems that provide services, and government bodies and private insurers that pay for them, have found that clinical guidelines may be effective in improving efficiency (often by standardising care) and optimising value for money.¹³ Implementation of certain guidelines reduces outlays for hospitalisation, prescription drugs, surgery, and other procedures. Publicising adherence to guidelines may also improve public image, sending messages of commitment to excellence and quality. Such messages can promote good will, political support, and (in some healthcare systems) revenue. Many believe that the economic motive behind clinical guidelines is the principal reason for their popularity.

Potential limitations and harms of guidelines

The most important limitation of guidelines is that the recommendations may be wrong (or at least wrong for individual patients). Apart from human considerations such as inadvertent oversights by busy or weary members of the guideline group, guideline developers may err in determining what is best for patients for three important reasons.

Firstly, scientific evidence about what to recommend is often lacking, misleading, or misinterpreted. Only a small subset of what is done in medicine has been tested in appropriate, well designed studies. Where studies do exist, the findings may be misleading because of design flaws which contribute to bias or poor generalisability. Guideline development groups often lack the time, resources, and skills to gather and scrutinise every last piece of evidence. Even when the data are certain, recommendations for or against interventions will involve subjective value judgments when the benefits are weighed against the harms. The value judgment made by a guideline development group may be the wrong choice for individual patients.

Secondly, recommendations are influenced by the opinions and clinical experience and composition of the guideline development group. Tests and treatments that experts believe are good for patients may in practice be inferior to other options, ineffective, or even harmful. The beliefs to which experts subscribe, often in the face of conflicting data, can be based on misconceptions and personal recollections that misrepresent population norms.¹⁴

Thirdly, patients’ needs may not be the only priority in making recommendations. Practices that are sub-optimal from the patient’s perspective may be recommended to help control costs, serve societal needs, or protect special interests (those of doctors, risk managers, or politicians, for example).



MARK MCCONNELL

The promotion of flawed guidelines by practices, payers, or healthcare systems can encourage, if not institutionalise, the delivery of ineffective, harmful, or wasteful interventions. The same parties that stand to benefit from guidelines—patients, healthcare professionals, the healthcare system—may all be harmed.

Potential harms to patients

The greatest danger of flawed clinical guidelines is to patients. Recommendations that do not take due account of the evidence can result in suboptimal, ineffective, or harmful practices. Guidelines that are inflexible can harm by leaving insufficient room for clinicians to tailor care to patients’ personal circumstances and medical history. What is best for patients overall, as recommended in guidelines, may be inappropriate for individuals; blanket recommendations, rather than a menu of options or recommendations for shared decision making, ignore patients’ preferences.¹⁵ Thus the frequently touted benefit of clinical guidelines—more consistent practice patterns and reduced variation—may come at the expense of reducing individualised care for patients with special needs. Lay versions of guidelines, if improperly constructed and worded, may mislead or confuse patients and disrupt the doctor-patient relationship.

Clinical guidelines can adversely affect public policy for patients. Recommendations against an intervention may lead providers to drop access to or coverage for services. Imprudent recommendations for costly interventions may displace limited resources that are needed for other services of greater value to patients. The tendency of guidelines to focus attention on specific health issues is subject to misuse by proponents and advocacy groups, giving the public (and health professionals) the wrong impression about the relative importance of diseases and the effectiveness of interventions.

Potential harms to healthcare professionals

Flawed clinical guidelines harm practitioners by providing inaccurate scientific information and clinical advice, thereby compromising the quality of

care. They may encourage ineffective, harmful, or wasteful interventions. Even when guidelines are correct, clinicians often find them inconvenient and time consuming to use. Conflicting guidelines from different professional bodies can also confuse and frustrate practitioners.¹⁶ Outdated recommendations may perpetuate outmoded practices and technologies.

Clinical guidelines can also hurt clinicians professionally. Auditors and managers may unfairly judge the quality of care based on criteria from invalid guidelines. The well intentioned effort to make guidelines explicit and practical encourages the injudicious use of certain words ("should" instead of "may," for example), arbitrary numbers (such as months of treatment, intervals between screening tests), and simplistic algorithms when supporting evidence may be lacking. Algorithms that reduce patient care into a sequence of binary (yes/no) decisions often do injustice to the complexity of medicine and the parallel and iterative thought processes inherent in clinical judgment. Words, numbers, and simplistic algorithms can be used by those who judge clinicians to repudiate unfairly those who, for legitimate reasons, follow different practice policies. Guidelines are also potentially harmful to doctors as citable evidence for malpractice litigation and because of their economic implications. Referral guidelines can shift patients from one specialty to another. A negative (or neutral) recommendation may prompt providers to withdraw availability or coverage. A theoretical concern is that clinicians may be sued for not adhering to guidelines although, as discussed in the third paper in this series,⁵ this has not yet become an important reality.

Guidelines can harm medical investigators and scientific progress if further research is inappropriately discouraged. Guidelines that conclude that a procedure or treatment lacks evidence of benefit may be misinterpreted by funding bodies as grounds for not investing in further research and for not supporting efforts to refine previously ineffective technologies.

Potential harms to healthcare systems

Healthcare systems and payers may be harmed by guidelines if following them escalates utilisation, compromises operating efficiency, or wastes limited resources. Some clinical guidelines, especially those developed by medical and other groups unconcerned about financing, may advocate costly interventions that are unaffordable or that cut into resources needed for more effective services.

Conclusion

In the face of these mixed consequences, attitudes about whether clinical guidelines are good or bad for medicine vary from one group to another. Guidelines produced by governments or payers to control spiraling costs may constitute responsible public policy but may be resented by clinicians and patients as an invasion of personal autonomy. Guidelines developed by specialists may seem self serving, biased, and threatening to generalists. To specialists, guidelines developed without their input do not contain adequate expertise. Inflexible guidelines with rigid rules about

what is appropriate are popular with managers, quality auditors, and lawyers but are decried as "cookbook medicine" by doctors faced with non-uniform clinical problems and as invalid by those who cite the lack of supporting data.

These disparate sentiments and the growing awareness of their limitations and harms have done little to stem the rapid promulgation of guidelines around the world (see box). The unbridled enthusiasm for guidelines, and the unrealistic expectations about what they will accomplish, frequently betrays inexperience and unfamiliarity with their limitations and potential hazards. Naïve consumers of guidelines accept official recommendations on face value, especially when they carry the imprimatur of prominent professional groups or government bodies.

More discerning users of clinical guidelines scrutinise the methods by which they have been developed.⁴ Moreover, a more fundamental problem is that guidelines may do little to change practice behaviour.⁶

Clinical guidelines are only one option for improving the quality of care. Too often, advocates view guidelines as a "magic bullet" for healthcare problems and ignore more effective solutions. Clinical guidelines make sense when practitioners are unclear about appropriate practice and when scientific evidence can provide an answer. They are a poor remedy in other settings. When clinicians already know the information contained in guidelines, those concerned with improving quality should redirect their efforts to identify the specific barriers, beyond knowledge, that stand in the way of behaviour change.

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WPATH WORLD PROFESSIONAL
ASSOCIATION for
TRANSGENDER HEALTH

Standards of Care for the Health of Transsexual, Transgender, and Gender- Nonconforming People

The World Professional Association for Transgender Health







Standards of Care

for the Health of Transsexual, Transgender, and Gender- Nonconforming People

Eli Coleman, Walter Bockting, Marsha Botzer, Peggy Cohen-Kettenis, Griet DeCuypere, Jamie Feldman, Lin Fraser, Jamison Green, Gail Knudson, Walter J. Meyer, Stan Monstrey, Richard K. Adler, George R. Brown, Aaron H. Devor, Randall Ehrbar, Randi Ettner, Evan Eyler, Rob Garofalo, Dan H. Karasic, Arlene Istar Lev, Gal Mayer, Heino Meyer-Bahlburg, Blaine Paxton Hall, Friedmann Pfäfflin, Katherine Rachlin, Bean Robinson, Loren S. Schechter, Vin Tangpricha, Mick van Trotsenburg, Anne Vitale, Sam Winter, Stephen Whittle, Kevan R. Wylie & Ken Zucker

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¹ This is the seventh version of the *Standards of Care* since the original 1979 document. Previous revisions were in 1980, 1981, 1990, 1998, and 2001. Version seven was published in the *International Journal of Transgenderism*, 13(4), 165–232. doi:10.1080/15532739.2011.700873

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Purpose and Use of the *Standards of Care*

The World Professional Association for Transgender Health (WPATH)^I is an international, multidisciplinary, professional association whose mission is to promote evidence-based care, education, research, advocacy, public policy, and respect in transsexual and transgender health. The vision of WPATH is a world wherein transsexual, transgender, and gender-nonconforming people benefit from access to evidence-based health care, social services, justice, and equality.

One of the main functions of WPATH is to promote the highest standards of health care for individuals through the articulation of *Standards of Care (SOC) for the Health of Transsexual, Transgender, and Gender Nonconforming People*. The SOC are based on the best available science and expert professional consensus.^{II} Most of the research and experience in this field comes from a North American and Western European perspective; thus, adaptations of the SOC to other parts of the world are necessary. Suggestions for ways of thinking about cultural relativity and cultural competence are included in this version of the SOC.

The overall goal of the SOC is to provide clinical guidance for health professionals to assist transsexual, transgender, and gender-nonconforming people with safe and effective pathways to achieving lasting personal comfort with their gendered selves, in order to maximize their overall health, psychological well-being, and self-fulfillment. This assistance may include primary care, gynecologic and urologic care, reproductive options, voice and communication therapy, mental health services (e.g., assessment, counseling, psychotherapy), and hormonal and surgical treatments. While this is primarily a document for health professionals, the SOC may also be used by individuals, their families, and social institutions to understand how they can assist with promoting optimal health for members of this diverse population.

WPATH recognizes that health is dependent upon not only good clinical care but also social and political climates that provide and ensure social tolerance, equality, and the full rights of citizenship. Health is promoted through public policies and legal reforms that promote tolerance and equity

I Formerly the Harry Benjamin International Gender Dysphoria Association

II The *Standards of Care (SOC)*, Version 7, represents a significant departure from previous versions. Changes in this version are based upon significant cultural shifts, advances in clinical knowledge, and appreciation of the many health care issues that can arise for transsexual, transgender, and gender-nonconforming people beyond hormone therapy and surgery (Coleman, 2009a, b, c, d).

for gender and sexual diversity and that eliminate prejudice, discrimination, and stigma. WPATH is committed to advocacy for these changes in public policies and legal reforms.

The *Standards of Care* Are Flexible Clinical Guidelines

The SOC are intended to be flexible in order to meet the diverse health care needs of transsexual, transgender, and gender-nonconforming people. While flexible, they offer standards for promoting optimal health care and guiding the treatment of people experiencing gender dysphoria—broadly defined as discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b).

As in all previous versions of the SOC, the criteria put forth in this document for hormone therapy and surgical treatments for gender dysphoria are clinical guidelines; individual health professionals and programs may modify them. Clinical departures from the SOC may come about because of a patient's unique anatomic, social, or psychological situation; an experienced health professional's evolving method of handling a common situation; a research protocol; lack of resources in various parts of the world; or the need for specific harm-reduction strategies. These departures should be recognized as such, explained to the patient, and documented through informed consent for quality patient care and legal protection. This documentation is also valuable for the accumulation of new data, which can be retrospectively examined to allow for health care—and the SOC—to evolve.

The SOC articulate standards of care but also acknowledge the role of making informed choices and the value of harm-reduction approaches. In addition, this version of the SOC recognizes and validates various expressions of gender that may not necessitate psychological, hormonal, or surgical treatments. Some patients who present for care will have made significant self-directed progress towards gender role changes, transition, or other resolutions regarding their gender identity or gender dysphoria. Other patients will require more intensive services. Health professionals can use the SOC to help patients consider the full range of health services open to them, in accordance with their clinical needs and goals for gender expression.

Global Applicability of the *Standards of Care*

While the SOC are intended for worldwide use, WPATH acknowledges that much of the recorded clinical experience and knowledge in this area of health care is derived from North American and Western European sources. From place to place, both across and within nations, there are differences in all of the following: social attitudes towards transsexual, transgender, and gender-nonconforming people; constructions of gender roles and identities; language used to describe different gender identities; epidemiology of gender dysphoria; access to and cost of treatment; therapies offered; number and type of professionals who provide care; and legal and policy issues related to this area of health care (Winter, 2009).

It is impossible for the SOC to reflect all of these differences. In applying these standards to other cultural contexts, health professionals must be sensitive to these differences and adapt the SOC according to local realities. For example, in a number of cultures, gender-nonconforming people are found in such numbers and living in such ways as to make them highly socially visible (Peletz, 2006). In settings such as these, it is common for people to initiate a change in their gender expression and physical characteristics while in their teens or even earlier. Many grow up and live in a social, cultural, and even linguistic context quite unlike that of Western cultures. Yet almost all experience prejudice (Peletz, 2006; Winter, 2009). In many cultures, social stigma towards gender nonconformity is widespread and gender roles are highly prescriptive (Winter et al., 2009). Gender-nonconforming people in these settings are forced to be hidden and, therefore, may lack opportunities for adequate health care (Winter, 2009).

The SOC are not intended to limit efforts to provide the best available care to all individuals. Health professionals throughout the world—even in areas with limited resources and training opportunities—can apply the many core principles that undergird the SOC. These principles include the following: Exhibit respect for patients with nonconforming gender identities (do not pathologize differences in gender identity or expression); provide care (or refer to knowledgeable colleagues) that affirms patients' gender identities and reduces the distress of gender dysphoria, when present; become knowledgeable about the health care needs of transsexual, transgender, and gender-nonconforming people, including the benefits and risks of treatment options for gender dysphoria; match the treatment approach to the specific needs of patients, particularly their goals for gender expression and need for relief from gender dysphoria; facilitate access to appropriate care; seek patients' informed consent before providing treatment; offer continuity of care; and be prepared to support and advocate for patients within their families and communities (schools, workplaces, and other settings).

Terminology is culture- and time-dependent and is rapidly evolving. It is important to use respectful language in different places and times, and among different people. As the SOC are translated into other languages, great care must be taken to ensure that the meanings of terms are accurately translated. Terminology in English may not be easily translated into other languages, and vice versa. Some languages do not have equivalent words to describe the various terms within this document; hence, translators should be cognizant of the underlying goals of treatment and articulate culturally applicable guidance for reaching those goals.



The Difference Between Gender Nonconformity and Gender Dysphoria

Being Transsexual, Transgender, or Gender-Nonconforming Is a Matter of Diversity, Not Pathology

WPATH released a statement in May 2010 urging the de-psychopathologization of gender nonconformity worldwide (WPATH Board of Directors, 2010). This statement noted that “the expression of gender characteristics, including identities, that are not stereotypically associated with one’s assigned sex at birth is a common and culturally diverse human phenomenon [that] should not be judged as inherently pathological or negative.”

Unfortunately, there is stigma attached to gender nonconformity in many societies around the world. Such stigma can lead to prejudice and discrimination, resulting in “minority stress” (I. H. Meyer, 2003). Minority stress is unique (additive to general stressors experienced by all people), socially based, and chronic, and may make transsexual, transgender, and gender-nonconforming individuals more vulnerable to developing mental health concerns such as anxiety and depression (Institute of Medicine, 2011). In addition to prejudice and discrimination in society at large, stigma can contribute to abuse and neglect in one’s relationships with peers and family members, which in turn can lead to psychological distress. However, these symptoms are socially induced and are not inherent to being transsexual, transgender, or gender-nonconforming.

Gender Nonconformity Is Not the Same as Gender Dysphoria

Gender nonconformity refers to the extent to which a person's gender identity, role, or expression differs from the cultural norms prescribed for people of a particular sex (Institute of Medicine, 2011). *Gender dysphoria* refers to discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b). Only *some* gender-nonconforming people experience gender dysphoria at *some* point in their lives.

Treatment is available to assist people with such distress to explore their gender identity and find a gender role that is comfortable for them (Bockting & Goldberg, 2006). Treatment is individualized: What helps one person alleviate gender dysphoria might be very different from what helps another person. This process may or may not involve a change in gender expression or body modifications. Medical treatment options include, for example, feminization or masculinization of the body through hormone therapy and/or surgery, which are effective in alleviating gender dysphoria and are medically necessary for many people. Gender identities and expressions are diverse, and hormones and surgery are just two of many options available to assist people with achieving comfort with self and identity.

Gender dysphoria can in large part be alleviated through treatment (Murad et al., 2010). Hence, while transsexual, transgender, and gender-nonconforming people may experience gender dysphoria at some points in their lives, many individuals who receive treatment will find a gender role and expression that is comfortable for them, even if these differ from those associated with their sex assigned at birth, or from prevailing gender norms and expectations.

Diagnoses Related to Gender Dysphoria

Some people experience gender dysphoria at such a level that the distress meets criteria for a formal diagnosis that might be classified as a mental disorder. Such a diagnosis is not a license for stigmatization or for the deprivation of civil and human rights. Existing classification systems such as the *Diagnostic Statistical Manual of Mental Disorders (DSM)* (American Psychiatric Association, 2000) and the *International Classification of Diseases (ICD)* (World Health Organization, 2007) define hundreds of mental disorders that vary in onset, duration, pathogenesis, functional disability, and treatability. All of these systems attempt to classify clusters of symptoms and conditions, not the individuals themselves. A disorder is a description of something with which a person might struggle, not a description of the person or the person's identity.

Thus, transsexual, transgender, and gender-nonconforming individuals are not inherently disordered. Rather, the distress of gender dysphoria, when present, is the concern that might be diagnosable and for which various treatment options are available. The existence of a diagnosis for such dysphoria often facilitates access to health care and can guide further research into effective treatments.

Research is leading to new diagnostic nomenclatures, and terms are changing in both the *DSM* (Cohen-Kettenis & Pfäfflin, 2010; Knudson, De Cuypere, & Bockting, 2010b; Meyer-Bahlburg, 2010; Zucker, 2010) and the *ICD*. For this reason, familiar terms are employed in the *SOC* and definitions are provided for terms that may be emerging. Health professionals should refer to the most current diagnostic criteria and appropriate codes to apply in their practice areas.

IV Epidemiologic Considerations

Formal epidemiologic studies on the incidence^{III} and prevalence^{IV} of transsexualism specifically or transgender and gender-nonconforming identities in general have not been conducted, and efforts to achieve realistic estimates are fraught with enormous difficulties (Institute of Medicine, 2011; Zucker & Lawrence, 2009). Even if epidemiologic studies established that a similar proportion of transsexual, transgender, or gender-nonconforming people existed all over the world, it is likely that cultural differences from one country to another would alter both the behavioral expressions of different gender identities and the extent to which gender dysphoria—distinct from one's gender identity—is actually occurring in a population. While in most countries, crossing normative gender boundaries generates moral censure rather than compassion, there are examples in certain cultures of gender-nonconforming behaviors (e.g., in spiritual leaders) that are less stigmatized and even revered (Besnier, 1994; Bolin, 1988; Chiñas, 1995; Coleman, Colgan, & Gooren, 1992; Costa & Matzner, 2007; Jackson & Sullivan, 1999; Nanda, 1998; Taywaditap, Coleman, & Dumronggittigule, 1997).

For various reasons, researchers who have studied incidence and prevalence have tended to focus on the most easily counted subgroup of gender-nonconforming individuals: transsexual individuals who experience gender dysphoria and who present for gender-transition-related care at specialist gender clinics (Zucker & Lawrence, 2009). Most studies have been conducted in European countries such as Sweden (Wålinder, 1968, 1971), the United Kingdom (Hoenig & Kenna, 1974),

III **incidence**—the number of new cases arising in a given period (e.g., a year)

IV **prevalence**—the number of individuals having a condition, divided by the number of people in the general population

the Netherlands (Bakker, Van Kesteren, Gooren, & Bezemer, 1993; Eklund, Gooren, & Bezemer, 1988; van Kesteren, Gooren, & Megens, 1996), Germany (Weitze & Osburg, 1996), and Belgium (De Cuypere et al., 2007). One was conducted in Singapore (Tsoi, 1988).

De Cuypere and colleagues (2007) reviewed such studies, as well as conducted their own. Together, those studies span 39 years. Leaving aside two outlier findings from Pauly in 1965 and Tsoi in 1988, ten studies involving eight countries remain. The prevalence figures reported in these ten studies range from 1:11,900 to 1:45,000 for male-to-female individuals (MtF) and 1:30,400 to 1:200,000 for female-to-male (FtM) individuals. Some scholars have suggested that the prevalence is much higher, depending on the methodology used in the research (e.g., Olyslager & Conway, 2007).

Direct comparisons across studies are impossible, as each differed in their data collection methods and in their criteria for documenting a person as transsexual (e.g., whether or not a person had undergone genital reconstruction, versus had initiated hormone therapy, versus had come to the clinic seeking medically supervised transition services). The trend appears to be towards higher prevalence rates in the more recent studies, possibly indicating increasing numbers of people seeking clinical care. Support for this interpretation comes from research by Reed and colleagues (2009), who reported a doubling of the numbers of people accessing care at gender clinics in the United Kingdom every five or six years. Similarly, Zucker and colleagues (2008) reported a four- to five-fold increase in child and adolescent referrals to their Toronto, Canada clinic over a 30-year period.

The numbers yielded by studies such as these can be considered minimum estimates at best. The published figures are mostly derived from clinics where patients met criteria for severe gender dysphoria and had access to health care at those clinics. These estimates do not take into account that treatments offered in a particular clinic setting might not be perceived as affordable, useful, or acceptable by all self-identified gender dysphoric individuals in a given area. By counting only those people who present at clinics for a specific type of treatment, an unspecified number of gender dysphoric individuals are overlooked.

Other clinical observations (not yet firmly supported by systematic study) support the likelihood of a higher prevalence of gender dysphoria: (i) Previously unrecognized gender dysphoria is occasionally diagnosed when patients are seen with anxiety, depression, conduct disorder, substance abuse, dissociative identity disorders, borderline personality disorder, sexual disorders, and disorders of sex development (Cole, O'Boyle, Emory, & Meyer III, 1997). (ii) Some crossdressers, drag queens/kings or female/male impersonators, and gay and lesbian individuals may be experiencing gender dysphoria (Bullough & Bullough, 1993). (iii) The intensity of some people's gender dysphoria fluctuates below and above a clinical threshold (Docter, 1988). (iv) Gender nonconformity among FtM individuals tends to be relatively invisible in many cultures, particularly to Western health

professionals and researchers who have conducted most of the studies on which the current estimates of prevalence and incidence are based (Winter, 2009).

Overall, the existing data should be considered a starting point, and health care would benefit from more rigorous epidemiologic study in different locations worldwide.



Overview of Therapeutic Approaches for Gender Dysphoria

Advancements in the Knowledge and Treatment of Gender Dysphoria

In the second half of the 20th century, awareness of the phenomenon of gender dysphoria increased when health professionals began to provide assistance to alleviate gender dysphoria by supporting changes in primary and secondary sex characteristics through hormone therapy and surgery, along with a change in gender role. Although Harry Benjamin already acknowledged a spectrum of gender nonconformity (Benjamin, 1966), the initial clinical approach largely focused on identifying who was an appropriate candidate for sex reassignment to facilitate a physical change from male to female or female to male as completely as possible (e.g., Green & Fleming, 1990; Hastings, 1974). This approach was extensively evaluated and proved to be highly effective. Satisfaction rates across studies ranged from 87% of MtF patients to 97% of FtM patients (Green & Fleming, 1990), and regrets were extremely rare (1–1.5% of MtF patients and <1% of FtM patients; Pfäfflin, 1993). Indeed, hormone therapy and surgery have been found to be medically necessary to alleviate gender dysphoria in many people (American Medical Association, 2008; Anton, 2009; World Professional Association for Transgender Health, 2008).

As the field matured, health professionals recognized that while many individuals need both hormone therapy and surgery to alleviate their gender dysphoria, others need only one of these treatment options and some need neither (Bockting & Goldberg, 2006; Bockting, 2008; Lev, 2004). Often with the help of psychotherapy, some individuals integrate their trans- or cross-gender feelings into the gender role they were assigned at birth and do not feel the need to feminize or masculinize their body. For others, changes in gender role and expression are sufficient to alleviate

gender dysphoria. Some patients may need hormones, a possible change in gender role, but not surgery; others may need a change in gender role along with surgery, but not hormones. In other words, treatment for gender dysphoria has become more individualized.

As a generation of transsexual, transgender, and gender-nonconforming individuals has come of age—many of whom have benefitted from different therapeutic approaches—they have become more visible as a community and demonstrated considerable diversity in their gender identities, roles, and expressions. Some individuals describe themselves not as gender-nonconforming but as unambiguously cross-sexed (i.e., as a member of the other sex; Bockting, 2008). Other individuals affirm their unique gender identity and no longer consider themselves to be either male or female (Bornstein, 1994; Kimberly, 1997; Stone, 1991; Warren, 1993). Instead, they may describe their gender identity in specific terms such as transgender, bigender, or genderqueer, affirming their unique experiences that may transcend a male/female binary understanding of gender (Bockting, 2008; Ekins & King, 2006; Nestle, Wilchins, & Howell, 2002). They may not experience their process of identity affirmation as a “transition,” because they never fully embraced the gender role they were assigned at birth or because they actualize their gender identity, role, and expression in a way that does not involve a change from one gender role to another. For example, some youth identifying as genderqueer have always experienced their gender identity and role as such (genderqueer). Greater public visibility and awareness of gender diversity (Feinberg, 1996) has further expanded options for people with gender dysphoria to actualize an identity and find a gender role and expression that are comfortable for them.

Health professionals can assist gender dysphoric individuals with affirming their gender identity, exploring different options for expression of that identity, and making decisions about medical treatment options for alleviating gender dysphoria.

Options for Psychological and Medical Treatment of Gender Dysphoria

For individuals seeking care for gender dysphoria, a variety of therapeutic options can be considered. The number and type of interventions applied and the order in which these take place may differ from person to person (e.g., Bockting, Knudson, & Goldberg, 2006; Bolin, 1994; Rachlin, 1999; Rachlin, Green, & Lombardi, 2008; Rachlin, Hansbury, & Pardo, 2010). Treatment options include the following:

- Changes in gender expression and role (which may involve living part time or full time in another gender role, consistent with one’s gender identity);
- Hormone therapy to feminize or masculinize the body;

- Surgery to change primary and/or secondary sex characteristics (e.g., breasts/chest, external and/or internal genitalia, facial features, body contouring);
- Psychotherapy (individual, couple, family, or group) for purposes such as exploring gender identity, role, and expression; addressing the negative impact of gender dysphoria and stigma on mental health; alleviating internalized transphobia; enhancing social and peer support; improving body image; or promoting resilience.

Options for Social Support and Changes in Gender Expression

In addition (or as an alternative) to the psychological- and medical-treatment options described above, other options can be considered to help alleviate gender dysphoria, for example:

- In-person and online peer support resources, groups, or community organizations that provide avenues for social support and advocacy;
- In-person and online support resources for families and friends;
- Voice and communication therapy to help individuals develop verbal and non-verbal communication skills that facilitate comfort with their gender identity;
- Hair removal through electrolysis, laser treatment, or waxing;
- Breast binding or padding, genital tucking or penile prostheses, padding of hips or buttocks;
- Changes in name and gender marker on identity documents.

VI

Assessment and Treatment of Children and Adolescents With Gender Dysphoria

There are a number of differences in the phenomenology, developmental course, and treatment approaches for gender dysphoria in children, adolescents, and adults. In children and adolescents, a rapid and dramatic developmental process (physical, psychological, and sexual) is involved and

there is greater fluidity and variability in outcomes, particularly in prepubertal children. Accordingly, this section of the SOC offers specific clinical guidelines for the assessment and treatment of gender dysphoric children and adolescents.

Differences Between Children and Adolescents with Gender Dysphoria

An important difference between gender dysphoric children and adolescents is in the proportion for whom dysphoria persists into adulthood. Gender dysphoria during childhood does not inevitably continue into adulthood.^V Rather, in follow-up studies of prepubertal children (mainly boys) who were referred to clinics for assessment of gender dysphoria, the dysphoria persisted into adulthood for only 6–23% of children (Cohen-Kettenis, 2001; Zucker & Bradley, 1995). Boys in these studies were more likely to identify as gay in adulthood than as transgender (Green, 1987; Money & Russo, 1979; Zucker & Bradley, 1995; Zuger, 1984). Newer studies, also including girls, showed a 12–27% persistence rate of gender dysphoria into adulthood (Drummond, Bradley, Peterson-Badali, & Zucker, 2008; Wallien & Cohen-Kettenis, 2008).

In contrast, the persistence of gender dysphoria into adulthood appears to be much higher for adolescents. No formal prospective studies exist. However, in a follow-up study of 70 adolescents who were diagnosed with gender dysphoria and given puberty-suppressing hormones, all continued with actual sex reassignment, beginning with feminizing/masculinizing hormone therapy (de Vries, Steensma, Doreleijers, & Cohen-Kettenis, 2010).

Another difference between gender dysphoric children and adolescents is in the sex ratios for each age group. In clinically referred, gender dysphoric children under age 12, the male/female ratio ranges from 6:1 to 3:1 (Zucker, 2004). In clinically referred, gender dysphoric adolescents older than age 12, the male/female ratio is close to 1:1 (Cohen-Kettenis & Pfäfflin, 2003).

As discussed in section IV and by Zucker and Lawrence (2009), formal epidemiologic studies on gender dysphoria—in children, adolescents, and adults—are lacking. Additional research is needed to refine estimates of its prevalence and persistence in different populations worldwide.

^V Gender-nonconforming behaviors in children may continue into adulthood, but such behaviors are not necessarily indicative of gender dysphoria and a need for treatment. As described in section III, gender dysphoria is not synonymous with diversity in gender expression.

Phenomenology in Children

Children as young as age two may show features that could indicate gender dysphoria. They may express a wish to be of the other sex and be unhappy about their physical sex characteristics and functions. In addition, they may prefer clothes, toys, and games that are commonly associated with the other sex and prefer playing with other-sex peers. There appears to be heterogeneity in these features: Some children demonstrate extremely gender-nonconforming behavior and wishes, accompanied by persistent and severe discomfort with their primary sex characteristics. In other children, these characteristics are less intense or only partially present (Cohen-Kettenis et al., 2006; Knudson, De Cuypere, & Bockting, 2010a).

It is relatively common for gender dysphoric children to have coexisting internalizing disorders such as anxiety and depression (Cohen-Kettenis, Owen, Kaijser, Bradley, & Zucker, 2003; Wallien, Swaab, & Cohen-Kettenis, 2007; Zucker, Owen, Bradley, & Ameeriar, 2002). The prevalence of autism spectrum disorders seems to be higher in clinically referred, gender dysphoric children than in the general population (de Vries, Noens, Cohen-Kettenis, van Berckelaer-Onnes, & Doreleijers, 2010).

Phenomenology in Adolescents

In most children, gender dysphoria will disappear before, or early in, puberty. However, in some children these feelings will intensify and body aversion will develop or increase as they become adolescents and their secondary sex characteristics develop (Cohen-Kettenis, 2001; Cohen-Kettenis & Pfäfflin, 2003; Drummond et al., 2008; Wallien & Cohen-Kettenis, 2008; Zucker & Bradley, 1995). Data from one study suggest that more extreme gender nonconformity in childhood is associated with persistence of gender dysphoria into late adolescence and early adulthood (Wallien & Cohen-Kettenis, 2008). Yet many adolescents and adults presenting with gender dysphoria do not report a history of childhood gender-nonconforming behaviors (Docter, 1988; Landén, Wälinder, & Lundström, 1998). Therefore, it may come as a surprise to others (parents, other family members, friends, and community members) when a youth's gender dysphoria first becomes evident in adolescence.

Adolescents who experience their primary and/or secondary sex characteristics and their sex assigned at birth as inconsistent with their gender identity may be intensely distressed about it. Many, but not all, gender dysphoric adolescents have a strong wish for hormones and surgery. Increasing numbers of adolescents have already started living in their desired gender role upon entering high school (Cohen-Kettenis & Pfäfflin, 2003).

Among adolescents who are referred to gender identity clinics, the number considered eligible for early medical treatment—starting with GnRH analogues to suppress puberty in the first Tanner stages—differs among countries and centers. Not all clinics offer puberty suppression. If such treatment is offered, the pubertal stage at which adolescents are allowed to start varies from Tanner stage 2 to stage 4 (Delemarre-van de Waal & Cohen-Kettenis, 2006; Zucker et al., 2012). The percentages of treated adolescents are likely influenced by the organization of health care, insurance aspects, cultural differences, opinions of health professionals, and diagnostic procedures offered in different settings.

Inexperienced clinicians may mistake indications of gender dysphoria for delusions. Phenomenologically, there is a qualitative difference between the presentation of gender dysphoria and the presentation of delusions or other psychotic symptoms. The vast majority of children and adolescents with gender dysphoria are not suffering from underlying severe psychiatric illness such as psychotic disorders (Steensma, Biemond, de Boer, & Cohen-Kettenis, published online ahead of print January 7, 2011).

It is more common for adolescents with gender dysphoria to have coexisting internalizing disorders such as anxiety and depression, and/or externalizing disorders such as oppositional defiant disorder (de Vries et al., 2010). As in children, there seems to be a higher prevalence of autistic spectrum disorders in clinically referred, gender dysphoric adolescents than in the general adolescent population (de Vries et al., 2010).

Competency of Mental Health Professionals Working with Children or Adolescents with Gender Dysphoria

The following are recommended minimum credentials for mental health professionals who assess, refer, and offer therapy to children and adolescents presenting with gender dysphoria:

1. Meet the competency requirements for mental health professionals working with adults, as outlined in section VII;
2. Trained in childhood and adolescent developmental psychopathology;
3. Competent in diagnosing and treating the ordinary problems of children and adolescents.

Roles of Mental Health Professionals Working with Children and Adolescents with Gender Dysphoria

The roles of mental health professionals working with gender dysphoric children and adolescents may include the following:

1. Directly assess gender dysphoria in children and adolescents (see general guidelines for assessment, below).
2. Provide family counseling and supportive psychotherapy to assist children and adolescents with exploring their gender identity, alleviating distress related to their gender dysphoria, and ameliorating any other psychosocial difficulties.
3. Assess and treat any coexisting mental health concerns of children or adolescents (or refer to another mental health professional for treatment). Such concerns should be addressed as part of the overall treatment plan.
4. Refer adolescents for additional physical interventions (such as puberty-suppressing hormones) to alleviate gender dysphoria. The referral should include documentation of an assessment of gender dysphoria and mental health, the adolescent's eligibility for physical interventions (outlined below), the mental health professional's relevant expertise, and any other information pertinent to the youth's health and referral for specific treatments.
5. Educate and advocate on behalf of gender dysphoric children, adolescents, and their families in their community (e.g., day care centers, schools, camps, other organizations). This is particularly important in light of evidence that children and adolescents who do not conform to socially prescribed gender norms may experience harassment in school (Grossman, D'Augelli, & Salter, 2006; Grossman, D'Augelli, Howell, & Hubbard, 2006; Sausa, 2005), putting them at risk for social isolation, depression, and other negative sequelae (Nuttbrock et al., 2010).
6. Provide children, youth, and their families with information and referral for peer support, such as support groups for parents of gender-nonconforming and transgender children (Gold & MacNish, 2011; Pleak, 1999; Rosenberg, 2002).

Assessment and psychosocial interventions for children and adolescents are often provided within a multidisciplinary gender identity specialty service. If such a multidisciplinary service is not available, a mental health professional should provide consultation and liaison arrangements with a pediatric endocrinologist for the purpose of assessment, education, and involvement in any decisions about physical interventions.

Psychological Assessment of Children and Adolescents

When assessing children and adolescents who present with gender dysphoria, mental health professionals should broadly conform to the following guidelines:

1. Mental health professionals should not dismiss or express a negative attitude towards nonconforming gender identities or indications of gender dysphoria. Rather, they should acknowledge the presenting concerns of children, adolescents, and their families; offer a thorough assessment for gender dysphoria and any coexisting mental health concerns; and educate clients and their families about therapeutic options, if needed. Acceptance, and alleviation of secrecy, can bring considerable relief to gender dysphoric children/adolescents and their families.
2. Assessment of gender dysphoria and mental health should explore the nature and characteristics of a child's or adolescent's gender identity. A psychodiagnostic and psychiatric assessment—covering the areas of emotional functioning, peer and other social relationships, and intellectual functioning/school achievement—should be performed. Assessment should include an evaluation of the strengths and weaknesses of family functioning. Emotional and behavioral problems are relatively common, and unresolved issues in a child's or youth's environment may be present (de Vries, Doreleijers, Steensma, & Cohen-Kettenis, 2011; Di Ceglie & Thümmel, 2006; Wallien et al., 2007).
3. For adolescents, the assessment phase should also be used to inform youth and their families about the possibilities and limitations of different treatments. This is necessary for informed consent, but also important for assessment. The way that adolescents respond to information about the reality of sex reassignment can be diagnostically informative. Correct information may alter a youth's desire for certain treatment, if the desire was based on unrealistic expectations of its possibilities.

Psychological and Social Interventions for Children and Adolescents

When supporting and treating children and adolescents with gender dysphoria, health professionals should broadly conform to the following guidelines:

1. Mental health professionals should help families to have an accepting and nurturing response to the concerns of their gender dysphoric child or adolescent. Families play an important role in the psychological health and well-being of youth (Brill & Pepper, 2008; Lev, 2004). This also applies to peers and mentors from the community, who can be another source of social support.

2. Psychotherapy should focus on reducing a child's or adolescent's distress related to the gender dysphoria and on ameliorating any other psychosocial difficulties. For youth pursuing sex reassignment, psychotherapy may focus on supporting them before, during, and after reassignment. Formal evaluations of different psychotherapeutic approaches for this situation have not been published, but several counseling methods have been described (Cohen-Kettenis, 2006; de Vries, Cohen-Kettenis, & Delemarre-van de Waal, 2006; Di Ceglie & Thümmel, 2006; Hill, Menvielle, Sica, & Johnson, 2010; Malpas, in press; Menvielle & Tuerk, 2002; Rosenberg, 2002; Vanderburgh, 2009; Zucker, 2006).

Treatment aimed at trying to change a person's gender identity and expression to become more congruent with sex assigned at birth has been attempted in the past without success (Gelder & Marks, 1969; Greenson, 1964), particularly in the long term (Cohen-Kettenis & Kuiper, 1984; Pauly, 1965). Such treatment is no longer considered ethical.

3. Families should be supported in managing uncertainty and anxiety about their child's or adolescent's psychosexual outcomes and in helping youth to develop a positive self-concept.
4. Mental health professionals should not impose a binary view of gender. They should give ample room for clients to explore different options for gender expression. Hormonal or surgical interventions are appropriate for some adolescents, but not for others.
5. Clients and their families should be supported in making difficult decisions regarding the extent to which clients are allowed to express a gender role that is consistent with their gender identity, as well as the timing of changes in gender role and possible social transition. For example, a client might attend school while undergoing social transition only partly (e.g., by wearing clothing and having a hairstyle that reflects gender identity) or completely (e.g., by also using a name and pronouns congruent with gender identity). Difficult issues include whether and when to inform other people of the client's situation, and how others in their lives might respond.
6. Health professionals should support clients and their families as educators and advocates in their interactions with community members and authorities such as teachers, school boards, and courts.
7. Mental health professionals should strive to maintain a therapeutic relationship with gender-nonconforming children/adolescents and their families throughout any subsequent social changes or physical interventions. This ensures that decisions about gender expression and the treatment of gender dysphoria are thoughtfully and recurrently considered. The same reasoning applies if a child or adolescent has already socially changed gender role prior to being seen by a mental health professional.

Social Transition in Early Childhood

Some children state that they want to make a social transition to a different gender role long before puberty. For some children, this may reflect an expression of their gender identity. For others, this could be motivated by other forces. Families vary in the extent to which they allow their young children to make a social transition to another gender role. Social transitions in early childhood do occur within some families with early success. This is a controversial issue, and divergent views are held by health professionals. The current evidence base is insufficient to predict the long-term outcomes of completing a gender role transition during early childhood. Outcomes research with children who completed early social transitions would greatly inform future clinical recommendations.

Mental health professionals can help families to make decisions regarding the timing and process of any gender role changes for their young children. They should provide information and help parents to weigh the potential benefits and challenges of particular choices. Relevant in this respect are the previously described relatively low persistence rates of childhood gender dysphoria (Drummond et al., 2008; Wallien & Cohen-Kettenis, 2008). A change back to the original gender role can be highly distressing and even result in postponement of this second social transition on the child's part (Steensma & Cohen-Kettenis, 2011). For reasons such as these, parents may want to present this role change as an exploration of living in another gender role rather than an irreversible situation. Mental health professionals can assist parents in identifying potential in-between solutions or compromises (e.g., only when on vacation). It is also important that parents explicitly let the child know that there is a way back.

Regardless of a family's decisions regarding transition (timing, extent), professionals should counsel and support them as they work through the options and implications. If parents do not allow their young child to make a gender-role transition, they may need counseling to assist them with meeting their child's needs in a sensitive and nurturing way, ensuring that the child has ample possibilities to explore gender feelings and behavior in a safe environment. If parents do allow their young child to make a gender role transition, they may need counseling to facilitate a positive experience for their child. For example, they may need support in using correct pronouns, maintaining a safe and supportive environment for their transitioning child (e.g., in school, peer group settings), and communicating with other people in their child's life. In either case, as a child nears puberty, further assessment may be needed as options for physical interventions become relevant.

Physical Interventions for Adolescents

Before any physical interventions are considered for adolescents, extensive exploration of psychological, family, and social issues should be undertaken, as outlined above. The duration of this exploration may vary considerably depending on the complexity of the situation.

Physical interventions should be addressed in the context of adolescent development. Some identity beliefs in adolescents may become firmly held and strongly expressed, giving a false impression of irreversibility. An adolescent's shift towards gender conformity can occur primarily to please the parents and may not persist or reflect a permanent change in gender dysphoria (Hembree et al., 2009; Steensma et al., published online ahead of print January 7, 2011).

Physical interventions for adolescents fall into three categories or stages (Hembree et al., 2009):

1. *Fully reversible interventions.* These involve the use of GnRH analogues to suppress estrogen or testosterone production and consequently delay the physical changes of puberty. Alternative treatment options include progestins (most commonly medroxyprogesterone) or other medications (such as spironolactone) that decrease the effects of androgens secreted by the testicles of adolescents who are not receiving GnRH analogues. Continuous oral contraceptives (or depot medroxyprogesterone) may be used to suppress menses.
2. *Partially reversible interventions.* These include hormone therapy to masculinize or feminize the body. Some hormone-induced changes may need reconstructive surgery to reverse the effect (e.g., gynaecomastia caused by estrogens), while other changes are not reversible (e.g., deepening of the voice caused by testosterone).
3. *Irreversible interventions.* These are surgical procedures.

A staged process is recommended to keep options open through the first two stages. Moving from one stage to another should not occur until there has been adequate time for adolescents and their parents to assimilate fully the effects of earlier interventions.

Fully Reversible Interventions

Adolescents may be eligible for puberty-suppressing hormones as soon as pubertal changes have begun. In order for adolescents and their parents to make an informed decision about pubertal delay, it is recommended that adolescents experience the onset of puberty to at least Tanner Stage 2. Some children may arrive at this stage at very young ages (e.g., 9 years of age). Studies

evaluating this approach have only included children who were at least 12 years of age (Cohen-Kettenis, Schagen, Steensma, de Vries, & Delemarre-van de Waal, 2011; de Vries, Steensma et al., 2010; Delemarre-van de Waal, van Weissenbruch, & Cohen Kettenis, 2004; Delemarre-van de Waal & Cohen-Kettenis, 2006).

Two goals justify intervention with puberty-suppressing hormones: (i) their use gives adolescents more time to explore their gender nonconformity and other developmental issues; and (ii) their use may facilitate transition by preventing the development of sex characteristics that are difficult or impossible to reverse if adolescents continue on to pursue sex reassignment.

Puberty suppression may continue for a few years, at which time a decision is made to either discontinue all hormone therapy or transition to a feminizing/masculinizing hormone regimen. Pubertal suppression does not inevitably lead to social transition or to sex reassignment.

Criteria for Puberty-Suppressing Hormones

In order for adolescents to receive puberty-suppressing hormones, the following minimum criteria must be met:

1. The adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed);
2. Gender dysphoria emerged or worsened with the onset of puberty;
3. Any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment;
4. The adolescent has given informed consent and, particularly when the adolescent has not reached the age of medical consent, the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process.

Regimens, Monitoring, and Risks for Puberty Suppression

For puberty suppression, adolescents with male genitalia should be treated with GnRH analogues, which stop luteinizing hormone secretion and therefore testosterone secretion. Alternatively, they may be treated with progestins (such as medroxyprogesterone) or with other medications that block testosterone secretion and/or neutralize testosterone action. Adolescents with female genitalia should be treated with GnRH analogues, which stop the production of estrogens and

progesterone. Alternatively, they may be treated with progestins (such as medroxyprogesterone). Continuous oral contraceptives (or depot medroxyprogesterone) may be used to suppress menses. In both groups of adolescents, use of GnRH analogues is the preferred treatment (Hembree et al., 2009), but their high cost is prohibitive for some patients.

During pubertal suppression, an adolescent's physical development should be carefully monitored—preferably by a pediatric endocrinologist—so that any necessary interventions can occur (e.g., to establish an adequate gender appropriate height, to improve iatrogenic low bone mineral density) (Hembree et al., 2009).

Early use of puberty-suppressing hormones may avert negative social and emotional consequences of gender dysphoria more effectively than their later use would. Intervention in early adolescence should be managed with pediatric endocrinological advice, when available. Adolescents with male genitalia who start GnRH analogues early in puberty should be informed that this could result in insufficient penile tissue for penile inversion vaginoplasty techniques (alternative techniques, such as the use of a skin graft or colon tissue, are available).

Neither puberty suppression nor allowing puberty to occur is a neutral act. On the one hand, functioning in later life can be compromised by the development of irreversible secondary sex characteristics during puberty and by years spent experiencing intense gender dysphoria. On the other hand, there are concerns about negative physical side effects of GnRH analogue use (e.g., on bone development and height). Although the very first results of this approach (as assessed for adolescents followed over 10 years) are promising (Cohen-Kettenis et al., 2011; Delemarre-van de Waal & Cohen-Kettenis, 2006), the long-term effects can only be determined when the earliest-treated patients reach the appropriate age.

Partially Reversible Interventions

Adolescents may be eligible to begin feminizing/masculinizing hormone therapy, preferably with parental consent. In many countries, 16-year-olds are legal adults for medical decision-making and do not require parental consent. Ideally, treatment decisions should be made among the adolescent, the family, and the treatment team.

Regimens for hormone therapy in gender dysphoric adolescents differ substantially from those used in adults (Hembree et al., 2009). The hormone regimens for youth are adapted to account for the somatic, emotional, and mental development that occurs throughout adolescence (Hembree et al., 2009).

Irreversible Interventions

Genital surgery should not be carried out until (i) patients reach the legal age of majority to give consent for medical procedures in a given country, and (ii) patients have lived continuously for at least 12 months in the gender role that is congruent with their gender identity. The age threshold should be seen as a minimum criterion and not an indication in and of itself for active intervention.

Chest surgery in FtM patients could be carried out earlier, preferably after ample time of living in the desired gender role and after one year of testosterone treatment. The intent of this suggested sequence is to give adolescents sufficient opportunity to experience and socially adjust in a more masculine gender role, before undergoing irreversible surgery. However, different approaches may be more suitable, depending on an adolescent's specific clinical situation and goals for gender identity expression.

Risks of Withholding Medical Treatment for Adolescents

Refusing timely medical interventions for adolescents might prolong gender dysphoria and contribute to an appearance that could provoke abuse and stigmatization. As the level of gender-related abuse is strongly associated with the degree of psychiatric distress during adolescence (Nuttbrock et al., 2010), withholding puberty suppression and subsequent feminizing or masculinizing hormone therapy is not a neutral option for adolescents.

VII

Mental Health

Transsexual, transgender, and gender-nonconforming people might seek the assistance of a mental health professional for any number of reasons. Regardless of a person's reason for seeking care, mental health professionals should have familiarity with gender nonconformity, act with appropriate cultural competence, and exhibit sensitivity in providing care.

This section of the SOC focuses on the role of mental health professionals in the care of adults seeking help for gender dysphoria and related concerns. Professionals working with gender dysphoric children, adolescents, and their families should consult section VI.

Competency of Mental Health Professionals Working with Adults Who Present with Gender Dysphoria

The training of mental health professionals competent to work with gender dysphoric adults rests upon basic general clinical competence in the assessment, diagnosis, and treatment of mental health concerns. Clinical training may occur within any discipline that prepares mental health professionals for clinical practice, such as psychology, psychiatry, social work, mental health counseling, marriage and family therapy, nursing, or family medicine with specific training in behavioral health and counseling. The following are recommended minimum credentials for mental health professionals who work with adults presenting with gender dysphoria:

1. A master's degree or its equivalent in a clinical behavioral science field. This degree, or a more advanced one, should be granted by an institution accredited by the appropriate national or regional accrediting board. The mental health professional should have documented credentials from a relevant licensing board or equivalent for that country.
2. Competence in using the *Diagnostic Statistical Manual of Mental Disorders* and/or the *International Classification of Diseases* for diagnostic purposes.
3. Ability to recognize and diagnose coexisting mental health concerns and to distinguish these from gender dysphoria.
4. Documented supervised training and competence in psychotherapy or counseling.
5. Knowledgeable about gender-nonconforming identities and expressions, and the assessment and treatment of gender dysphoria.
6. Continuing education in the assessment and treatment of gender dysphoria. This may include attending relevant professional meetings, workshops, or seminars; obtaining supervision from a mental health professional with relevant experience; or participating in research related to gender nonconformity and gender dysphoria.

In addition to the minimum credentials above, it is recommended that mental health professionals develop and maintain cultural competence to facilitate their work with transsexual, transgender, and gender-nonconforming clients. This may involve, for example, becoming knowledgeable about current community, advocacy, and public policy issues relevant to these clients and their families. Additionally, knowledge about sexuality, sexual health concerns, and the assessment and treatment of sexual disorders is preferred.

Mental health professionals who are new to the field (irrespective of their level of training and other experience) should work under the supervision of a mental health professional with established competence in the assessment and treatment of gender dysphoria.

Tasks of Mental Health Professionals Working with Adults Who Present with Gender Dysphoria

Mental health professionals may serve transsexual, transgender, and gender-nonconforming individuals and their families in many ways, depending on a client's needs. For example, mental health professionals may serve as a psychotherapist, counselor, or family therapist, or as a diagnostician/assessor, advocate, or educator.

Mental health professionals should determine a client's reasons for seeking professional assistance. For example, a client may be presenting for any combination of the following health care services: psychotherapeutic assistance to explore gender identity and expression or to facilitate a coming-out process; assessment and referral for feminizing/masculinizing medical interventions; psychological support for family members (partners, children, extended family); psychotherapy unrelated to gender concerns; or other professional services.

Below are general guidelines for common tasks that mental health professionals may fulfill in working with adults who present with gender dysphoria.

Tasks Related to Assessment and Referral

1. Assess Gender Dysphoria

Mental health professionals assess clients' gender dysphoria in the context of an evaluation of their psychosocial adjustment (Bockting et al., 2006; Lev, 2004, 2009). The evaluation includes, at a minimum, assessment of gender identity and gender dysphoria, history and development of gender dysphoric feelings, the impact of stigma attached to gender nonconformity on mental health, and the availability of support from family, friends, and peers (for example, in-person or online contact with other transsexual, transgender, or gender-nonconforming individuals or groups). The evaluation may result in no diagnosis, in a formal diagnosis related to gender dysphoria, and/or in other diagnoses that describe aspects of the client's health and psychosocial adjustment. The role

of mental health professionals includes making reasonably sure that the gender dysphoria is not secondary to, or better accounted for, by other diagnoses.

Mental health professionals with the competencies described above (hereafter called “a qualified mental health professional”) are best prepared to conduct this assessment of gender dysphoria. However, this task may instead be conducted by another type of health professional who has appropriate training in behavioral health and is competent in the assessment of gender dysphoria, particularly when functioning as part of a multidisciplinary specialty team that provides access to feminizing/masculinizing hormone therapy. This professional may be the prescribing hormone therapy provider or a member of that provider’s health care team.

2. Provide Information Regarding Options for Gender Identity and Expression and Possible Medical Interventions

An important task of mental health professionals is to educate clients regarding the diversity of gender identities and expressions and the various options available to alleviate gender dysphoria. Mental health professionals then may facilitate a process (or refer elsewhere) in which clients explore these various options, with the goals of finding a comfortable gender role and expression and becoming prepared to make a fully informed decision about available medical interventions, if needed. This process may include referral for individual, family, and group therapy and/or to community resources and avenues for peer support. The professional and the client discuss the implications, both short- and long-term, of any changes in gender role and use of medical interventions. These implications can be psychological, social, physical, sexual, occupational, financial, and legal (Bockting et al., 2006; Lev, 2004).

This task is also best conducted by a qualified mental health professional, but may be conducted by another health professional with appropriate training in behavioral health and with sufficient knowledge about gender-nonconforming identities and expressions and about possible medical interventions for gender dysphoria, particularly when functioning as part of a multidisciplinary specialty team that provides access to feminizing/masculinizing hormone therapy.

3. Assess, Diagnose, and Discuss Treatment Options for Coexisting Mental Health Concerns

Clients presenting with gender dysphoria may struggle with a range of mental health concerns (Gómez-Gil, Trilla, Salamero, Godás, & Valdés, 2009; Murad et al., 2010) whether related or unrelated to what is often a long history of gender dysphoria and/or chronic minority stress. Possible concerns include anxiety, depression, self-harm, a history of abuse and neglect, compulsivity, substance abuse, sexual concerns, personality disorders, eating disorders, psychotic disorders, and autistic spectrum disorders (Bockting et al., 2006; Nuttbrock et al., 2010; Robinow, 2009). Mental health professionals should screen for these and other mental health concerns and incorporate

the identified concerns into the overall treatment plan. These concerns can be significant sources of distress and, if left untreated, can complicate the process of gender identity exploration and resolution of gender dysphoria (Bockting et al., 2006; Fraser, 2009a; Lev, 2009). Addressing these concerns can greatly facilitate the resolution of gender dysphoria, possible changes in gender role, the making of informed decisions about medical interventions, and improvements in quality of life.

Some clients may benefit from psychotropic medications to alleviate symptoms or treat coexisting mental health concerns. Mental health professionals are expected to recognize this and either provide pharmacotherapy or refer to a colleague who is qualified to do so. The presence of coexisting mental health concerns does not necessarily preclude possible changes in gender role or access to feminizing/masculinizing hormones or surgery; rather, these concerns need to be optimally managed prior to, or concurrent with, treatment of gender dysphoria. In addition, clients should be assessed for their ability to provide educated and informed consent for medical treatments.

Qualified mental health professionals are specifically trained to assess, diagnose, and treat (or refer to treatment for) these coexisting mental health concerns. Other health professionals with appropriate training in behavioral health, particularly when functioning as part of a multidisciplinary specialty team providing access to feminizing/masculinizing hormone therapy, may also screen for mental health concerns and, if indicated, provide referral for comprehensive assessment and treatment by a qualified mental health professional.

4. If Applicable, Assess Eligibility, Prepare, and Refer for Hormone Therapy

The SOC provide criteria to guide decisions regarding feminizing/masculinizing hormone therapy (outlined in section VIII and Appendix C). Mental health professionals can help clients who are considering hormone therapy to be both psychologically prepared (e.g., client has made a fully informed decision with clear and realistic expectations; is ready to receive the service in line with the overall treatment plan; has included family and community as appropriate) and practically prepared (e.g., has been evaluated by a physician to rule out or address medical contraindications to hormone use; has considered the psychosocial implications). If clients are of childbearing age, reproductive options (section IX) should be explored before initiating hormone therapy.

It is important for mental health professionals to recognize that decisions about hormones are first and foremost a client's decisions—as are all decisions regarding healthcare. However, mental health professionals have a responsibility to encourage, guide, and assist clients with making fully informed decisions and becoming adequately prepared. To best support their clients' decisions, mental health professionals need to have functioning working relationships with their clients and sufficient information about them. Clients should receive prompt and attentive evaluation, with the goal of alleviating their gender dysphoria and providing them with appropriate medical services.

Referral for feminizing/masculinizing hormone therapy

People may approach a specialized provider in any discipline to pursue feminizing/masculinizing hormone therapy. However, transgender health care is an interdisciplinary field, and coordination of care and referral among a client's overall care team is recommended.

Hormone therapy can be initiated with a referral from a qualified mental health professional. Alternatively, a health professional who is appropriately trained in behavioral health and competent in the assessment of gender dysphoria may assess eligibility, prepare, and refer the patient for hormone therapy, particularly in the absence of significant coexisting mental health concerns and when working in the context of a multidisciplinary specialty team. The referring health professional should provide documentation—in the chart and/or referral letter—of the patient's personal and treatment history, progress, and eligibility. Health professionals who recommend hormone therapy share the ethical and legal responsibility for that decision with the physician who provides the service.

The recommended content of the referral letter for feminizing/masculinizing hormone therapy is as follows:

1. The client's general identifying characteristics;
2. Results of the client's psychosocial assessment, including any diagnoses;
3. The duration of the referring health professional's relationship with the client, including the type of evaluation and therapy or counseling to date;
4. An explanation that the criteria for hormone therapy have been met, and a brief description of the clinical rationale for supporting the client's request for hormone therapy;
5. A statement that informed consent has been obtained from the patient;
6. A statement that the referring health professional is available for coordination of care and welcomes a phone call to establish this.

For providers working within a multidisciplinary specialty team, a letter may not be necessary; rather, the assessment and recommendation can be documented in the patient's chart.

5. If Applicable, Assess Eligibility, Prepare, and Refer for Surgery

The SOC also provide criteria to guide decisions regarding breast/chest surgery and genital surgery (outlined in section XI and Appendix C). Mental health professionals can help clients who are

considering surgery to be both psychologically prepared (e.g., has made a fully informed decision with clear and realistic expectations; is ready to receive the service in line with the overall treatment plan; has included family and community as appropriate) and practically prepared (e.g., has made an informed choice about a surgeon to perform the procedure; has arranged aftercare). If clients are of childbearing age, reproductive options (section IX) should be explored before undergoing genital surgery.

The SOC do not state criteria for other surgical procedures, such as feminizing or masculinizing facial surgery; however, mental health professionals can play an important role in helping their clients to make fully informed decisions about the timing and implications of such procedures in the context of the overall coming-out or transition process.

It is important for mental health professionals to recognize that decisions about surgery are first and foremost a client's decisions—as are all decisions regarding healthcare. However, mental health professionals have a responsibility to encourage, guide, and assist clients with making fully informed decisions and becoming adequately prepared. To best support their clients' decisions, mental health professionals need to have functioning working relationships with their clients and sufficient information about them. Clients should receive prompt and attentive evaluation, with the goal of alleviating their gender dysphoria and providing them with appropriate medical services.

Referral for surgery

Surgical treatments for gender dysphoria can be initiated by a referral (one or two, depending on the type of surgery) from a qualified mental health professional. The mental health professional provides documentation—in the chart and/or referral letter—of the patient's personal and treatment history, progress, and eligibility. Mental health professionals who recommend surgery share the ethical and legal responsibility for that decision with the surgeon.

- One referral from a qualified mental health professional is needed for breast/chest surgery (e.g., mastectomy, chest reconstruction, or augmentation mammoplasty).
- Two referrals—from qualified mental health professionals who have independently assessed the patient—are needed for genital surgery (i.e., hysterectomy/salpingo-oophorectomy, orchiectomy, genital reconstructive surgeries). If the first referral is from the patient's psychotherapist, the second referral should be from a person who has only had an evaluative role with the patient. Two separate letters, or one letter signed by both (e.g., if practicing within the same clinic) may be sent. Each referral letter, however, is expected to cover the same topics in the areas outlined below.

The recommended content of the referral letters for surgery is as follows:

1. The client's general identifying characteristics;
2. Results of the client's psychosocial assessment, including any diagnoses;
3. The duration of the mental health professional's relationship with the client, including the type of evaluation and therapy or counseling to date;
4. An explanation that the criteria for surgery have been met, and a brief description of the clinical rationale for supporting the patient's request for surgery;
5. A statement about the fact that informed consent has been obtained from the patient;
6. A statement that the mental health professional is available for coordination of care and welcomes a phone call to establish this.

For providers working within a multidisciplinary specialty team, a letter may not be necessary, rather, the assessment and recommendation can be documented in the patient's chart.

Relationship of Mental Health Professionals with Hormone-Prescribing Physicians, Surgeons, and Other Health Professionals

It is ideal for mental health professionals to perform their work and periodically discuss progress and obtain peer consultation from other professionals (both in mental health care and other health disciplines) who are competent in the assessment and treatment of gender dysphoria. The relationship among professionals involved in a client's health care should remain collaborative, with coordination and clinical dialogue taking place as needed. Open and consistent communication may be necessary for consultation, referral, and management of postoperative concerns.

Tasks Related to Psychotherapy

1. Psychotherapy Is Not an Absolute Requirement for Hormone Therapy and Surgery

A mental health screening and/or assessment as outlined above is needed for referral to hormonal and surgical treatments for gender dysphoria. In contrast, psychotherapy—although highly recommended—is not a requirement.

The SOC do not recommend a minimum number of psychotherapy sessions prior to hormone therapy or surgery. The reasons for this are multifaceted (Lev, 2009). First, a minimum number of sessions tends to be construed as a hurdle, which discourages the genuine opportunity for personal growth. Second, mental health professionals can offer important support to clients throughout all phases of exploration of gender identity, gender expression, and possible transition—not just prior to any possible medical interventions. Third, clients and their psychotherapists differ in their abilities to attain similar goals in a specified time period.

2. Goals of Psychotherapy for Adults with Gender Concerns

The general goal of psychotherapy is to find ways to maximize a person's overall psychological well-being, quality of life, and self-fulfillment. Psychotherapy is not intended to alter a person's gender identity; rather, psychotherapy can help an individual to explore gender concerns and find ways to alleviate gender dysphoria, if present (Bockting et al., 2006; Bockting & Coleman, 2007; Fraser, 2009a; Lev, 2004). Typically, the overarching treatment goal is to help transsexual, transgender, and gender-nonconforming individuals achieve long-term comfort in their gender identity expression, with realistic chances for success in their relationships, education, and work. For additional details, see Fraser (Fraser, 2009c).

Therapy may consist of individual, couple, family, or group psychotherapy, the latter being particularly important to foster peer support.

3. Psychotherapy for Transsexual, Transgender, and Gender-Nonconforming Clients, Including Counseling and Support for Changes in Gender Role

Finding a comfortable gender role is, first and foremost, a psychosocial process. Psychotherapy can be invaluable in assisting transsexual, transgender, and gender-nonconforming individuals with all of the following: (i) clarifying and exploring gender identity and role, (ii) addressing the impact of stigma and minority stress on one's mental health and human development, and (iii) facilitating a coming-out process (Bockting & Coleman, 2007; Devor, 2004; Lev, 2004), which for some individuals may include changes in gender role expression and the use of feminizing/masculinizing medical interventions.

Mental health professionals can provide support and promote interpersonal skills and resilience in individuals and their families as they navigate a world that often is ill-prepared to accommodate and respect transgender, transsexual, and gender-nonconforming people. Psychotherapy can also aid in alleviating any coexisting mental health concerns (e.g., anxiety, depression) identified during screening and assessment.

For transsexual, transgender, and gender-nonconforming individuals who plan to change gender roles permanently and make a social gender role transition, mental health professionals can facilitate the development of an individualized plan with specific goals and timelines. While the experience of changing one's gender role differs from person to person, the social aspects of the experience are usually challenging—often more so than the physical aspects. Because changing gender role can have profound personal and social consequences, the decision to do so should include an awareness of what the familial, interpersonal, educational, vocational, economic, and legal challenges are likely to be, so that people can function successfully in their gender role.

Many transsexual, transgender, and gender-nonconforming people will present for care without ever having been related to, or accepted in, the gender role that is most congruent with their gender identity. Mental health professionals can help these clients to explore and anticipate the implications of changes in gender role, and to pace the process of implementing these changes. Psychotherapy can provide a space for clients to begin to express themselves in ways that are congruent with their gender identity and, for some clients, overcome fears about changes in gender expression. Calculated risks can be taken outside of therapy to gain experience and build confidence in the new role. Assistance with coming out to family and community (friends, school, workplace) can be provided.

Other transsexual, transgender, and gender-nonconforming individuals will present for care already having acquired experience (minimal, moderate, or extensive) living in a gender role that differs from that associated with their birth-assigned sex. Mental health professionals can help these clients to identify and work through potential challenges and foster optimal adjustment as they continue to express changes in their gender role.

4. Family Therapy or Support for Family Members

Decisions about changes in gender role and medical interventions for gender dysphoria have implications for, not only clients, but also their families (Emerson & Rosenfeld, 1996; Fraser, 2009a; Lev, 2004). Mental health professionals can assist clients with making thoughtful decisions about communicating with family members and others about their gender identity and treatment decisions. Family therapy may include work with spouses or partners, as well as with children and other members of a client's extended family.

Clients may also request assistance with their relationships and sexual health. For example, they may want to explore their sexuality and intimacy-related concerns.

Family therapy might be offered as part of the client's individual therapy and, if clinically appropriate, by the same provider. Alternatively, referrals can be made to other therapists with relevant expertise

for working with family members or to sources of peer support (e.g., in-person or offline support networks of partners or families).

5. Follow-Up Care Throughout Life

Mental health professionals may work with clients and their families at many stages of their lives. Psychotherapy may be helpful at different times and for various issues throughout the life cycle.

6. E-Therapy, Online Counseling, or Distance Counseling

Online or e-therapy has been shown to be particularly useful for people who have difficulty accessing competent in-person psychotherapeutic treatment and who may experience isolation and stigma (Derrig-Palumbo & Zeine, 2005; Fenichel et al., 2004; Fraser, 2009b). By extrapolation, e-therapy may be a useful modality for psychotherapy with transsexual, transgender, and gender-nonconforming people. E-therapy offers opportunities for potentially enhanced, expanded, creative, and tailored delivery of services; however, as a developing modality it may also carry unexpected risk. Telemedicine guidelines are clear in some disciplines in some parts of the United States (Fraser, 2009b; Maheu, Pulier, Wilhelm, McMenamin, & Brown-Connolly, 2005) but not all; the international situation is even less well-defined (Maheu et al., 2005). Until sufficient evidence-based data on this use of e-therapy is available, caution in its use is advised.

Mental health professionals engaging in e-therapy are advised to stay current with their particular licensing board, professional association, and country's regulations, as well as the most recent literature pertaining to this rapidly evolving medium. A more thorough description of the potential uses, processes, and ethical concerns related to e-therapy has been published (Fraser, 2009b).

Other Tasks of Mental Health Professionals

1. Educate and Advocate on Behalf of Clients Within Their Community (Schools, Workplaces, Other Organizations) and Assist Clients with Making Changes in Identity Documents

Transsexual, transgender, and gender-nonconforming people may face challenges in their professional, educational, and other types of settings as they actualize their gender identity and expression (Lev, 2004, 2009). Mental health professionals can play an important role by educating people in these settings regarding gender nonconformity and by advocating on behalf of their clients (Currah, Juang, & Minter, 2006; Currah & Minter, 2000). This role may involve consultation

with school counselors, teachers, and administrators, human resources staff, personnel managers and employers, and representatives from other organizations and institutions. In addition, health providers may be called upon to support changes in a client's name and/or gender marker on identity documents such as passports, driver's licenses, birth certificates, and diplomas.

2. Provide Information and Referral for Peer Support

For some transsexual, transgender, and gender-nonconforming people, an experience in peer support groups may be more instructive regarding options for gender expression than anything individual psychotherapy could offer (Rachlin, 2002). Both experiences are potentially valuable, and all people exploring gender issues should be encouraged to participate in community activities, if possible. Resources for peer support and information should be made available.

Culture and Its Ramifications for Assessment and Psychotherapy

Health professionals work in enormously different environments across the world. Forms of distress that cause people to seek professional assistance in any culture are understood and classified by people in terms that are products of their own cultures (Frank & Frank, 1993). Cultural settings also largely determine how such conditions are understood by mental health professionals. Cultural differences related to gender identity and expression can affect patients, mental health professionals, and accepted psychotherapy practice. WPATH recognizes that the SOC have grown out of a Western tradition and may need to be adapted depending on the cultural context.

Ethical Guidelines Related to Mental Health Care

Mental health professionals need to be certified or licensed to practice in a given country according to that country's professional regulations (Fraser, 2009b; Pope & Vasquez, 2011). Professionals must adhere to the ethical codes of their professional licensing or certifying organizations in all of their work with transsexual, transgender, and gender-nonconforming clients.

Treatment aimed at trying to change a person's gender identity and lived gender expression to become more congruent with sex assigned at birth has been attempted in the past (Gelder & Marks, 1969; Greenson, 1964), yet without success, particularly in the long-term (Cohen-Kettenis & Kuiper, 1984; Pauly, 1965). Such treatment is no longer considered ethical.

If mental health professionals are uncomfortable with, or inexperienced in, working with transsexual, transgender, and gender-nonconforming individuals and their families, they should refer clients to a competent provider or, at minimum, consult with an expert peer. If no local practitioners are available, consultation may be done via telehealth methods, assuming local requirements for distance consultation are met.

Issues of Access to Care

Qualified mental health professionals are not universally available; thus, access to quality care might be limited. WPATH aims to improve access and provides regular continuing education opportunities to train professionals from various disciplines to provide quality, transgender-specific health care. Providing mental health care from a distance through the use of technology may be one way to improve access (Fraser, 2009b).

In many places around the world, access to health care for transsexual, transgender, and gender-nonconforming people is also limited by a lack of health insurance or other means to pay for needed care. WPATH urges health insurance companies and other third-party payers to cover the medically necessary treatments to alleviate gender dysphoria (American Medical Association, 2008; Anton, 2009; The World Professional Association for Transgender Health, 2008).

When faced with a client who is unable to access services, referral to available peer support resources (offline and online) is recommended. Finally, harm-reduction approaches might be indicated to assist clients with making healthy decisions to improve their lives.

VIII

Hormone Therapy

Medical Necessity of Hormone Therapy

Feminizing/masculinizing hormone therapy—the administration of exogenous endocrine agents to induce feminizing or masculinizing changes—is a medically necessary intervention for many transsexual, transgender, and gender-nonconforming individuals with gender dysphoria

(Newfield, Hart, Dibble, & Kohler, 2006; Pfäfflin & Junge, 1998). Some people seek maximum feminization/masculinization, while others experience relief with an androgynous presentation resulting from hormonal minimization of existing secondary sex characteristics (Factor & Rothblum, 2008). Evidence for the psychosocial outcomes of hormone therapy is summarized in Appendix D.

Hormone therapy must be individualized based on a patient's goals, the risk/benefit ratio of medications, the presence of other medical conditions, and consideration of social and economic issues. Hormone therapy can provide significant comfort to patients who do not wish to make a social gender role transition or undergo surgery, or who are unable to do so (Meyer III, 2009). Hormone therapy is a recommended criterion for some, but not all, surgical treatments for gender dysphoria (see section XI and Appendix C).

Criteria for Hormone Therapy

Initiation of hormone therapy may be undertaken after a psychosocial assessment has been conducted and informed consent has been obtained by a qualified health professional, as outlined in section VII of the SOC. A referral is required from the mental health professional who performed the assessment, unless the assessment was done by a hormone provider who is also qualified in this area.

The criteria for hormone therapy are as follows:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country (if younger, follow the SOC outlined in section VI);
4. If significant medical or mental health concerns are present, they must be reasonably well-controlled.

As noted in section VII of the SOC, the presence of coexisting mental health concerns does not necessarily preclude access to feminizing/masculinizing hormones; rather, these concerns need to be managed prior to, or concurrent with, treatment of gender dysphoria.

In selected circumstances, it can be acceptable practice to provide hormones to patients who have not fulfilled these criteria. Examples include facilitating the provision of monitored therapy using hormones of known quality as an alternative to illicit or unsupervised hormone use or to patients

who have already established themselves in their affirmed gender and who have a history of prior hormone use. It is unethical to deny availability or eligibility for hormone therapy solely on the basis of blood seropositivity for blood-borne infections such as HIV or hepatitis B or C.

In rare cases, hormone therapy may be contraindicated due to serious individual health conditions. Health professionals should assist these patients with accessing nonhormonal interventions for gender dysphoria. A qualified mental health professional familiar with the patient is an excellent resource in these circumstances.

Informed Consent

Feminizing/masculinizing hormone therapy may lead to irreversible physical changes. Thus, hormone therapy should be provided only to those who are legally able to provide informed consent. This includes people who have been declared by a court to be emancipated minors, incarcerated people, and cognitively impaired people who are considered competent to participate in their medical decisions (Bockting et al., 2006). Providers should document in the medical record that comprehensive information has been provided and understood about all relevant aspects of the hormone therapy, including both possible benefits and risks and the impact on reproductive capacity.

Relationship Between the *Standards of Care* and Informed Consent Model Protocols

A number of community health centers in the United States have developed protocols for providing hormone therapy based on an approach that has become known as the Informed Consent Model (Callen Lorde Community Health Center, 2000, 2011; Fenway Community Health Transgender Health Program, 2007; Tom Waddell Health Center, 2006). These protocols are consistent with the guidelines presented in the WPATH *Standards of Care, Version 7*. The SOC are flexible clinical guidelines; they allow for tailoring of interventions to the needs of the individual receiving services and for tailoring of protocols to the approach and setting in which these services are provided (Ehrbar & Gorton, 2010).

Obtaining informed consent for hormone therapy is an important task of providers to ensure that patients understand the psychological and physical benefits and risks of hormone therapy, as well as its psychosocial implications. Providers prescribing the hormones or health professionals recommending the hormones should have the knowledge and experience to assess gender

dysphoria. They should inform individuals of the particular benefits, limitations, and risks of hormones, given the patient's age, previous experience with hormones, and concurrent physical or mental health concerns.

Screening for and addressing acute or current mental health concerns is an important part of the informed consent process. This may be done by a mental health professional or by an appropriately trained prescribing provider (see section VII of the SOC). The same provider or another appropriately trained member of the health care team (e.g., a nurse) can address the psychosocial implications of taking hormones when necessary (e.g., the impact of masculinization/feminization on how one is perceived and its potential impact on relationships with family, friends, and coworkers). If indicated, these providers will make referrals for psychotherapy and for the assessment and treatment of coexisting mental health concerns such as anxiety or depression.

The difference between the Informed Consent Model and *SOC, Version 7*, is that the SOC puts greater emphasis on the important role that mental health professionals can play in alleviating gender dysphoria and facilitating changes in gender role and psychosocial adjustment. This may include a comprehensive mental health assessment and psychotherapy, when indicated. In the Informed Consent Model, the focus is on obtaining informed consent as the threshold for the initiation of hormone therapy in a multidisciplinary, harm-reduction environment. Less emphasis is placed on the provision of mental health care until the patient requests it, unless significant mental health concerns are identified that would need to be addressed before hormone prescription.

Physical Effects of Hormone Therapy

Feminizing/masculinizing hormone therapy will induce physical changes that are more congruent with a patient's gender identity.

- In FtM patients, the following physical changes are expected to occur: deepened voice, clitoral enlargement (variable), growth in facial and body hair, cessation of menses, atrophy of breast tissue, and decreased percentage of body fat compared to muscle mass.
- In MtF patients, the following physical changes are expected to occur: breast growth (variable), decreased erectile function, decreased testicular size, and increased percentage of body fat compared to muscle mass.

Most physical changes, whether feminizing or masculinizing, occur over the course of two years. The amount of physical change and the exact timeline of effects can be highly variable. Tables 1a and 1b outline the approximate time course of these physical changes.

TABLE 1A: EFFECTS AND EXPECTED TIME COURSE OF MASCULINIZING HORMONES ^A

Effect	Expected onset ^B	Expected maximum effect ^B
Skin oiliness/acne	1–6 months	1–2 years
Facial/body hair growth	3–6 months	3–5 years
Scalp hair loss	>12 months ^C	Variable
Increased muscle mass/strength	6–12 months	2–5 years ^D
Body fat redistribution	3–6 months	2–5 years
Cessation of menses	2–6 months	n/a
Clitoral enlargement	3–6 months	1–2 years
Vaginal atrophy	3–6 months	1–2 years
Deepened voice	3–12 months	1–2 years

^A Adapted with permission from Hembree et al.(2009). Copyright 2009, The Endocrine Society.^B Estimates represent published and unpublished clinical observations.^C Highly dependent on age and inheritance; may be minimal.^D Significantly dependent on amount of exercise.

TABLE 1B: EFFECTS AND EXPECTED TIME COURSE OF FEMINIZING HORMONES ^A

Effect	Expected onset ^B	Expected maximum effect ^B
Body fat redistribution	3–6 months	2–5 years
Decreased muscle mass/ strength	3–6 months	1–2 years ^C
Softening of skin/decreased oiliness	3–6 months	Unknown
Decreased libido	1–3 months	1–2 years
Decreased spontaneous erections	1–3 months	3–6 months
Male sexual dysfunction	Variable	Variable
Breast growth	3–6 months	2–3 years
Decreased testicular volume	3–6 months	2–3 years
Decreased sperm production	Variable	Variable
Thinning and slowed growth of body and facial hair	6–12 months	> 3 years ^D
Male pattern baldness	No regrowth, loss stops 1–3 months	1–2 years

^A Adapted with permission from Hembree et al. (2009). Copyright 2009, The Endocrine Society.^B Estimates represent published and unpublished clinical observations.^C Significantly dependent on amount of exercise.^D Complete removal of male facial and body hair requires electrolysis, laser treatment, or both.

The degree and rate of physical effects depends in part on the dose, route of administration, and medications used, which are selected in accordance with a patient's specific medical goals (e.g., changes in gender role expression, plans for sex reassignment) and medical risk profile. There is no current evidence that response to hormone therapy—with the possible exception of voice deepening in FtM persons—can be reliably predicted based on age, body habitus, ethnicity, or family appearance. All other factors being equal, there is no evidence to suggest that any medically approved type or method of administering hormones is more effective than any other in producing the desired physical changes.

Risks of Hormone Therapy

All medical interventions carry risks. The likelihood of a serious adverse event is dependent on numerous factors: the medication itself, dose, route of administration, and a patient's clinical characteristics (age, comorbidities, family history, health habits). It is thus impossible to predict whether a given adverse effect will happen in an individual patient.

The risks associated with feminizing/masculinizing hormone therapy for the transsexual, transgender, and gender-nonconforming population as a whole are summarized in Table 2. Based on the level of evidence, risks are categorized as follows: (i) likely increased risk with hormone therapy, (ii) possibly increased risk with hormone therapy, or (iii) inconclusive or no increased risk. Items in the last category include those that may present risk, but for which the evidence is so minimal that no clear conclusion can be reached.

Additional detail about these risks can be found in Appendix B, which is based on two comprehensive, evidence-based literature reviews of masculinizing/feminizing hormone therapy (Feldman & Safer, 2009; Hembree et al., 2009), along with a large cohort study (Asscheman et al., 2011). These reviews can serve as detailed references for providers, along with other widely recognized, published clinical materials (Dahl, Feldman, Goldberg, & Jaber, 2006; Ettner, Monstrey, & Eyler, 2007).

TABLE 2: RISKS ASSOCIATED WITH HORMONE THERAPY. BOLDED ITEMS ARE CLINICALLY SIGNIFICANT

Risk Level	Feminizing hormones	Masculinizing hormones
Likely increased risk	Venous thromboembolic disease^A Gallstones Elevated liver enzymes Weight gain Hypertriglyceridemia	Polycythemia Weight gain Acne Androgenic alopecia (balding) Sleep apnea
Likely increased risk with presence of additional risk factors ^B	Cardiovascular disease	
Possible increased risk	Hypertension Hyperprolactinemia or prolactinoma	Elevated liver enzymes Hyperlipidemia
Possible increased risk with presence of additional risk factors ^B	Type 2 diabetes^A	Destabilization of certain psychiatric disorders^C Cardiovascular disease Hypertension Type 2 diabetes
No increased risk or inconclusive	Breast cancer	Loss of bone density Breast cancer Cervical cancer Ovarian cancer Uterine cancer

* **Note:** Risk is greater with oral estrogen administration than with transdermal estrogen administration.

^A Risk is greater with oral estrogen administration than with transdermal estrogen administration.

^B Additional risk factors include age.

^C Includes bipolar, schizoaffective, and other disorders that may include manic or psychotic symptoms. This adverse event appears to be associated with higher doses or supraphysiologic blood levels of testosterone.

Competency of Hormone-Prescribing Physicians, Relationship with Other Health Professionals

Feminizing/masculinizing hormone therapy is best undertaken in the context of a complete approach to health care that includes comprehensive primary care and a coordinated approach to psychosocial issues (Feldman & Safer, 2009). While psychotherapy or ongoing counseling is not required for the initiation of hormone therapy, if a therapist is involved, then regular communication among health professionals is advised (with the patient's consent) to ensure that the transition process is going well, both physically and psychosocially.

With appropriate training, feminizing/masculinizing hormone therapy can be managed by a variety of providers, including nurse practitioners, physician assistants, and primary care physicians (Dahl et al., 2006). Medical visits relating to hormone maintenance provide an opportunity to deliver broader care to a population that is often medically underserved (Clements, Wilkinson, Kitano, & Marx, 1999; Feldman, 2007; Xavier, 2000). Many of the screening tasks and management of comorbidities associated with long-term hormone use, such as cardiovascular risk factors and cancer screening, fall more uniformly within the scope of primary care rather than specialist care (American Academy of Family Physicians, 2005; Eyler, 2007; World Health Organization, 2008), particularly in locations where dedicated gender teams or specialized physicians are not available.

Given the multidisciplinary needs of transsexual, transgender, and gender-nonconforming people seeking hormone therapy, as well as the difficulties associated with fragmentation of care in general (World Health Organization, 2008), WPATH strongly encourages the increased training and involvement of primary care providers in the area of feminizing/masculinizing hormone therapy. If hormones are prescribed by a specialist, there should be close communication with the patient's primary care provider. Conversely, an experienced hormone provider or endocrinologist should be involved if the primary care physician has no experience with this type of hormone therapy, or if the patient has a pre-existing metabolic or endocrine disorder that could be affected by endocrine therapy.

While formal training programs in transgender medicine do not yet exist, hormone providers have a responsibility to obtain appropriate knowledge and experience in this field. Clinicians can increase their experience and comfort in providing feminizing/masculinizing hormone therapy by co-managing care or consulting with a more experienced provider, or by providing more limited types of hormone therapy before progressing to initiation of hormone therapy. Because this field of medicine is evolving, clinicians should become familiar and keep current with the medical literature, and discuss emerging issues with colleagues. Such discussions might occur through networks established by WPATH and other national/local organizations.

Responsibilities of Hormone-Prescribing Physicians

In general, clinicians who prescribe hormone therapy should engage in the following tasks:

1. Perform an initial evaluation that includes discussion of a patient's physical transition goals, health history, physical examination, risk assessment, and relevant laboratory tests.
2. Discuss with patients the expected effects of feminizing/masculinizing medications and the possible adverse health effects. These effects can include a reduction in fertility (Feldman & Safer, 2009; Hembree et al., 2009). Therefore, reproductive options should be discussed with patients before starting hormone therapy (see section IX).
3. Confirm that patients have the capacity to understand the risks and benefits of treatment and are capable of making an informed decision about medical care.
4. Provide ongoing medical monitoring, including regular physical and laboratory examination to monitor hormone effectiveness and side effects.
5. Communicate as needed with a patient's primary care provider, mental health professional, and surgeon.
6. If needed, provide patients with a brief written statement indicating that they are under medical supervision and care that includes feminizing/masculinizing hormone therapy. Particularly during the early phases of hormone treatment, a patient may wish to carry this statement at all times to help prevent difficulties with the police and other authorities.

Depending on the clinical situation for providing hormones (see below), some of these responsibilities are less relevant. Thus, the degree of counseling, physical examinations, and laboratory evaluations should be individualized to a patient's needs.

Clinical Situations for Hormone Therapy

There are circumstances in which clinicians may be called upon to provide hormones without necessarily initiating or maintaining long-term feminizing/masculinizing hormone therapy. By acknowledging these different clinical situations (see below, from least to highest level of complexity), it may be possible to involve clinicians in feminizing/masculinizing hormone therapy who might not otherwise feel able to offer this treatment.

1. Bridging

Whether prescribed by another clinician or obtained through other means (e.g., purchased over the Internet), patients may present for care already on hormone therapy. Clinicians can provide a limited (1–6 month) prescription for hormones while helping patients find a provider who can prescribe long-term hormone therapy. Providers should assess a patient's current regimen for safety and drug interactions and substitute safer medications or doses when indicated (Dahl et al., 2006; Feldman & Safer, 2009). If hormones were previously prescribed, medical records should be requested (with the patient's permission) to obtain the results of baseline examinations and laboratory tests and any adverse events. Hormone providers should also communicate with any mental health professional who is currently involved in a patient's care. If a patient has never had a psychosocial assessment as recommended by the SOC (see section VII), clinicians should refer the patient to a qualified mental health professional if appropriate and feasible (Feldman & Safer, 2009). Providers who prescribe bridging hormones need to work with patients to establish limits as to the duration of bridging therapy.

2. Hormone Therapy Following Gonad Removal

Hormone replacement with estrogen or testosterone is usually continued lifelong after an oophorectomy or orchiectomy, unless medical contraindications arise. Because hormone doses are often decreased after these surgeries (Basson, 2001; Levy, Crown, & Reid, 2003; Moore, Wisniewski, & Dobs, 2003) and only adjusted for age and comorbid health concerns, hormone management in this situation is quite similar to hormone replacement in any hypogonadal patient.

3. Hormone Maintenance Prior to Gonad Removal

Once patients have achieved maximal feminizing/masculinizing benefits from hormones (typically two or more years), they remain on a maintenance dose. The maintenance dose is then adjusted for changes in health conditions, aging, or other considerations such as lifestyle changes (Dahl et al., 2006). When a patient on maintenance hormones presents for care, the provider should assess the patient's current regimen for safety and drug interactions and substitute safer medications or doses when indicated. The patient should continue to be monitored by physical examinations and laboratory testing on a regular basis, as outlined in the literature (Feldman & Safer, 2009; Hembree et al., 2009). The dose and form of hormones should be revisited regularly with any changes in the patient's health status and available evidence on the potential long-term risks of hormones (See *Hormone Regimens*, below).

4. Initiating Hormonal Feminization/Masculinization

This clinical situation requires the greatest commitment in terms of provider time and expertise. Hormone therapy must be individualized based on a patient's goals, the risk/benefit ratio of medications, the presence of other medical conditions, and consideration of social and economic issues. Although a wide variety of hormone regimens have been published (Dahl et al., 2006; Hembree et al., 2009; Moore et al., 2003), there are no published reports of randomized clinical trials comparing safety and efficacy. Despite this variation, a reasonable framework for initial risk assessment and ongoing monitoring of hormone therapy can be constructed, based on the efficacy and safety evidence presented above.

Risk Assessment and Modification for Initiating Hormone Therapy

The initial evaluation for hormone therapy assesses a patient's clinical goals and risk factors for hormone-related adverse events. During the risk assessment, the patient and clinician should develop a plan for reducing risks wherever possible, either prior to initiating therapy or as part of ongoing harm reduction.

All assessments should include a thorough physical exam, including weight, height, and blood pressure. The need for breast, genital, and rectal exams, which are sensitive issues for most transsexual, transgender, and gender-nonconforming patients, should be based on individual risks and preventive health care needs (Feldman & Goldberg, 2006; Feldman, 2007).

Preventive Care

Hormone providers should address preventive health care with patients, particularly if a patient does not have a primary care provider. Depending on a patient's age and risk profile, there may be appropriate screening tests or exams for conditions affected by hormone therapy. Ideally, these screening tests should be carried out prior to the start of hormone therapy.

Risk Assessment and Modification for Feminizing Hormone Therapy (MtF)

There are no absolute contraindications to feminizing therapy per se, but absolute contraindications exist for the different feminizing agents, particularly estrogen. These include previous venous thrombotic events related to an underlying hypercoagulable condition, history of estrogen-sensitive neoplasm, and end-stage chronic liver disease (Gharib et al., 2005).

Other medical conditions, as noted in Table 2 and Appendix B, can be exacerbated by estrogen or androgen blockade, and therefore should be evaluated and reasonably well controlled prior to starting hormone therapy (Feldman & Safer, 2009; Hembree et al., 2009). Clinicians should particularly attend to tobacco use, as it is associated with increased risk of venous thrombosis, which is further increased with estrogen use. Consultation with a cardiologist may be advisable for patients with known cardio- or cerebrovascular disease.

Baseline laboratory values are important to both assess initial risk and evaluate possible future adverse events. Initial labs should be based on the risks of feminizing hormone therapy outlined in Table 2, as well as individual patient risk factors, including family history. Suggested initial lab panels have been published (Feldman & Safer, 2009; Hembree et al., 2009). These can be modified for patients or health care systems with limited resources, and in otherwise healthy patients.

Risk Assessment and Modification for Masculinizing Hormone Therapy (FtM)

Absolute contraindications to testosterone therapy include pregnancy, unstable coronary artery disease, and untreated polycythemia with a hematocrit of 55% or higher (Carnegie, 2004). Because the aromatization of testosterone to estrogen may increase risk in patients with a history of breast or other estrogen dependent cancers (Moore et al., 2003), consultation with an oncologist may be indicated prior to hormone use. Comorbid conditions likely to be exacerbated by testosterone use should be evaluated and treated, ideally prior to starting hormone therapy (Feldman & Safer, 2009; Hembree et al., 2009). Consultation with a cardiologist may be advisable for patients with known cardio- or cerebrovascular disease. (Dhejne et al., 2011).

An increased prevalence of polycystic ovarian syndrome (PCOS) has been noted among FtM patients even in the absence of testosterone use (Baba et al., 2007; Balen, Schachter, Montgomery, Reid, & Jacobs, 1993; Bosinski et al., 1997). While there is no evidence that PCOS is related to the development of a transsexual, transgender, or gender-nonconforming identity, PCOS is associated with increased risk of diabetes, cardiac disease, high blood pressure, and ovarian and endometrial cancers (Cattrall & Healy, 2004). Signs and symptoms of PCOS should be evaluated prior to initiating testosterone therapy, as testosterone may affect many of these conditions. Testosterone can affect the developing fetus (*Physicians' Desk Reference*, 2010), and patients at risk of becoming pregnant require highly effective birth control.

Baseline laboratory values are important to both assess initial risk and evaluate possible future adverse events. Initial labs should be based on the risks of masculinizing hormone therapy outlined in Table 2, as well as individual patient risk factors, including family history. Suggested initial lab panels have been published (Feldman & Safer, 2009; Hembree et al., 2009). These can be modified for patients or health care systems with limited resources, and in otherwise healthy patients.

Clinical Monitoring During Hormone Therapy for Efficacy and Adverse Events

The purpose of clinical monitoring during hormone use is to assess the degree of feminization/masculinization and the possible presence of adverse effects of medication. However, as with the monitoring of any long-term medication, monitoring should take place in the context of comprehensive health care. Suggested clinical monitoring protocols have been published (Feldman & Safer, 2009; Hembree et al., 2009). Patients with comorbid medical conditions may need to be monitored more frequently. Healthy patients in geographically remote or resource-poor areas may be able to use alternative strategies, such as telehealth, or cooperation with local providers such as nurses and physician assistants. In the absence of other indications, health professionals may prioritize monitoring for those risks that are either likely to be increased by hormone therapy or possibly increased by hormone therapy but clinically serious in nature.

Efficacy and Risk Monitoring During Feminizing Hormone Therapy (MtF)

The best assessment of hormone efficacy is clinical response: Is a patient developing a feminized body while minimizing masculine characteristics, consistent with that patient's gender goals? In order to more rapidly predict the hormone dosages that will achieve clinical response, one can measure testosterone levels for suppression below the upper limit of the normal female range and estradiol levels within a premenopausal female range but well below supraphysiologic levels (Feldman & Safer, 2009; Hembree et al., 2009).

Monitoring for adverse events should include both clinical and laboratory evaluation. Follow-up should include careful assessment for signs of cardiovascular impairment and venous thromboembolism (VTE) through measurement of blood pressure, weight, and pulse; heart and lung exams; and examination of the extremities for peripheral edema, localized swelling, or pain (Feldman & Safer, 2009). Laboratory monitoring should be based on the risks of hormone therapy described above, a patient's individual comorbidities and risk factors, and the specific hormone regimen itself. Specific lab-monitoring protocols have been published (Feldman & Safer, 2009; Hembree et al., 2009).

Efficacy and Risk Monitoring During Masculinizing Hormone Therapy (FtM)

The best assessment of hormone efficacy is clinical response: Is a patient developing a masculinized body while minimizing feminine characteristics, consistent with that patient's gender goals? Clinicians can achieve a good clinical response with the least likelihood of adverse events by maintaining testosterone levels within the normal male range while avoiding supraphysiologic

levels (Dahl et al., 2006; Hembree et al., 2009). For patients using intramuscular (IM) testosterone cypionate or enanthate, some clinicians check trough levels while others prefer midcycle levels (Dahl et al., 2006; Hembree et al., 2009; Tangpricha, Turner, Malabanan, & Holick, 2001; Tangpricha, Ducharme, Barber, & Chipkin, 2003).

Monitoring for adverse events should include both clinical and laboratory evaluation. Follow-up should include careful assessment for signs and symptoms of excessive weight gain, acne, uterine break-through bleeding, and cardiovascular impairment, as well as psychiatric symptoms in at-risk patients. Physical examinations should include measurement of blood pressure, weight, and pulse; and heart, lung, and skin exams (Feldman & Safer, 2009). Laboratory monitoring should be based on the risks of hormone therapy described above, a patient's individual comorbidities and risk factors, and the specific hormone regimen itself. Specific lab monitoring protocols have been published (Feldman & Safer, 2009; Hembree et al., 2009).

Hormone Regimens

To date, no controlled clinical trials of any feminizing/masculinizing hormone regimen have been conducted to evaluate safety or efficacy in producing physical transition. As a result, wide variation in doses and types of hormones have been published in the medical literature (Moore et al., 2003; Tangpricha et al., 2003; van Kesteren, Asscheman, Megens, & Gooren, 1997). In addition, access to particular medications may be limited by a patient's geographical location and/or social or economic situations. For these reasons, WPATH does not describe or endorse a particular feminizing/masculinizing hormone regimen. Rather, the medication classes and routes of administration used in most published regimens are broadly reviewed.

As outlined above, there are demonstrated safety differences in individual elements of various regimens. The Endocrine Society Guidelines (Hembree et al., 2009) and Feldman and Safer (2009) provide specific guidance regarding the types of hormones and suggested dosing to maintain levels within physiologic ranges for a patient's desired gender expression (based on goals of full feminization/masculinization). It is strongly recommend that hormone providers regularly review the literature for new information and use those medications that safely meet individual patient needs with available local resources.

Regimens for Feminizing Hormone Therapy (MtF)Estrogen

Use of oral estrogen, and specifically ethinyl estradiol, appears to increase the risk of VTE. Because of this safety concern, ethinyl estradiol is not recommended for feminizing hormone therapy. Transdermal estrogen is recommended for those patients with risks factors for VTE. The risk of adverse events increases with higher doses, particular doses resulting in supraphysiologic levels (Hembree et al., 2009). Patients with co-morbid conditions that can be affected by estrogen should avoid oral estrogen if possible and be started at lower levels. Some patients may not be able to safely use the levels of estrogen needed to get the desired results. This possibility needs to be discussed with patients well in advance of starting hormone therapy.

Androgen-reducing medications (“anti-androgens”)

A combination of estrogen and “anti-androgens” is the most commonly studied regimen for feminization. Androgen-reducing medications, from a variety of classes of drugs, have the effect of reducing either endogenous testosterone levels or testosterone activity, and thus diminishing masculine characteristics such as body hair. They minimize the dosage of estrogen needed to suppress testosterone, thereby reducing the risks associated with high-dose exogenous estrogen (Prior, Vigna, Watson, Diewold, & Robinow, 1986; Prior, Vigna, & Watson, 1989).

Common anti-androgens include the following:

- Spironolactone, an antihypertensive agent, directly inhibits testosterone secretion and androgen binding to the androgen receptor. Blood pressure and electrolytes need to be monitored because of the potential for hyperkalemia.
- Cyproterone acetate is a progestational compound with anti-androgenic properties. This medication is not approved in the United States because of concerns over potential hepatotoxicity, but it is widely used elsewhere (De Cuypere et al., 2005).
- GnRH agonists (e.g., goserelin, buserelin, triptorelin) are neurohormones that block the gonadotropin-releasing hormone receptor, thus blocking the release of follicle stimulating hormone and luteinizing hormone. This leads to highly effective gonadal blockade. However, these medications are expensive and only available as injectables or implants.
- 5-alpha reductase inhibitors (finasteride and dutasteride) block the conversion of testosterone to the more active agent, 5-alpha-dihydrotestosterone. These medications have beneficial effects on scalp hair loss, body hair growth, sebaceous glands, and skin consistency.

Cyproterone and spironolactone are the most commonly used anti-androgens and are likely the most cost-effective.

Progestins

With the exception of cyproterone, the inclusion of progestins in feminizing hormone therapy is controversial (Oriel, 2000). Because progestins play a role in mammary development on a cellular level, some clinicians believe that these agents are necessary for full breast development (Basson & Prior, 1998; Oriel, 2000). However, a clinical comparison of feminization regimens with and without progestins found that the addition of progestins neither enhanced breast growth nor lowered serum levels of free testosterone (Meyer et al., 1986). There are concerns regarding potential adverse effects of progestins, including depression, weight gain, and lipid changes (Meyer et al., 1986; Tangpricha et al., 2003). Progestins (especially medroxyprogesterone) are also suspected to increase breast cancer risk and cardiovascular risk in women (Rossouw et al., 2002). Micronized progesterone may be better tolerated and have a more favorable impact on the lipid profile than medroxyprogesterone does (de Lignières, 1999; Fitzpatrick, Pace, & Wiita, 2000).

Regimens for Masculinizing Hormone Therapy (FtM)

Testosterone

Testosterone generally can be given orally, transdermally, or parenterally (IM), although buccal and implantable preparations are also available. Oral testosterone undecanoate, available outside the United States, results in lower serum testosterone levels than nonoral preparations and has limited efficacy in suppressing menses (Feldman, 2005, April; Moore et al., 2003). Because intramuscular testosterone cypionate or enanthate are often administered every 2–4 weeks, some patients may notice cyclic variation in effects (e.g., fatigue and irritability at the end of the injection cycle, aggression or expansive mood at the beginning of the injection cycle), as well as more time outside the normal physiologic levels (Jockenhövel, 2004). This may be mitigated by using a lower but more frequent dosage schedule or by using a daily transdermal preparation (Dobs et al., 1999; Jockenhövel, 2004; Nieschlag et al., 2004). Intramuscular testosterone undecanoate (not currently available in the United States) maintains stable, physiologic testosterone levels over approximately 12 weeks and has been effective in both the setting of hypogonadism and in FtM individuals (Mueller, Kiesewetter, Binder, Beckmann, & Dittrich, 2007; Zitzmann, Saad, & Nieschlag, 2006). There is evidence that transdermal and intramuscular testosterone achieve similar masculinizing results, although the timeframe may be somewhat slower with transdermal preparations (Feldman, 2005, April). Especially as patients age, the goal is to use the lowest dose needed to maintain the desired clinical result, with appropriate precautions being made to maintain bone density.

Other agents

Progestins, most commonly medroxyprogesterone, can be used for a short period of time to assist with menstrual cessation early in hormone therapy. GnRH agonists can be used similarly, as well as for refractory uterine bleeding in patients without an underlying gynecological abnormality.

Bioidentical and Compounded Hormones

As discussion surrounding the use of bioidentical hormones in postmenopausal hormone replacement has heightened, interest has also increased in the use of similar compounds in feminizing/masculinizing hormone therapy. There is no evidence that custom compounded bioidentical hormones are safer or more effective than government agency-approved bioidentical hormones (Sood, Shuster, Smith, Vincent, & Jatoi, 2011). Therefore, it has been advised by the North American Menopause Society (2010) and others to assume that, whether the hormone is from a compounding pharmacy or not, if the active ingredients are similar, it should have a similar side-effect profile. WPATH concurs with this assessment.

IX

Reproductive Health

Many transgender, transsexual, and gender-nonconforming people will want to have children. Because feminizing/masculinizing hormone therapy limits fertility (Darney, 2008; Zhang, Gu, Wang, Cui, & Bremner, 1999), it is desirable for patients to make decisions concerning fertility before starting hormone therapy or undergoing surgery to remove/alter their reproductive organs. Cases are known of people who received hormone therapy and genital surgery and later regretted their inability to parent genetically related children (De Sutter, Kira, Verschoor, & Hotimsky, 2002).

Health care professionals—including mental health professionals recommending hormone therapy or surgery, hormone-prescribing physicians, and surgeons—should discuss reproductive options with patients prior to initiation of these medical treatments for gender dysphoria. These discussions should occur even if patients are not interested in these issues at the time of treatment, which may be more common for younger patients (De Sutter, 2009). Early discussions are desirable, but not always possible. If an individual has not had complete sex reassignment surgery, it may be possible to stop hormones long enough for natal hormones to recover, allowing

the production of mature gametes (Payer, Meyer, & Walker, 1979; Van den Broecke, Van der Elst, Liu, Hovatta, & Dhont, 2001).

Besides debate and opinion papers, very few research papers have been published on the reproductive health issues of individuals receiving different medical treatments for gender dysphoria. Another group who faces the need to preserve reproductive function in light of loss or damage to their gonads are people with malignancies that require removal of reproductive organs or use of damaging radiation or chemotherapy. Lessons learned from that group can be applied to people treated for gender dysphoria.

MtF patients, especially those who have not already reproduced, should be informed about sperm-preservation options and encouraged to consider banking their sperm prior to hormone therapy. In a study examining testes that were exposed to high-dose estrogen (Payer et al., 1979), findings suggest that stopping estrogen may allow the testes to recover. In an article reporting on the opinions of MtF individuals towards sperm freezing (De Sutter et al., 2002), the vast majority of 121 survey respondents felt that the availability of freezing sperm should be discussed and offered by the medical world. Sperm should be collected before hormone therapy or after stopping the therapy until the sperm count rises again. Cryopreservation should be discussed even if there is poor semen quality. In adults with azoospermia, a testicular biopsy with subsequent cryopreservation of biopsied material for sperm is possible, but may not be successful.

Reproductive options for FtM patients might include oocyte (egg) or embryo freezing. The frozen gametes and embryo could later be used with a surrogate woman to carry to pregnancy. Studies of women with polycystic ovarian disease suggest that the ovary can recover in part from the effects of high testosterone levels (Hunter & Sterrett, 2000). Stopping the testosterone briefly might allow for ovaries to recover enough to release eggs; success likely depends on the patient's age and duration of testosterone treatment. While not systematically studied, some FtM individuals are doing exactly that, and some have been able to become pregnant and deliver children (More, 1998).

Patients should be advised that these techniques are not available everywhere and can be very costly. Transsexual, transgender, and gender-nonconforming people should not be refused reproductive options for any reason.

A special group of individuals are prepubertal or pubertal adolescents who will never develop reproductive function in their natal sex due to blockers or cross-gender hormones. At this time there is no technique for preserving function from the gonads of these individuals.



Voice and Communication Therapy

Communication, both verbal and nonverbal, is an important aspect of human behavior and gender expression. Transsexual, transgender, and gender-nonconforming people might seek the assistance of a voice and communication specialist to develop vocal characteristics (e.g., pitch, intonation, resonance, speech rate, phrasing patterns) and non-verbal communication patterns (e.g., gestures, posture/movement, facial expressions) that facilitate comfort with their gender identity. Voice and communication therapy may help to alleviate gender dysphoria and be a positive and motivating step towards achieving one's goals for gender role expression.

Competency of Voice and Communication Specialists Working with Transsexual, Transgender, and Gender-Nonconforming Clients

Specialists may include speech-language pathologists, speech therapists, and speech-voice clinicians. In most countries the professional association for speech-language pathologists requires specific qualifications and credentials for membership. In some countries the government regulates practice through licensing, certification, or registration processes (American Speech-Language-Hearing Association, 2011; Canadian Association of Speech-Language Pathologists and Audiologists; Royal College of Speech Therapists, United Kingdom; Speech Pathology Australia).

The following are recommended minimum credentials for voice and communication specialists working with transsexual, transgender, and gender-nonconforming clients:

1. Specialized training and competence in the assessment and development of communication skills in transsexual, transgender, and gender-nonconforming clients.
2. A basic understanding of transgender health, including hormonal and surgical treatments for feminization/masculinization and trans-specific psychosocial issues as outlined in the SOC; and familiarity with basic sensitivity protocols such as the use of preferred gender pronoun and name (Canadian Association of Speech-Language Pathologists and Audiologists; Royal College of Speech Therapists, United Kingdom; Speech Pathology Australia).

3. Continuing education in the assessment and development of communication skills in transsexual, transgender, and gender-nonconforming clients. This may include attendance at professional meetings, workshops, or seminars; participation in research related to gender identity issues; independent study; or mentoring from an experienced, certified clinician.

Other professionals such as vocal coaches, theatre professionals, singing teachers, and movement experts may play a valuable adjunct role. Such professionals will ideally have experience working with, or be actively collaborating with, speech-language pathologists.

Assessment and Treatment Considerations

The overall purpose of voice and communication therapy is to help clients adapt their voice and communication in a way that is both safe and authentic, resulting in communication patterns that clients feel are congruent with their gender identity and that reflect their sense of self (Adler, Hirsch, & Mordaunt, 2006). It is essential that voice and communication specialists be sensitive to individual communication preferences. Communication—style, voice, choice of language, etc.—is personal. Individuals should not be counseled to adopt behaviors with which they are not comfortable or which do not feel authentic. Specialists can best serve their clients by taking the time to understand a person's gender concerns and goals for gender-role expression (American Speech-Language-Hearing Association, 2011; Canadian Association of Speech-Language Pathologists and Audiologists; Royal College of Speech Therapists, United Kingdom; Speech Pathology Australia).

Individuals may choose the communication behaviors that they wish to acquire in accordance with their gender identity. These decisions are also informed and supported by the knowledge of the voice and communication specialist and by the assessment data for a specific client (Hancock, Krissinger, & Owen, 2010). Assessment includes a client's self-evaluation and a specialist's evaluation of voice, resonance, articulation, spoken language, and non-verbal communication (Adler et al., 2006; Hancock et al., 2010).

Voice-and-communication treatment plans are developed by considering the available research evidence, the clinical knowledge and experience of the specialist, and the client's own goals and values (American Speech-Language-Hearing Association, 2011; Canadian Association of Speech-Language Pathologists and Audiologists; Royal College of Speech Therapists, United Kingdom; Speech Pathology Australia). Targets of treatment typically include pitch, intonation, loudness and stress patterns, voice quality, resonance, articulation, speech rate and phrasing, language, and nonverbal communication (Adler et al., 2006; Davies & Goldberg, 2006; de Bruin, Coerts, & Greven, 2000; Gelfer, 1999; McNeill, 2006; Oates & Dacakis, 1983). Treatment may involve individual and/or group sessions. The frequency and duration of treatment will vary according to a client's needs. Existing protocols for voice-and-communication treatment can be considered in

developing an individualized therapy plan (Carew, Dacakis, & Oates, 2007; Dacakis, 2000; Davies & Goldberg, 2006; Gelfer, 1999; McNeill, Wilson, Clark, & Deakin, 2008; Mount & Salmon, 1988).

Feminizing or masculinizing the voice involves non-habitual use of the voice production mechanism. Prevention measures are necessary to avoid the possibility of vocal misuse and long-term vocal damage. All voice and communication therapy services should therefore include a vocal health component (Adler et al., 2006).

Vocal Health Considerations After Voice Feminization Surgery

As noted in section XI, some transsexual, transgender, and gender-nonconforming people will undergo voice feminization surgery. (Voice deepening can be achieved through masculinizing hormone therapy, but feminizing hormones do not have an impact on the adult MtF voice.) There are varying degrees of satisfaction, safety, and long-term improvement in patients who have had such surgery. It is recommended that individuals undergoing voice feminization surgery also consult a voice and communication specialist to maximize the surgical outcome, help protect vocal health, and learn nonpitch related aspects of communication. Voice surgery procedures should include follow-up sessions with a voice and communication specialist who is licensed and/or credentialed by the board responsible for speech therapists/speech-language pathologists in that country (Kanagalingam et al., 2005; Neumann & Welzel, 2004).

XI

Surgery

Sex Reassignment Surgery Is Effective and Medically Necessary

Surgery – particularly genital surgery – is often the last and the most considered step in the treatment process for gender dysphoria. While many transsexual, transgender, and gender-nonconforming individuals find comfort with their gender identity, role, and expression without surgery, for many others surgery is essential and medically necessary to alleviate their gender dysphoria (Hage & Karim, 2000). For the latter group, relief from gender dysphoria cannot be achieved

without modification of their primary and/or secondary sex characteristics to establish greater congruence with their gender identity. Moreover, surgery can help patients feel more at ease in the presence of sex partners or in venues such as physicians' offices, swimming pools, or health clubs. In some settings, surgery might reduce risk of harm in the event of arrest or search by police or other authorities.

Follow-up studies have shown an undeniable beneficial effect of sex reassignment surgery on postoperative outcomes such as subjective well-being, cosmesis, and sexual function (De Cuypere et al., 2005; Gijs & Brewaeys, 2007; Klein & Gorzalka, 2009; Pfäfflin & Junge, 1998). Additional information on the outcomes of surgical treatments are summarized in Appendix D.

Ethical Questions Regarding Sex Reassignment Surgery

In ordinary surgical practice, pathological tissues are removed to restore disturbed functions, or alterations are made to body features to improve a patient's self image. Some people, including some health professionals, object on ethical grounds to surgery as a treatment for gender dysphoria, because these conditions are thought not to apply.

It is important that health professionals caring for patients with gender dysphoria feel comfortable about altering anatomically normal structures. In order to understand how surgery can alleviate the psychological discomfort and distress of individuals with gender dysphoria, professionals need to listen to these patients discuss their symptoms, dilemmas, and life histories. The resistance against performing surgery on the ethical basis of "above all do no harm" should be respected, discussed, and met with the opportunity to learn from patients themselves about the psychological distress of having gender dysphoria and the potential for harm caused by denying access to appropriate treatments.

Genital and breast/chest surgical treatments for gender dysphoria are not merely another set of elective procedures. Typical elective procedures involve only a private mutually consenting contract between a patient and a surgeon. Genital and breast/chest surgeries as medically necessary treatments for gender dysphoria are to be undertaken only after assessment of the patient by qualified mental health professionals, as outlined in section VII of the SOC. These surgeries may be performed once there is written documentation that this assessment has occurred and that the person has met the criteria for a specific surgical treatment. By following this procedure, mental health professionals, surgeons, and patients share responsibility for the decision to make irreversible changes to the body.

It is unethical to deny availability or eligibility for sex reassignment surgeries solely on the basis of blood seropositivity for blood-borne infections such as HIV or hepatitis C or B.

Relationship of Surgeons with Mental Health Professionals, Hormone-Prescribing Physicians (if Applicable), and Patients (Informed Consent)

The role of a surgeon in the treatment of gender dysphoria is not that of a mere technician. Rather, conscientious surgeons will have insight into each patient's history and the rationale that led to the referral for surgery. To that end, surgeons must talk at length with their patients and have close working relationships with other health professionals who have been actively involved in their clinical care.

Consultation is readily accomplished when a surgeon practices as part of an interdisciplinary health care team. In the absence of this, a surgeon must be confident that the referring mental health professional(s), and if applicable the physician who prescribes hormones, is/are competent in the assessment and treatment of gender dysphoria, because the surgeon is relying heavily on his/her/their expertise.

Once a surgeon is satisfied that the criteria for specific surgeries have been met (as outlined below), surgical treatment should be considered and a preoperative surgical consultation should take place. During this consultation, the procedure and postoperative course should be extensively discussed with the patient. Surgeons are responsible for discussing all of the following with patients seeking surgical treatments for gender dysphoria:

- The different surgical techniques available (with referral to colleagues who provide alternative options);
- The advantages and disadvantages of each technique;
- The limitations of a procedure to achieve “ideal” results; surgeons should provide a full range of before-and-after photographs of their own patients, including both successful and unsuccessful outcomes;
- The inherent risks and possible complications of the various techniques; surgeons should inform patients of their own complication rates with each procedure.

These discussions are the core of the informed consent process, which is both an ethical and legal requirement for any surgical procedure. Ensuring that patients have a realistic expectation of outcomes is important in achieving a result that will alleviate their gender dysphoria.

All of this information should be provided to patients in writing, in a language in which they are fluent, and in graphic illustrations. Patients should receive the information in advance (possibly

via the Internet) and be given ample time to review it carefully. The elements of informed consent should always be discussed face-to-face prior to the surgical intervention. Questions can then be answered and written informed consent can be provided by the patient. Because these surgeries are irreversible, care should be taken to ensure that patients have sufficient time to absorb information fully before they are asked to provide informed consent. A minimum of 24 hours is suggested.

Surgeons should provide immediate aftercare and consultation with other physicians serving the patient in the future. Patients should work with their surgeon to develop an adequate aftercare plan for the surgery.

Overview of Surgical Procedures for the Treatment of Patients with Gender Dysphoria

For the Male-to-Female (MtF) Patient, Surgical Procedures May Include the Following:

1. Breast/chest surgery: augmentation mammoplasty (implants/lipofilling);
2. Genital surgery: penectomy, orchiectomy, vaginoplasty, clitoroplasty, vulvoplasty;
3. Nongenital, nonbreast surgical interventions: facial feminization surgery, liposuction, lipofilling, voice surgery, thyroid cartilage reduction, gluteal augmentation (implants/lipofilling), hair reconstruction, and various aesthetic procedures.

For the Female-to-Male (FtM) Patient, Surgical Procedures May Include the Following:

1. Breast/chest surgery: subcutaneous mastectomy, creation of a male chest;
2. Genital surgery: hysterectomy/salpingo-oophorectomy, reconstruction of the fixed part of the urethra, which can be combined with a metoidioplasty or with a phalloplasty (employing a pedicled or free vascularized flap), vaginectomy, scrotoplasty, and implantation of erection and/or testicular prostheses;
3. Nongenital, nonbreast surgical interventions: voice surgery (rare), liposuction, lipofilling, pectoral implants, and various aesthetic procedures.

Reconstructive Versus Aesthetic Surgery

The question of whether sex reassignment surgery should be considered “aesthetic” surgery or “reconstructive” surgery is pertinent not only from a philosophical point of view, but also from a financial point of view. Aesthetic or cosmetic surgery is mostly regarded as not medically necessary and therefore is typically paid for entirely by the patient. In contrast, reconstructive procedures are considered medically necessary—with unquestionable therapeutic results—and thus paid for partially or entirely by national health systems or insurance companies.

Unfortunately, in the field of plastic and reconstructive surgery (both in general and specifically for gender-related surgeries), there is no clear distinction between what is purely reconstructive and what is purely cosmetic. Most plastic surgery procedures actually are a mixture of both reconstructive and cosmetic components.

While most professionals agree that genital surgery and mastectomy cannot be considered purely cosmetic, opinions diverge as to what degree other surgical procedures (e.g., breast augmentation, facial feminization surgery) can be considered purely reconstructive. Although it may be much easier to see a phalloplasty or a vaginoplasty as an intervention to end lifelong suffering, for certain patients an intervention like a reduction rhinoplasty can have a radical and permanent effect on their quality of life, and therefore is much more medically necessary than for somebody without gender dysphoria.

Criteria for Surgeries

As for all of the *SOC*, the criteria for initiation of surgical treatments for gender dysphoria were developed to promote optimal patient care. While the *SOC* allow for an individualized approach to best meet a patient's health care needs, a criterion for all breast/chest and genital surgeries is documentation of persistent gender dysphoria by a qualified mental health professional. For some surgeries, additional criteria include preparation and treatment consisting of feminizing/masculinizing hormone therapy and one year of continuous living in a gender role that is congruent with one's gender identity.

These criteria are outlined below. Based on the available evidence and expert clinical consensus, different recommendations are made for different surgeries.

The *SOC* do not specify an order in which different surgeries should occur. The number and sequence of surgical procedures may vary from patient to patient, according to their clinical needs.

Criteria for Breast/Chest Surgery (One Referral)

Criteria for mastectomy and creation of a male chest in FtM patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country (if younger, follow the SOC for children and adolescents);
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.

Hormone therapy is not a prerequisite.

Criteria for breast augmentation (implants/lipofilling) in MtF patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country (if younger, follow the SOC for children and adolescents);
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.

Although not an explicit criterion, it is recommended that MtF patients undergo feminizing hormone therapy (minimum 12 months) prior to breast augmentation surgery. The purpose is to maximize breast growth in order to obtain better surgical (aesthetic) results.

Criteria for Genital Surgery (Two Referrals)

The criteria for genital surgery are specific to the type of surgery being requested.

Criteria for hysterectomy and salpingo-oophorectomy in FtM patients and for orchiectomy in MtF patients:

1. Persistent, well-documented gender dysphoria;

2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country;
4. If significant medical or mental health concerns are present, they must be well controlled.
5. 12 continuous months of hormone therapy as appropriate to the patient's gender goals (unless hormones are not clinically indicated for the individual).

The aim of hormone therapy prior to gonadectomy is primarily to introduce a period of reversible estrogen or testosterone suppression, before the patient undergoes irreversible surgical intervention.

These criteria do not apply to patients who are having these procedures for medical indications other than gender dysphoria.

Criteria for metoidioplasty or phalloplasty in FtM patients and for vaginoplasty in MtF patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country;
4. If significant medical or mental health concerns are present, they must be well controlled;
5. 12 continuous months of hormone therapy as appropriate to the patient's gender goals (unless hormones are not clinically indicated for the individual).
6. 12 continuous months of living in a gender role that is congruent with their gender identity.

Although not an explicit criterion, it is recommended that these patients also have regular visits with a mental health or other medical professional.

Rationale for a preoperative, 12-month experience of living in an identity-congruent gender role:

The criterion noted above for some types of genital surgeries—i.e., that patients engage in 12 continuous months of living in a gender role that is congruent with their gender identity—is based on expert clinical consensus that this experience provides ample opportunity for patients to experience and socially adjust in their desired gender role, before undergoing irreversible surgery. As noted in section VII, the social aspects of changing one's gender role are usually challenging—

often more so than the physical aspects. Changing gender role can have profound personal and social consequences, and the decision to do so should include an awareness of what the familial, interpersonal, educational, vocational, economic, and legal challenges are likely to be, so that people can function successfully in their gender role. Support from a qualified mental health professional and from peers can be invaluable in ensuring a successful gender role adaptation (Bockting, 2008).

The duration of 12 months allows for a range of different life experiences and events that may occur throughout the year (e.g., family events, holidays, vacations, season-specific work or school experiences). During this time, patients should present consistently, on a day-to-day basis and across all settings of life, in their desired gender role. This includes coming out to partners, family, friends, and community members (e.g., at school, work, other settings).

Health professionals should clearly document a patient's experience in the gender role in the medical chart, including the start date of living full time for those who are preparing for genital surgery. In some situations, if needed, health professionals may request verification that this criterion has been fulfilled: They may communicate with individuals who have related to the patient in an identity-congruent gender role, or request documentation of a legal name and/or gender marker change, if applicable.

Surgery for People with Psychotic Conditions and Other Serious Mental Illnesses

When patients with gender dysphoria are also diagnosed with severe psychiatric disorders and impaired reality testing (e.g., psychotic episodes, bipolar disorder, dissociative identity disorder, borderline personality disorder), an effort must be made to improve these conditions with psychotropic medications and/or psychotherapy before surgery is contemplated. (Dhejne et al., 2011). Reevaluation by a mental health professional qualified to assess and manage psychotic conditions should be conducted prior to surgery, describing the patient's mental status and readiness for surgery. It is preferable that this mental health professional be familiar with the patient. No surgery should be performed while a patient is actively psychotic (De Cuypere & Vercruysse, 2009).

Competency of Surgeons Performing Breast/Chest or Genital Surgery

Physicians who perform surgical treatments for gender dysphoria should be urologists, gynecologists, plastic surgeons, or general surgeons, and board-certified as such by the relevant national

and/or regional association. Surgeons should have specialized competence in genital reconstructive techniques as indicated by documented supervised training with a more experienced surgeon. Even experienced surgeons must be willing to have their surgical skills reviewed by their peers. An official audit of surgical outcomes and publication of these results would be greatly reassuring to both referring health professionals and patients. Surgeons should regularly attend professional meetings where new techniques are presented. The internet is often effectively used by patients to share information on their experience with surgeons and their teams.

Ideally, surgeons should be knowledgeable about more than one surgical technique for genital reconstruction so that they, in consultation with patients, can choose the ideal technique for each individual. Alternatively, if a surgeon is skilled in a single technique and this procedure is either not suitable for or desired by a patient, the surgeon should inform the patient about other procedures and offer referral to another appropriately skilled surgeon.

Breast/Chest Surgery Techniques and Complications

Although breast/chest appearance is an important secondary sex characteristic, breast presence or size is not involved in the legal definitions of sex and gender and is not necessary for reproduction. The performance of breast/chest operations for treatment of gender dysphoria should be considered with the same care as beginning hormone therapy, as both produce relatively irreversible changes to the body.

For the MtF patient, a breast augmentation (sometimes called “chest reconstruction”) is not different from the procedure in a natal female patient. It is usually performed through implantation of breast prostheses and occasionally with the lipofilling technique. Infections and capsular fibrosis are rare complications of augmentation mammoplasty in MtF patients (Kanhai, Hage, Karim, & Mulder, 1999).

For the FtM patient, a mastectomy or “male chest contouring” procedure is available. For many FtM patients, this is the only surgery undertaken. When the amount of breast tissue removed requires skin removal, a scar will result and the patient should be so informed. Complications of subcutaneous mastectomy can include nipple necrosis, contour irregularities, and unsightly scarring (Monstrey et al., 2008).

Genital Surgery Techniques and Complications

Genital surgical procedures for the MtF patient may include orchiectomy, penectomy, vaginoplasty, clitoroplasty, and labiaplasty. Techniques include penile skin inversion, pedicled colosigmoid

transplant, and free skin grafts to line the neovagina. Sexual sensation is an important objective in vaginoplasty, along with creation of a functional vagina and acceptable cosmesis.

Surgical complications of MtF genital surgery may include complete or partial necrosis of the vagina and labia, fistulas from the bladder or bowel into the vagina, stenosis of the urethra, and vaginas that are either too short or too small for coitus. While the surgical techniques for creating a neovagina are functionally and aesthetically excellent, anorgasmia following the procedure has been reported, and a second stage labiaplasty may be needed for cosmesis (Klein & Gorzalka, 2009; Lawrence, 2006).

Genital surgical procedures for FtM patients may include hysterectomy, salpingo-oophorectomy, vaginectomy, metoidioplasty, scrotoplasty, urethroplasty, placement of testicular prostheses, and phalloplasty. For patients without former abdominal surgery, the laparoscopic technique for hysterectomy and salpingo-oophorectomy is recommended to avoid a lower-abdominal scar. Vaginal access may be difficult as most patients are nulliparous and have often not experienced penetrative intercourse. Current operative techniques for phalloplasty are varied. The choice of techniques may be restricted by anatomical or surgical considerations and by a client's financial considerations. If the objectives of phalloplasty are a neophallus of good appearance, standing micturition, sexual sensation, and/or coital ability, patients should be clearly informed that there are several separate stages of surgery and frequent technical difficulties, which may require additional operations. Even metoidioplasty, which in theory is a one-stage procedure for construction of a microphallus, often requires more than one operation. The objective of standing micturition with this technique can not always be ensured (Monstrey et al., 2009).

Complications of phalloplasty in FtMs may include frequent urinary tract stenoses and fistulas, and occasionally necrosis of the neophallus. Metoidioplasty results in a micropenis, without the capacity for standing urination. Phalloplasty, using a pedicled or a free vascularized flap, is a lengthy, multi-stage procedure with significant morbidity that includes frequent urinary complications and unavoidable donor site scarring. For this reason, many FtM patients never undergo genital surgery other than hysterectomy and salpingo-oophorectomy (Hage & De Graaf, 1993).

Even patients who develop severe surgical complications seldom regret having undergone surgery. The importance of surgery can be appreciated by the repeated finding that quality of surgical results is one of the best predictors of the overall outcome of sex reassignment (Lawrence, 2006).

Other Surgeries

Other surgeries for assisting in body feminization include reduction thyroid chondroplasty (reduction of the Adam's apple), voice modification surgery, suction-assisted lipoplasty (contour

modeling) of the waist, rhinoplasty (nose correction), facial bone reduction, face-lift, and blepharoplasty (rejuvenation of the eyelid). Other surgeries for assisting in body masculinization include liposuction, lipofilling, and pectoral implants. Voice surgery to obtain a deeper voice is rare but may be recommended in some cases, such as when hormone therapy has been ineffective.

Although these surgeries do not require referral by mental health professionals, such professionals can play an important role in assisting clients in making a fully informed decision about the timing and implications of such procedures in the context of the social transition.

Although most of these procedures are generally labeled “purely aesthetic,” these same operations in an individual with severe gender dysphoria can be considered medically necessary, depending on the unique clinical situation of a given patient’s condition and life situation. This ambiguity reflects reality in clinical situations, and allows for individual decisions as to the need and desirability of these procedures.

XII

Postoperative Care and Follow-Up

Long-term postoperative care and follow-up after surgical treatments for gender dysphoria are associated with good surgical and psychosocial outcomes (Monstrey et al., 2009). Follow-up is important to a patient’s subsequent physical and mental health and to a surgeon’s knowledge about the benefits and limitations of surgery. Surgeons who operate on patients coming from long distances should include personal follow-up in their care plan and attempt to ensure affordable local long-term aftercare in their patients’ geographic region.

Postoperative patients may sometimes exclude themselves from follow-up by specialty providers, including the hormone-prescribing physician (for patients receiving hormones), not recognizing that these providers are often best able to prevent, diagnose, and treat medical conditions that are unique to hormonally and surgically treated patients. The need for follow-up equally extends to mental health professionals, who may have spent a longer period of time with the patient than any other professional and therefore are in an excellent position to assist in any postoperative adjustment difficulties. Health professionals should stress the importance of postoperative follow-up care with their patients and offer continuity of care.

Postoperative patients should undergo regular medical screening according to recommended guidelines for their age. This is discussed more in the next section.

XIII

Lifelong Preventive and Primary Care

Transsexual, transgender, and gender-nonconforming people need health care throughout their lives. For example, to avoid the negative secondary effects of having a gonadectomy at a relatively young age and/or receiving long-term, high-dose hormone therapy, patients need thorough medical care by providers experienced in primary care and transgender health. If one provider is not able to provide all services, ongoing communication among providers is essential.

Primary care and health maintenance issues should be addressed before, during, and after any possible changes in gender role and medical interventions to alleviate gender dysphoria. While hormone providers and surgeons play important roles in preventive care, every transsexual, transgender, and gender-nonconforming person should partner with a primary care provider for overall health care needs (Feldman, 2007).

General Preventive Health Care

Screening guidelines developed for the general population are appropriate for organ systems that are unlikely to be affected by feminizing/masculinizing hormone therapy. However, in areas such as cardiovascular risk factors, osteoporosis, and some cancers (breast, cervical, ovarian, uterine, and prostate), such general guidelines may either over- or underestimate the cost-effectiveness of screening individuals who are receiving hormone therapy.

Several resources provide detailed protocols for the primary care of patients undergoing feminizing/masculinizing hormone therapy, including therapy that is provided after sex reassignment surgeries (Center of Excellence for Transgender Health, UCSF, 2011; Feldman & Goldberg, 2006; Feldman, 2007; Gorton, Buth, & Spade, 2005). Clinicians should consult their national evidence-based guidelines and discuss screening with their patients in light of the effects of hormone therapy on their baseline risk.

Cancer Screening

Cancer screening of organ systems that are associated with sex can present particular medical and psychosocial challenges for transsexual, transgender, and gender-nonconforming patients and their health care providers. In the absence of large-scale prospective studies, providers are unlikely to have enough evidence to determine the appropriate type and frequency of cancer screenings for this population. Over-screening results in higher health care costs, high false positive rates, and often unnecessary exposure to radiation and/or diagnostic interventions such as biopsies. Under-screening results in diagnostic delay for potentially treatable cancers. Patients may find cancer screening gender affirming (such as mammograms for MtF patients) or both physically and emotionally painful (such as Pap smears offer continuity of care for FtM patients).

Urogenital Care

Gynecologic care may be necessary for transsexual, transgender, and gender-nonconforming people of both sexes. For FtM patients, such care is needed predominantly for individuals who have not had genital surgery. For MtF patients, such care is needed after genital surgery. While many surgeons counsel patients regarding postoperative urogenital care, primary care clinicians and gynecologists should also be familiar with the special genital concerns of this population.

All MtF patients should receive counseling regarding genital hygiene, sexuality, and prevention of sexually transmitted infections; those who have had genital surgery should also be counseled on the need for regular vaginal dilation or penetrative intercourse in order to maintain vaginal depth and width (van Trotsenburg, 2009). Due to the anatomy of the male pelvis, the axis and the dimensions of the neovagina differ substantially from those of a biologic vagina. This anatomic difference can affect intercourse if not understood by MtF patients and their partners (van Trotsenburg, 2009).

Lower urinary tract infections occur frequently in MtF patients who have had surgery because of the reconstructive requirements of the shortened urethra. In addition, these patients may suffer from functional disorders of the lower urinary tract; such disorders may be caused by damage of the autonomous nerve supply of the bladder floor during dissection between the rectum and the bladder, and by a change of the position of the bladder itself. A dysfunctional bladder (e.g., overactive bladder, stress or urge urinary incontinence) may occur after sex reassignment surgery (Hoebeker et al., 2005; Kuhn, Hildebrand, & Birkhauser, 2007).

Most FtM patients do not undergo vaginectomy (colpectomy). For patients who take masculinizing hormones, despite considerable conversion of testosterone to estrogens, atrophic changes of the vaginal lining can be observed regularly and may lead to pruritus or burning. Examination can be

both physically and emotionally painful, but lack of treatment can seriously aggravate the situation. Gynecologists treating the genital complaints of FtM patients should be aware of the sensitivity that patients with a male gender identity and masculine gender expression might have around having genitals typically associated with the female sex.

XIV

Applicability of the *Standards of Care* to People Living in Institutional Environments

The SOC in their entirety apply to all transsexual, transgender, and gender-nonconforming people, irrespective of their housing situation. People should not be discriminated against in their access to appropriate health care based on where they live, including institutional environments such as prisons or long-/intermediate-term health care facilities (Brown, 2009). Health care for transsexual, transgender, and gender-nonconforming people living in an institutional environment should mirror that which would be available to them if they were living in a non-institutional setting within the same community.

All elements of assessment and treatment as described in the SOC can be provided to people living in institutions (Brown, 2009). Access to these medically necessary treatments should not be denied on the basis of institutionalization or housing arrangements. If the in-house expertise of health professionals in the direct or indirect employ of the institution does not exist to assess and/or treat people with gender dysphoria, it is appropriate to obtain outside consultation from professionals who are knowledgeable about this specialized area of health care.

People with gender dysphoria in institutions may also have coexisting mental health conditions (Cole et al., 1997). These conditions should be evaluated and treated appropriately.

People who enter an institution on an appropriate regimen of hormone therapy should be continued on the same, or similar, therapies and monitored according to the SOC. A “freeze frame” approach is not considered appropriate care in most situations (*Kosilek v. Massachusetts Department of Corrections/Maloney*, C.A. No. 92–12820-MLW, 2002). People with gender dysphoria who are deemed appropriate for hormone therapy (following the SOC) should be started on such therapy. The consequences of abrupt withdrawal of hormones or lack of initiation of hormone therapy when medically necessary include a high likelihood of negative outcomes such as surgical self-treatment by autocastration, depressed mood, dysphoria, and/or suicidality (Brown, 2010).

Reasonable accommodations to the institutional environment can be made in the delivery of care consistent with the SOC, if such accommodations do not jeopardize the delivery of medically necessary care to people with gender dysphoria. An example of a reasonable accommodation is the use of injectable hormones, if not medically contraindicated, in an environment where diversion of oral preparations is highly likely (Brown, 2009). Denial of needed changes in gender role or access to treatments, including sex reassignment surgery, on the basis of residence in an institution are not reasonable accommodations under the SOC (Brown, 2010).

Housing and shower/bathroom facilities for transsexual, transgender, and gender-nonconforming people living in institutions should take into account their gender identity and role, physical status, dignity, and personal safety. Placement in a single-sex housing unit, ward, or pod on the sole basis of the appearance of the external genitalia may not be appropriate and may place the individual at risk for victimization (Brown, 2009).

Institutions where transsexual, transgender, and gender-nonconforming people reside and receive health care should monitor for a tolerant and positive climate to ensure that residents are not under attack by staff or other residents.

XV

Applicability of the *Standards of Care* to People With Disorders of Sex Development

Terminology

The term *disorder of sex development* (DSD) refers to a somatic condition of atypical development of the reproductive tract (Hughes, Houk, Ahmed, Lee, & LWPES/ESPE Consensus Group, 2006). DSDs include the condition that used to be called *intersexuality*. Although the terminology was changed to DSD during an international consensus conference in 2005 (Hughes et al., 2006), disagreement about language use remains. Some people object strongly to the “disorder” label, preferring instead to view these congenital conditions as a matter of diversity (Diamond, 2009) and to continue using the terms *intersex* or *intersexuality*. In the SOC, WPATH uses the term DSD in an objective and value-free manner, with the goal of ensuring that health professionals recognize this medical term and use it to access relevant literature as the field progresses. WPATH remains

open to new terminology that will further illuminate the experience of members of this diverse population and lead to improvements in health care access and delivery.

Rationale for Addition to the SOC

Previously, individuals with a DSD who also met the *DSM-IV-TR*'s behavioral criteria for Gender Identity Disorder (American Psychiatric Association, 2000) were excluded from that general diagnosis. Instead, they were categorized as having a "Gender Identity Disorder - Not Otherwise Specified." They were also excluded from the WPATH *Standards of Care*.

The current proposal for *DSM-5* (www.dsm5.org) is to replace the term *gender identity disorder* with *gender dysphoria*. Moreover, the proposed changes to the *DSM* consider gender dysphoric people with a DSD to have a subtype of gender dysphoria. This proposed categorization—which explicitly differentiates between gender dysphoric individuals with and without a DSD—is justified: In people with a DSD, gender dysphoria differs in its phenomenological presentation, epidemiology, life trajectories, and etiology (Meyer-Bahlburg, 2009).

Adults with a DSD and gender dysphoria have increasingly come to the attention of health professionals. Accordingly, a brief discussion of their care is included in this version of the SOC.

Health History Considerations

Health professionals assisting patients with both a DSD and gender dysphoria need to be aware that the medical context in which such patients have grown up is typically very different from that of people without a DSD.

Some people are recognized as having a DSD through the observation of gender-atypical genitals at birth. (Increasingly this observation is made during the prenatal period by way of imaging procedures such as ultrasound.) These infants then undergo extensive medical diagnostic procedures. After consultation among the family and health professionals—during which the specific diagnosis, physical and hormonal findings, and feedback from long-term outcome studies (Cohen-Kettenis, 2005; Dessens, Slijper, & Drop, 2005; Jurgensen, Hiort, Holterhus, & Thyen, 2007; Mazur, 2005; Meyer-Bahlburg, 2005; Stikkelbroeck et al., 2003; Wisniewski, Migeon, Malouf, & Gearhart, 2004) are considered—the newborn is assigned a sex, either male or female.

Other individuals with a DSD come to the attention of health professionals around the age of puberty through the observation of atypical development of secondary sex characteristics. This observation also leads to a specific medical evaluation.

The type of DSD and severity of the condition has significant implications for decisions about a patient's initial sex assignment, subsequent genital surgery, and other medical and psychosocial care (Meyer-Bahlburg, 2009). For instance, the degree of prenatal androgen exposure in individuals with a DSD has been correlated with the degree of masculinization of gender-related *behavior* (that is, *gender role and expression*); however, the correlation is only moderate, and considerable behavioral variability remains unaccounted for by prenatal androgen exposure (Jurgensen et al., 2007; Meyer-Bahlburg, Dolezal, Baker, Ehrhardt, & New, 2006). Notably, a similar correlation of prenatal hormone exposure with gender *identity* has not been demonstrated (e.g., Meyer-Bahlburg et al., 2004). This is underlined by the fact that people with the same (core) gender identity can vary widely in the degree of masculinization of their gender-related behavior.

Assessment and Treatment of Gender Dysphoria in People with Disorders of Sex Development

Very rarely are individuals with a DSD identified as having gender dysphoria *before* a DSD diagnosis has been made. Even so, a DSD diagnosis is typically apparent with an appropriate history and basic physical exam—both of which are part of a medical evaluation for the appropriateness of hormone therapy or surgical interventions for gender dysphoria. Mental health professionals should ask their clients presenting with gender dysphoria to have a physical exam, particularly if they are not currently seeing a primary care (or other health care) provider.

Most people with a DSD who are born with genital ambiguity do not develop gender dysphoria (e.g., Meyer-Bahlburg, Dolezal, et al., 2004; Wisniewski et al., 2004). However, some people with a DSD will develop chronic gender dysphoria and even undergo a change in their birth-assigned sex and/or their gender role (Meyer-Bahlburg, 2005; Wilson, 1999; Zucker, 1999). If there are persistent and strong indications that gender dysphoria is present, a comprehensive evaluation by clinicians skilled in the assessment and treatment of gender dysphoria is essential, irrespective of the patient's age. Detailed recommendations have been published for conducting such an assessment and for making treatment decisions to address gender dysphoria in the context of a DSD (Meyer-Bahlburg, 2011). Only after thorough assessment should steps be taken in the direction of changing a patient's birth-assigned sex or gender role.

Clinicians assisting these patients with treatment options to alleviate gender dysphoria may profit from the insights gained from providing care to patients without a DSD (Cohen-Kettenis, 2010).

However, certain criteria for treatment (e.g., age, duration of experience with living in the desired gender role) are usually not routinely applied to people with a DSD; rather, the criteria are interpreted in light of a patient's specific situation (Meyer-Bahlburg, 2011). In the context of a DSD, changes in birth-assigned sex and gender role have been made at any age between early elementary-school age and middle adulthood. Even genital surgery may be performed much earlier in these patients than in gender dysphoric individuals without a DSD if the surgery is well justified by the diagnosis, by the evidence-based gender-identity prognosis for the given syndrome and syndrome severity, and by the patient's wishes.

One reason for these treatment differences is that genital surgery in individuals with a DSD is quite common in infancy and adolescence. Infertility may already be present due to either early gonadal failure or to gonadectomy because of a malignancy risk. Even so, it is advisable for patients with a DSD to undergo a full social transition to another gender role only if there is a long-standing history of gender-atypical behavior, and if gender dysphoria and/or the desire to change one's gender role has been strong and persistent for a considerable period of time. Six months is the time period of full symptom expression required for the application of the gender dysphoria diagnosis proposed for *DSM-5* (Meyer-Bahlburg, 2011).

Additional Resources

The gender-relevant medical histories of people with a DSD are often complex. Their histories may include a great variety of inborn genetic, endocrine, and somatic atypicalities, as well as various hormonal, surgical, and other medical treatments. For this reason, many additional issues need to be considered in the psychosocial and medical care of such patients, regardless of the presence of gender dysphoria. Consideration of these issues is beyond what can be covered in the SOC. The interested reader is referred to existing publications (e.g., Cohen-Kettenis & Pfäfflin, 2003; Meyer-Bahlburg, 2002, 2008). Some families and patients also find it useful to consult or work with community support groups.

There is a very substantial medical literature on the medical management of patients with a DSD. Much of this literature has been produced by high-level specialists in pediatric endocrinology and urology, with input from specialized mental health professionals, especially in the area of gender. Recent international consensus conferences have addressed evidence-based care guidelines (including issues of gender and of genital surgery) for DSD in general (Hughes et al., 2006) and specifically for Congenital Adrenal Hyperplasia (Joint LWPES/ESPE CAH Working Group et al., 2002; Speiser et al., 2010). Others have addressed the research needs for DSD in general (Meyer-Bahlburg & Blizzard, 2004) and for selected syndromes such as 46,XXY (Simpson et al., 2003).



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The Standards of Care
VERSION 7

APPENDIX A

GLOSSARY

Terminology in the area of health care for transsexual, transgender, and gender-nonconforming people is rapidly evolving; new terms are being introduced, and the definitions of existing terms are changing. Thus, there is often misunderstanding, debate, or disagreement about language in this field. Terms that may be unfamiliar or that have specific meanings in the SOC are defined below for the purpose of this document only. Others may adopt these definitions, but WPATH acknowledges that these terms may be defined differently in different cultures, communities, and contexts.

WPATH also acknowledges that many terms used in relation to this population are not ideal. For example, the terms *transsexual* and *transvestite*—and, some would argue, the more recent term *transgender*—have been applied to people in an objectifying fashion. Yet such terms have been more or less adopted by many people who are making their best effort to make themselves understood. By continuing to use these terms, WPATH intends only to ensure that concepts and processes are comprehensible, in order to facilitate the delivery of quality health care to transsexual, transgender, and gender-nonconforming people. WPATH remains open to new terminology that will further illuminate the experience of members of this diverse population and lead to improvements in health care access and delivery.

Bioidentical hormones: Hormones that are *structurally* identical to those found in the human body (ACOG Committee of Gynecologic Practice, 2005). The hormones used in bioidentical hormone therapy (BHT) are generally derived from plant sources and are structurally similar to endogenous human hormones, but they need to be commercially processed to become bioidentical.

Bioidentical compounded hormone therapy (BCHT): Use of hormones that are prepared, mixed, assembled, packaged, or labeled as a drug by a pharmacist and custom-made for a patient according to a physician's specifications. Government drug agency approval is not possible for each compounded product made for an individual consumer.

Cross-dressing (transvestism): Wearing clothing and adopting a gender role presentation that, in a given culture, is more typical of the other sex.

Disorders of sex development (DSD): Congenital conditions in which the development of chromosomal, gonadal, or anatomic sex is atypical. Some people strongly object to the “disorder” label and instead view these conditions as a matter of diversity (Diamond, 2009), preferring the terms *intersex* and *intersexuality*.

Female-to-Male (FtM): Adjective to describe individuals assigned female at birth who are changing or who have changed their body and/or gender role from birth-assigned female to a more masculine body or role.

Gender dysphoria: Distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b).

Gender identity: A person's intrinsic sense of being male (a boy or a man), female (a girl or woman), or an alternative gender (e.g., boygirl, girlboy, transgender, genderqueer, eunuch) (Bockting, 1999; Stoller, 1964).

Gender identity disorder: Formal diagnosis set forth by the *Diagnostic Statistical Manual of Mental Disorders, 4th Edition, Text Rev (DSM IV-TR)* (American Psychiatric Association, 2000). Gender identity disorder is characterized by a strong and persistent cross-gender identification and a persistent discomfort with one's sex or sense of inappropriateness in the gender role of that sex, causing clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Gender-nonconforming: Adjective to describe individuals whose gender identity, role, or expression differs from what is normative for their assigned sex in a given culture and historical period.

Gender role or expression: Characteristics in personality, appearance, and behavior that in a given culture and historical period are designated as masculine or feminine (that is, more typical of the male or female social role) (Ruble, Martin, & Berenbaum, 2006). While most individuals present socially in clearly masculine or feminine gender roles, some people present in an alternative gender role such as genderqueer or specifically transgender. All people tend to incorporate both masculine and feminine characteristics in their gender expression in varying ways and to varying degrees (Bockting, 2008).

Genderqueer: Identity label that may be used by individuals whose gender identity and/or role does not conform to a binary understanding of gender as limited to the categories of man or woman, male or female (Bockting, 2008).

Internalized transphobia: Discomfort with one's own transgender feelings or identity as a result of internalizing society's normative gender expectations.

Male-to-Female (MtF): Adjective to describe individuals assigned male at birth who are changing or who have changed their body and/or gender role from birth-assigned male to a more feminine body or role.

Natural hormones: Hormones that are derived from natural *sources* such as plants or animals. Natural hormones may or may not be bioidentical.

Sex: Sex is assigned at birth as male or female, usually based on the appearance of the external genitalia. When the external genitalia are ambiguous, other components of sex (internal genitalia, chromosomal and hormonal sex) are considered in order to assign sex (Grumbach, Hughes, & Conte, 2003; MacLaughlin & Donahoe, 2004; Money & Ehrhardt, 1972; Vilain, 2000). For most people, gender identity and expression are consistent with their sex assigned at birth; for transsexual, transgender, and gender-nonconforming individuals, gender identity or expression differ from their sex assigned at birth.

Sex reassignment surgery (gender affirmation surgery): Surgery to change primary and/or secondary sex characteristics to affirm a person's gender identity. Sex reassignment surgery can be an important part of medically necessary treatment to alleviate gender dysphoria.

Transgender: Adjective to describe a diverse group of individuals who cross or transcend culturally defined categories of gender. The gender identity of transgender people differs to varying degrees from the sex they were assigned at birth (Bockting, 1999).

Transition: Period of time when individuals change from the gender role associated with their sex assigned at birth to a different gender role. For many people, this involves learning how to live socially in another gender role; for others this means finding a gender role and expression that are most comfortable for them. Transition may or may not include feminization or masculinization of the body through hormones or other medical procedures. The nature and duration of transition are variable and individualized.

Transsexual: Adjective (often applied by the medical profession) to describe individuals who seek to change or who have changed their primary and/or secondary sex characteristics through feminizing or masculinizing medical interventions (hormones and/or surgery), typically accompanied by a permanent change in gender role.

APPENDIX B

OVERVIEW OF MEDICAL RISKS OF HORMONE THERAPY

The risks outlined below are based on two comprehensive, evidence-based literature reviews of masculinizing/feminizing hormone therapy (Feldman & Safer, 2009; Hembree et al., 2009), along with a large cohort study (Asscheman et al., 2011). These reviews can serve as detailed references for providers, along with other widely recognized, published clinical materials (e.g., Dahl et al., 2006; Ettner et al., 2007).

Risks of Feminizing Hormone Therapy (MtF)

Likely Increased Risk:

Venous thromboembolic disease

- Estrogen use increases the risk of venous thromboembolic events (VTE), particularly in patients who are over age 40, smokers, highly sedentary, obese, and who have underlying thrombophilic disorders.
- This risk is increased with the additional use of third generation progestins.
- This risk is decreased with use of the transdermal (versus oral) route of estradiol administration, which is recommended for patients at higher risk of VTE.

Cardiovascular, cerebrovascular disease

- Estrogen use increases the risk of cardiovascular events in patients over age 50 with underlying cardiovascular risk factors. Additional progestin use may increase this risk.

Lipids

- Oral estrogen use may markedly increase triglycerides in patients, increasing the risk of pancreatitis and cardiovascular events.
- Different routes of administration will have different metabolic effects on levels of HDL cholesterol, LDL cholesterol and lipoprotein(a).
- In general, clinical evidence suggests that MtF patients with pre-existing lipid disorders may benefit from the use of transdermal rather than oral estrogen.

Liver/gallbladder

- Estrogen and cyproterone acetate use may be associated with transient liver enzyme elevations and, rarely, clinical hepatotoxicity.
- Estrogen use increases the risk of cholelithiasis (gall stones) and subsequent cholecystectomy.

Possible Increased Risk:Type 2 diabetes mellitus

- Feminizing hormone therapy, particularly estrogen, may increase the risk of type 2 diabetes, particularly among patients with a family history of diabetes or other risk factors for this disease.

Hypertension

- Estrogen use may increase blood pressure, but the effect on incidence of overt hypertension is unknown.
- Spironolactone reduces blood pressure and is recommended for at-risk or hypertensive patients desiring feminization.

Prolactinoma

- Estrogen use increases the risk of hyperprolactinemia among MtF patients in the first year of treatment, but this risk is unlikely thereafter.
- High-dose estrogen use may promote the clinical appearance of preexisting but clinically unapparent prolactinoma.

Inconclusive or No Increased Risk:

Items in this category include those that may present risk, but for which the evidence is so minimal that no clear conclusion can be reached.

Breast cancer

- MtF persons who have taken feminizing hormones do experience breast cancer, but it is unknown how their degree of risk compares to that of persons born with female genitalia.
- Longer duration of feminizing hormone exposure (i.e., number of years taking estrogen preparations), family history of breast cancer, obesity (BMI >35), and the use of progestins likely influence the level of risk.

Other Side Effects of Feminizing Therapy:

The following effects may be considered minor or even desired, depending on the patient, but are clearly associated with feminizing hormone therapy.

Fertility and sexual function

- Feminizing hormone therapy may impair fertility.
- Feminizing hormone therapy may decrease libido.
- Feminizing hormone therapy reduces nocturnal erections, with variable impact on sexually stimulated erections.

Risks of Anti-Androgen Medications:

Feminizing hormone regimens often include a variety of agents that affect testosterone production or action. These include GnRH agonists, progestins (including cyproterone acetate), spironolactone, and 5-alpha reductase inhibitors. An extensive discussion of the specific risks of these agents is beyond the scope of the SOC. However, both spironolactone and cyproterone acetate are widely used and deserve some comment.

Cyproterone acetate is a progestational compound with anti-androgenic properties (Gooren, 2005; Levy et al., 2003). Although widely used in Europe, it is not approved for use in the United States because of concerns about hepatotoxicity (Thole, Manso, Salgueiro, Revuelta, & Hidalgo, 2004). Spironolactone is commonly used as an anti-androgen in feminizing hormone therapy, particularly in regions where cyproterone is not approved for use (Dahl et al., 2006; Moore et al., 2003; Tangpricha et al., 2003). Spironolactone has a long history of use in treating hypertension and congestive heart failure. Its common side effects include hyperkalemia, dizziness, and gastrointestinal symptoms (*Physicians' Desk Reference*, 2007).

Risks of Masculinizing Hormone Therapy (FtM)

Likely Increased Risk:

Polycythemia

- Masculinizing hormone therapy involving testosterone or other androgenic steroids increases the risk of polycythemia (hematocrit > 50%), particularly in patients with other risk factors.
- Transdermal administration and adaptation of dosage may reduce this risk.

Weight gain/visceral fat

- Masculinizing hormone therapy can result in modest weight gain, with an increase in visceral fat.

Possible Increased Risk:

Lipids

- Testosterone therapy decreases HDL, but variably affects LDL and triglycerides.
- Supraphysiologic (beyond normal male range) serum levels of testosterone, often found with extended intramuscular dosing, may worsen lipid profiles, whereas transdermal administration appears to be more lipid neutral.
- Patients with underlying polycystic ovarian syndrome or dyslipidemia may be at increased risk of worsening dyslipidemia with testosterone therapy.

Liver

- Transient elevations in liver enzymes may occur with testosterone therapy.
- Hepatic dysfunction and malignancies have been noted with oral methyltestosterone. However, methyltestosterone is no longer available in most countries and should no longer be used.

Psychiatric

Masculinizing therapy involving testosterone or other androgenic steroids may increase the risk of hypomanic, manic, or psychotic symptoms in patients with underlying psychiatric disorders that include such symptoms. This adverse event appears to be associated with higher doses or supraphysiologic blood levels of testosterone.

Inconclusive or No Increased Risk:

Items in this category include those that may present risk, but for which the evidence is so minimal that no clear conclusion can be reached.

Osteoporosis

- Testosterone therapy maintains or increases bone mineral density among FtM patients prior to oophorectomy, at least in the first three years of treatment.
- There is an increased risk of bone density loss after oophorectomy, particularly if testosterone therapy is interrupted or insufficient. This includes patients utilizing solely oral testosterone.

Cardiovascular

- Masculinizing hormone therapy at normal physiologic doses does not appear to increase the risk of cardiovascular events among healthy patients.
- Masculinizing hormone therapy may increase the risk of cardiovascular disease in patients with underlying risks factors.

Hypertension

- Masculinizing hormone therapy at normal physiologic doses may increase blood pressure but does not appear to increase the risk of hypertension.
- Patients with risk factors for hypertension, such as weight gain, family history, or polycystic ovarian syndrome, may be at increased risk.

Type 2 diabetes mellitus

- Testosterone therapy does not appear to increase the risk of type 2 diabetes among FtM patients overall, unless other risk factors are present.
- Testosterone therapy may further increase the risk of type 2 diabetes in patients with other risk factors, such as significant weight gain, family history, and polycystic ovarian syndrome. There are no data that suggest or show an increase in risk in those with risk factors for dyslipidemia.

Breast cancer

- Testosterone therapy in FtM patients does not increase the risk of breast cancer.

Cervical cancer

- Testosterone therapy in FtM patients does not increase the risk of cervical cancer, although it may increase the risk of minimally abnormal Pap smears due to atrophic changes.

Ovarian cancer

- Analogous to persons born with female genitalia with elevated androgen levels, testosterone therapy in FtM patients may increase the risk of ovarian cancer, although evidence is limited.

Endometrial (uterine) cancer

- Testosterone therapy in FtM patients may increase the risk of endometrial cancer, although evidence is limited.

Other Side Effects of Masculinizing Therapy:

The following effects may be considered minor or even desired, depending on the patient, but are clearly associated with masculinization.

Fertility and sexual function

- Testosterone therapy in FtM patients reduces fertility, although the degree and reversibility are unknown.

- Testosterone therapy can induce permanent anatomic changes in the developing embryo or fetus.
- Testosterone therapy induces clitoral enlargement and increases libido.

Acne, androgenic alopecia

Acne and varying degrees of male pattern hair loss (androgenic alopecia) are common side effects of masculinizing hormone therapy.

APPENDIX C

SUMMARY OF CRITERIA FOR HORMONE THERAPY AND SURGERIES

As for all previous versions of the SOC, the criteria put forth in the SOC for hormone therapy and surgical treatments for gender dysphoria are clinical guidelines; individual health professionals and programs may modify them. Clinical departures from the SOC may come about because of a patient's unique anatomic, social, or psychological situation; an experienced health professional's evolving method of handling a common situation; a research protocol; lack of resources in various parts of the world; or the need for specific harm-reduction strategies. These departures should be recognized as such, explained to the patient, and documented through informed consent for quality patient care and legal protection. This documentation is also valuable to accumulate new data, which can be retrospectively examined to allow for health care—and the SOC—to evolve.

Criteria for Feminizing/Masculinizing Hormone Therapy (One Referral or Chart Documentation of Psychosocial Assessment)

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to give consent for treatment;
3. Age of majority in a given country (if younger, follow the SOC for children and adolescents);
4. If significant medical or mental concerns are present, they must be reasonably well controlled.

Criteria for Breast/Chest Surgery (One Referral)

Mastectomy and Creation of a Male Chest in FtM Patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to give consent for treatment;
3. Age of majority in a given country (if younger, follow the SOC for children and adolescents);
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.

Hormone therapy is not a prerequisite.

Breast Augmentation (Implants/Lipofilling) in MtF Patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to give consent for treatment;
3. Age of majority in a given country (if younger, follow the SOC for children and adolescents);
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.

Although not an explicit criterion, it is recommended that MtF patients undergo feminizing hormone therapy (minimum 12 months) prior to breast augmentation surgery. The purpose is to maximize breast growth in order to obtain better surgical (aesthetic) results.

Criteria for Genital Surgery (Two Referrals)

Hysterectomy and Salpingo-Oophorectomy in FtM Patients and Orchiectomy in MtF Patients:

1. Persistent, well documented gender dysphoria;
2. Capacity to make a fully informed decision and to give consent for treatment;

3. Age of majority in a given country;
4. If significant medical or mental health concerns are present, they must be well controlled;
5. 12 continuous months of hormone therapy as appropriate to the patient's gender goals (unless hormones are not clinically indicated for the individual).

The aim of hormone therapy prior to gonadectomy is primarily to introduce a period of reversible estrogen or testosterone suppression, before a patient undergoes irreversible surgical intervention.

These criteria do not apply to patients who are having these surgical procedures for medical indications other than gender dysphoria.

Metoidioplasty or Phalloplasty in FtM Patients and Vaginoplasty in MtF Patients:

1. Persistent, well documented gender dysphoria;
2. Capacity to make a fully informed decision and to give consent for treatment;
3. Age of majority in a given country;
4. If significant medical or mental health concerns are present, they must be well controlled;
5. 12 continuous months of hormone therapy as appropriate to the patient's gender goals (unless hormones are not clinically indicated for the individual);
6. 12 continuous months of living in a gender role that is congruent with their gender identity.

Although not an explicit criterion, it is recommended that these patients also have regular visits with a mental health or other medical professional.

The criterion noted above for some types of genital surgeries—that is, that patients engage in 12 continuous months of living in a gender role that is congruent with their gender identity—is based on expert clinical consensus that this experience provides ample opportunity for patients to experience and socially adjust in their desired gender role, before undergoing irreversible surgery.

APPENDIX D

EVIDENCE FOR CLINICAL OUTCOMES OF THERAPEUTIC APPROACHES

One of the real supports for any new therapy is an outcome analysis. Because of the controversial nature of sex reassignment surgery, this type of analysis has been very important. Almost all of the outcome studies in this area have been retrospective.

One of the first studies to examine the post-treatment psychosocial outcomes of transsexual patients was done in 1979 at Johns Hopkins University School of Medicine and Hospital (USA) (J. K. Meyer & Reter, 1979). This study focused on patients' occupational, educational, marital, and domiciliary stability. The results revealed several significant changes with treatment. These changes were not seen as positive; rather, they showed that many individuals who had entered the treatment program were no better off or were worse off in many measures after participation in the program. These findings resulted in closure of the treatment program at that hospital/medical school (Abramowitz, 1986).

Subsequently, a significant number of health professionals called for a standard for eligibility for sex reassignment surgery. This led to the formulation of the original *Standards of Care* of the Harry Benjamin International Gender Dysphoria Association (now WPATH) in 1979.

In 1981, Pauly published results from a large retrospective study of people who had undergone sex reassignment surgery. Participants in that study had much better outcomes: Among 83 FtM patients, 80.7% had a satisfactory outcome (i.e., patient self report of "improved social and emotional adjustment"), 6.0% unsatisfactory. Among 283 MtF patients, 71.4% had a satisfactory outcome, 8.1% unsatisfactory. This study included patients who were treated before the publication and use of the *Standards of Care*.

Since the *Standards of Care* have been in place, there has been a steady increase in patient satisfaction and decrease in dissatisfaction with the outcome of sex reassignment surgery. Studies conducted after 1996 focused on patients who were treated according to the *Standards of Care*. The findings of Rehman and colleagues (1999) and Krege and colleagues (2001) are typical of this body of work; none of the patients in these studies regretted having had surgery, and most reported being satisfied with the cosmetic and functional results of the surgery. Even patients who develop severe surgical complications seldom regret having undergone surgery. Quality of surgical results is one of the best predictors of the overall outcome of sex reassignment (Lawrence, 2003). The vast majority of follow-up studies have shown an undeniable beneficial effect of sex reassignment surgery on postoperative outcomes such as subjective well being, cosmesis, and sexual function (De Cuypere et al., 2005; Garaffa, Christopher, & Ralph, 2010; Klein & Gorzalka, 2009), although the specific magnitude of benefit is uncertain from

the currently available evidence. One study (Emory, Cole, Avery, Meyer, & Meyer, 2003) even showed improvement in patient income.

One troubling report (Newfield et al., 2006) documented lower scores on quality of life (measured with the SF-36) for FtM patients than for the general population. A weakness of that study is that it recruited its 384 participants by a general email rather than a systematic approach, and the degree and type of treatment were not recorded. Study participants who were taking testosterone had typically been doing so for less than 5 years. Reported quality of life was higher for patients who had undergone breast/chest surgery than for those who had not ($p < .001$). (A similar analysis was not done for genital surgery.) In other work, Kuhn and colleagues (2009) used the King's Health Questionnaire to assess the quality of life of 55 transsexual patients at 15 years after surgery. Scores were compared to those of 20 healthy female control patients who had undergone abdominal/pelvic surgery in the past. Quality of life scores for transsexual patients were the same or better than those of control patients for some subscales (emotions, sleep, incontinence, symptom severity, and role limitation), but worse in other domains (general health, physical limitation, and personal limitation).

Two long-term observational studies, both retrospective, compared the mortality and psychiatric morbidity of transsexual adults to those of general population samples (Asscheman et al., 2011; Dhejne et al., 2011). An analysis of data from the Swedish National Board of Health and Welfare information registry found that individuals who had received sex reassignment surgery (191 MtF and 133 FtM) had significantly higher rates of mortality, suicide, suicidal behavior, and psychiatric morbidity than those for a nontranssexual control group matched on age, immigrant status, prior psychiatric morbidity, and birth sex (Dhejne et al., 2011). Similarly, a study in the Netherlands reported a higher total mortality rate, including incidence of suicide, in both pre- and post-surgery transsexual patients (966 MtF and 365 FtM) than in the general population of that country (Asscheman et al., 2011). Neither of these studies questioned the efficacy of sex reassignment; indeed, both lacked an adequate comparison group of transsexuals who either did not receive treatment or who received treatment other than genital surgery. Moreover, transsexual people in these studies were treated as far back as the 1970s. However, these findings do emphasize the need to have good long-term psychological and psychiatric care available for this population. More studies are needed that focus on the outcomes of current assessment and treatment approaches for gender dysphoria.

It is difficult to determine the effectiveness of hormones alone in the relief of gender dysphoria. Most studies evaluating the effectiveness of masculinizing/feminizing hormone therapy on gender dysphoria have been conducted with patients who have also undergone sex reassignment surgery. Favorable effects of therapies that included both hormones and surgery were reported in a comprehensive review of over 3000 patients in 79 studies (mostly observational) conducted between 1961 and 1991 (Eldh, Berg, & Gustafsson, 1997; Gijs & Brewaeys, 2007; Murad et al., 2010; Pfäfflin & Junge, 1998). Patients operated on after 1986 did better than those before 1986; this reflects significant improvement in surgical complications (Eldh et al., 1997). Most patients have reported improved psychosocial outcomes, ranging between 87% for MtF patients and 97% for FtM patients (Green & Fleming, 1990).

Similar improvements were found in a Swedish study in which “almost all patients were satisfied with sex reassignment at 5 years, and 86% were assessed by clinicians at follow-up as stable or improved in global functioning” (Johansson, Sundbom, Höjerback, & Bodlund, 2010). Weaknesses of these earlier studies are their retrospective design and use of different criteria to evaluate outcomes.

A prospective study conducted in the Netherlands evaluated 325 consecutive adult and adolescent subjects seeking sex reassignment (Smith, Van Goozen, Kuiper, & Cohen-Kettenis, 2005). Patients who underwent sex reassignment therapy (both hormonal and surgical intervention) showed improvements in their mean gender dysphoria scores, measured by the Utrecht Gender Dysphoria Scale. Scores for body dissatisfaction and psychological function also improved in most categories. Fewer than 2% of patients expressed regret after therapy. This is the largest prospective study to affirm the results from retrospective studies that a combination of hormone therapy and surgery improves gender dysphoria and other areas of psychosocial functioning. There is a need for further research on the effects of hormone therapy without surgery, and without the goal of maximum physical feminization or masculinization.

Overall, studies have been reporting a steady improvement in outcomes as the field becomes more advanced. Outcome research has mainly focused on the outcome of sex reassignment surgery. In current practice there is a range of identity, role, and physical adaptations that could use additional follow-up or outcome research (Institute of Medicine, 2011).

APPENDIX E

DEVELOPMENT PROCESS FOR THE STANDARDS OF CARE, VERSION 7

The process of developing *Standards of Care, Version 7* began when an initial SOC “work group” was established in 2006. Members were invited to examine specific sections of SOC, *Version 6*. For each section, they were asked to review the relevant literature, identify where research was lacking and needed, and recommend potential revisions to the SOC as warranted by new evidence. Invited papers were submitted by the following authors: Aaron Devor, Walter Bockting, George Brown, Michael Brownstein, Peggy Cohen-Kettenis, Griet DeCuypere, Petra DeSutter, Jamie Feldman, Lin Fraser, Arlene Istar Lev, Stephen Levine, Walter Meyer, Heino Meyer-Bahlburg, Stan Monstrey, Loren Schechter, Mick van Trotsenburg, Sam Winter, and Ken Zucker. Some of these authors chose to add co-authors to assist them in their task.

Initial drafts of these papers were due June 1, 2007. Most were completed by September 2007, with the rest completed by the end of 2007. These manuscripts were then submitted to the *International*

Journal of Transgenderism (IJT). Each underwent the regular *IJT* peer review process. The final papers were published in Volume 11 (1–4) in 2009, making them available for discussion and debate.

After these articles were published, an SOC Revision Committee was established by the WPATH Board of Directors in 2010. The Revision Committee was first charged with debating and discussing the *IJT* background papers through a Google website. A subgroup of the Revision Committee was appointed by the Board of Directors to serve as the Writing Group. This group was charged with preparing the first draft of SOC, *Version 7* and continuing to work on revisions for consideration by the broader Revision Committee. The Board also appointed an International Advisory Group of transsexual, transgender, and gender-nonconforming individuals to give input on the revision.

A technical writer was hired to (1) review all of the recommendations for revision—both the original recommendations as outlined in the *IJT* articles and additional recommendations that emanated from the online discussion—and (2) create a survey to solicit further input on these potential revisions. From the survey results, the Writing Group was able to discern where these experts stood in terms of areas of agreement and areas in need of more discussion and debate. The technical writer then (3) created a very rough first draft of SOC, *Version 7* for the Writing Group to consider and build on.

The Writing Group met on March 4 and 5, 2011 in a face-to-face expert consultation meeting. They reviewed all recommended changes and debated and came to consensus on various controversial areas. Decisions were made based on the best available science and expert consensus. These decisions were incorporated into the draft, and additional sections were written by the Writing Group with the assistance of the technical writer.

The draft that emerged from the consultation meeting was then circulated among the Writing Group and finalized with the help of the technical writer. Once this initial draft was finalized, it was circulated among the broader SOC Revision Committee and the International Advisory Group. Discussion was opened up on the Google website and a conference call was held to resolve issues. Feedback from these groups was considered by the Writing Group, who then made further revisions. Two additional drafts were created and posted on the Google website for consideration by the broader SOC Revision Committee and the International Advisory Group. Upon completion of these three iterations of review and revision, the final document was presented to the WPATH Board of Directors for approval. The Board of Directors approved this version on September 14, 2011.

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1. Costs of a professional technical writer;
2. Process of soliciting international input on proposed changes from gender identity professionals and the transgender community;
3. Working meeting of the Writing Group;
4. Process of gathering additional feedback and arriving at final expert consensus from the professional and transgender communities, the *Standards of Care, Version 7*, Revision Committee, and WPATH Board of Directors;
5. Costs of printing and distributing *Standards of Care, Version 7*, and posting a free downloadable copy on the WPATH website;
6. Plenary session to launch the *Standards of Care, Version 7*, at the 2011 WPATH Biennial Symposium in Atlanta, Georgia, USA.

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[†] All members of the *Standards of Care, Version 7* Revision Committee donated their time to work on this revision.

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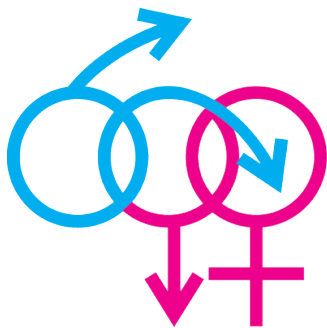
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WPATH WORLD PROFESSIONAL
ASSOCIATION for
TRANSGENDER HEALTH

21 December 2016

Position Statement on Medical Necessity of Treatment, Sex Reassignment, and Insurance Coverage in the U.S.A.

The World Professional Association for Transgender Health (WPATH) is an international, interdisciplinary, professional association devoted to the understanding and treatment of individuals with Gender Dysphoria (GD). Founded in 1979, and currently with over 1500 medical, mental health, social scientist, and legal professional members, all of whom are engaged in clinical practice and/or research that affects the lives of transgender and transsexual people, WPATH is the oldest professional association in the world that continuously has been concerned with this clinical specialty.

Gender Dysphoria (GD), often associated with transsexualism, is a condition recognized in the Diagnostic and Statistical Manual of Mental Disorders, (DSM-5, 2013), published by the American Psychiatric Association. Previous nomenclature for gender dysphoria includes transsexualism and gender identity disorder (GID), conditions which are also recognized in the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, published by the World Health Organization, of which the United States is a member. Nomenclature is subject to changes, and new terminology and classifications may be arrived at by various medical organizations or administrative bodies, but these events shall not in themselves change the meaning or intent of this WPATH statement.

The criteria currently listed for GD are descriptive of many people who experience dissonance between their sex as assigned at birth and their gender identity. Gender identity is common to all human beings, is developed in early childhood, and is thought to be firmly established in most people—transgender or not—by age 4,¹ though for some transgender individuals, gender identity may remain somewhat fluid for many years,² while for others, conditions specific to individual lives may constrain a person from acknowledging or even recognizing any gender dysphoria they may experience until they

¹ American Academy of Pediatrics, 1999.

² Fraser L and De Cuypere G, 2016.

are well into adulthood. The various The DSM-5 descriptive criteria for gender dysphoria were developed to aid in diagnosis and treatment to alleviate the clinically significant distress and impairment that is frequently, though not universally, associated with transsexual and transgender conditions.

The WPATH Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People (SOC) were first issued in 1979, and articulate the “professional consensus about the psychiatric, psychological, medical and surgical management of GD.” Periodically revised to reflect evolution in evidence-based clinical practice and scientific research, the Standards also unequivocally reflect this Association’s conclusion that treatment is medically necessary. The most recent version of the SOC (Version 7) was published in 2012.³ WPATH recommends that medical and mental health providers and administrators check www.wpath.org regularly to ensure they are working with the most up-to-date revision of the SOC.

MEDICAL NECESSITY is a term common to health care coverage and insurance policies in the United States. A common definition of medical necessity as used by insurers is:

“[H]ealth care services that a Physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are: (a) in accordance with generally accepted standards of medical practice; (b) clinically appropriate, in terms of type, frequency, extent, site and duration, and considered effective for the patient’s illness, injury, or disease; and (c) not primarily for the convenience of the patient, physician, or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.

“Generally accepted standards of medical practice means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.”⁴

The current Board of Directors of the WPATH herewith expresses its considered opinion based on clinical and peer reviewed evidence that gender affirming/confirming treatments and surgical procedures, properly indicated and performed as provided by the Standards of Care, have proven to be beneficial and effective in the treatment of individuals with transsexualism or gender dysphoria. Gender affirming/confirming surgery, also known as sex reassignment surgery, plays an undisputed role in contributing toward favorable outcomes. Treatment includes legal name and sex or gender change on identity

³ Coleman E, Bockting W, Botzer M, et al. 2012.

⁴ Definition from Blue Cross Blue Shield Settlement (Section 7.16(a)) available at www.hmosettlements.com

documents, as well as medically necessary hormone treatment, counseling, psychotherapy, and other medical procedures required to effectively treat an individual's gender dysphoria. Neither genital appearance nor reconstruction is required for social gender recognition, and so no surgery should be a prerequisite for identity document or record changes; changes to documentation so that identity documents reflect the individual's current lived expression and experience are crucial aids to social functioning, and can be a necessary component of the social transition and/or pre-surgical process. Delay of document changes may have a deleterious impact on a patient's social integration and personal safety.

In addition to hormonal balancing, medically necessary gender affirming/confirming surgical procedures are described in section XI of the SOC. These procedures include complete hysterectomy, bilateral mastectomy, chest reconstruction or augmentation as appropriate to each patient, including nipple resizing or placement of breast prostheses, as necessary; genital reconstruction by various techniques which must be appropriate to each patient, including, for example, skin flap hair removal, scrotoplasty, and penile and testicular prostheses, as necessary; facial hair removal, certain facial plastic reconstruction, voice therapy and/or surgery, and gender affirming counseling or psychotherapeutic treatment, as appropriate to the patient.

“Non-genital surgical procedures are routinely performed... notably, subcutaneous mastectomy in female-to-male transsexuals, and facial feminization surgery, and/or breast augmentation in male-to-female transsexuals. These surgical interventions are often of greater practical significance in the patient's daily life than reconstruction of the genitals.”⁵

It is important to understand that every patient will not have a medical need for identical procedures. Clinically appropriate treatments must be determined on an individualized and contextual basis, in consultation with the patient's medical providers.

The medical procedures attendant to gender affirming/confirming surgeries are not “cosmetic” or “elective” or “for the mere convenience of the patient.” These reconstructive procedures are not optional in any meaningful sense, but are understood to be medically necessary for the treatment of the diagnosed condition.⁶ In some cases, such surgery is the **only** effective treatment for the condition, and for some people genital surgery is essential and life-saving.

These medical procedures and treatment protocols are not experimental: Decades of both clinical experience and medical research show they are essential to achieving well-being for the transsexual patient. For example, a recent study of female-to-male transsexuals

⁵ Monstrey S, De Cuypere G, Ettner R (eds). (2007).

⁶ Victoria L. Davidson v. Aetna Insurance. (1979). Judicial finding that “...the treatment and surgery...is of a medical nature and is feasible and required for the health and well-being of the patient.”

found significantly improved quality of life following cross-gender hormonal therapy.⁷ Moreover, those who had also undergone chest reconstruction had significantly higher scores for general health, social functioning, as well as mental health.⁸

“[Hormone therapy and surgical] SRS [sex reassignment surgery] is an effective treatment for transsexualism and the only treatment that has been evaluated empirically with large clinical case series.”⁹

Available routinely in the United States and in many other countries, these treatments are cost effective rather than cost prohibitive. In the United States, numerous large employers (e.g., City and County of San Francisco, University of California, Emory University, University of Michigan, IBM, Johnson & Johnson, Bank of America, Apple, and hundreds more¹⁰) have negotiated contracts with their insurance carriers to enable medically necessary treatment for transsexualism and/or GD to be provided to covered individuals. As more carriers realize the validity and effectiveness of treatment (Aetna, Cigna, United Healthcare, and many others now have medical guidelines for transgender care), coverage is being offered, often at very low or no additional premium cost.¹¹ More than 15 states currently have regulations in place prohibiting insurance carriers from offering policies that contain exclusions restricting transgender people from accessing needed healthcare.¹² Further, in a decision rendered 30 May 2014, the US Department of Health and Human Services Departmental Appeals Board found that “transsexual surgery” should not be considered experimental or dangerous as it has been proven to be an effective treatment for gender dysphoria when properly diagnosed and administered, lifting a longstanding Medicare program ban on this treatment.¹³ More recently, in June, 2016, the Department of Defense lifted its ban on transgender military service, and will offer medically necessary hormone and surgical therapies for transgender active duty and reserve servicemen and women.¹⁴

⁷ Keo-Meier C L, et al. (2014).

⁸ Newfield E, et al. (2006).

⁹ Gijs L & Brewaeys A. (2007).

¹⁰ See the latest Corporate Equality Index, maintained by the Human Rights Campaign Workplace Project at www.hrc.org for the list of companies that have scored 100% in current and past years (since 2002).

¹¹ Herman JL. (2013).

¹² See <http://www.transequality.org/blog/pennsylvania-makes-17-states-dc-banning-trans-health-exclusions-hawaii-likely-next-0> for further information.

¹³ www.hhs.gov/dab/decisions/dabdecisions/dab2576.pdf; last accessed 11-03-2016.

¹⁴ Department of Defense Instruction (DoDI) 1300.28, “In-Service Transition for Transgender Service Members,” June 30, 2016, and Directive-Type Memorandum (DTM) 16-005, “Military Service of Transgender Service Members,” June 30, 2016.

“Professionals who provide services to patients with gender conditions understand the necessity of SRS, and concur that it is reconstructive, and as such should be reimbursed, as would any other medically necessary treatment.”¹⁵

Professional associations that have issued statements in support of the WPATH Standards of Care include the American Medical Association, the Endocrine Society, the American Psychiatric Association, the American Psychological Association, the American Academy of Family Physicians, the National Commission of Correctional Health Care, the American Public Health Association, the National Association of Social Workers, the American College of Obstetrics and Gynecology, the American Society of Plastic Surgeons, and the World Health Organization.

The WPATH Board of Directors urges health insurance carriers and healthcare providers in the United States to eliminate transgender or transsexual exclusions from their policy documents and medical guidelines, and to provide coverage for transgender patients; also to include in their policy documents and medical guidelines the medically prescribed sex reassignment or gender affirming/confirming services necessary for subscribers’ treatment and well-being; and to ensure that ongoing healthcare, both routine and specialized, is readily accessible and affordable to all their subscribers on an equal basis.

¹⁵ Monstrey S, De Cuypere G, Ettner R (eds). (2007).

This position statement constitutes the professional and clinical opinions of the signers below, comprising all members of the WPATH Board of Directors and Executive Officers as of this date, 21 December 2016.

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Endocrine Treatment of Gender-Dysphoric/ Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline

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***Cosponsoring Associations:** American Association of Clinical Endocrinologists, American Society of Andrology, European Society for Pediatric Endocrinology, European Society of Endocrinology, Pediatric Endocrine Society, and World Professional Association for Transgender Health.

Objective: To update the "Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline," published by the Endocrine Society in 2009.

Participants: The participants include an Endocrine Society-appointed task force of nine experts, a methodologist, and a medical writer.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation approach to describe the strength of recommendations and the quality of evidence. The task force commissioned two systematic reviews and used the best available evidence from other published systematic reviews and individual studies.

Consensus Process: Group meetings, conference calls, and e-mail communications enabled consensus. Endocrine Society committees, members and cosponsoring organizations reviewed and commented on preliminary drafts of the guidelines.

Conclusion: Gender affirmation is multidisciplinary treatment in which endocrinologists play an important role. Gender-dysphoric/gender-incongruent persons seek and/or are referred to endocrinologists to develop the physical characteristics of the affirmed gender. They require a safe and effective hormone regimen that will (1) suppress endogenous sex hormone secretion determined by the person's genetic/gonadal sex and (2) maintain sex hormone levels within the normal range for the person's affirmed gender. Hormone treatment is not recommended for prepubertal gender-dysphoric/gender-incongruent persons. Those clinicians who recommend gender-affirming endocrine treatments—appropriately trained diagnosing clinicians (required), a mental health provider for adolescents (required) and mental health

professional for adults (recommended)—should be knowledgeable about the diagnostic criteria and criteria for gender-affirming treatment, have sufficient training and experience in assessing psychopathology, and be willing to participate in the ongoing care throughout the endocrine transition. We recommend treating gender-dysphoric/gender-incongruent adolescents who have entered puberty at Tanner Stage G2/B2 by suppression with gonadotropin-releasing hormone agonists. Clinicians may add gender-affirming hormones after a multidisciplinary team has confirmed the persistence of gender dysphoria/gender incongruence and sufficient mental capacity to give informed consent to this partially irreversible treatment. Most adolescents have this capacity by age 16 years old. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to age 16 years, although there is minimal published experience treating prior to 13.5 to 14 years of age. For the care of peripubertal youths and older adolescents, we recommend that an expert multidisciplinary team comprised of medical professionals and mental health professionals manage this treatment. The treating physician must confirm the criteria for treatment used by the referring mental health practitioner and collaborate with them in decisions about gender-affirming surgery in older adolescents. For adult gender-dysphoric/gender-incongruent persons, the treating clinicians (collectively) should have expertise in transgender-specific diagnostic criteria, mental health, primary care, hormone treatment, and surgery, as needed by the patient. We suggest maintaining physiologic levels of gender-appropriate hormones and monitoring for known risks and complications. When high doses of sex steroids are required to suppress endogenous sex steroids and/or in advanced age, clinicians may consider surgically removing natal gonads along with reducing sex steroid treatment. Clinicians should monitor both transgender males (female to male) and transgender females (male to female) for reproductive organ cancer risk when surgical removal is incomplete. Additionally, clinicians should persistently monitor adverse effects of sex steroids. For gender-affirming surgeries in adults, the treating physician must collaborate with and confirm the criteria for treatment used by the referring physician. Clinicians should avoid harming individuals (via hormone treatment) who have conditions other than gender dysphoria/gender incongruence and who may not benefit from the physical changes associated with this treatment. (*J Clin Endocrinol Metab* 102: 3869–3903, 2017)

Summary of Recommendations

1.0 Evaluation of youth and adults

- 1.1. We advise that only trained mental health professionals (MHPs) who meet the following criteria should diagnose gender dysphoria (GD)/gender incongruence in adults: (1) competence in using the Diagnostic and Statistical Manual of Mental Disorders (DSM) and/or the International Statistical Classification of Diseases and Related Health Problems (ICD) for diagnostic purposes, (2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings. (Ungraded Good Practice Statement)

- 1.2. We advise that only MHPs who meet the following criteria should diagnose GD/gender incongruence in children and adolescents: (1) training in child and adolescent developmental psychology and psychopathology, (2) competence in using the DSM and/or the ICD for diagnostic purposes, (3) the ability to make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (4) training in diagnosing psychiatric conditions, (5) the ability to undertake or refer for appropriate treatment, (6) the ability to psychosocially assess the person's understanding and social conditions that can impact gender-affirming hormone therapy, (7) a practice of regularly attending relevant professional meetings, and (8) knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents. (Ungraded Good Practice Statement)
- 1.3. We advise that decisions regarding the social transition of prepubertal youths with GD/gender incongruence are made with the assistance of an MHP or another experienced professional. (Ungraded Good Practice Statement).

- 1.4. We recommend against puberty blocking and gender-affirming hormone treatment in pre-pubertal children with GD/gender incongruence. (1 ⊕⊕○○)
- 1.5. We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults. (1 ⊕⊕⊕○)

2.0 Treatment of adolescents

- 2.1. We suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment, and are requesting treatment should initially undergo treatment to suppress pubertal development. (2 ⊕⊕○○)
- 2.2. We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty. (2 ⊕⊕○○)
- 2.3. We recommend that, where indicated, GnRH analogues are used to suppress pubertal hormones. (1 ⊕⊕○○)
- 2.4. In adolescents who request sex hormone treatment (given this is a partly irreversible treatment), we recommend initiating treatment using a gradually increasing dose schedule after a multidisciplinary team of medical and MHPs has confirmed the persistence of GD/gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years. (1 ⊕⊕○○).
- 2.5. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to the age of 16 years in some adolescents with GD/gender incongruence, even though there are minimal published studies of gender-affirming hormone treatments administered before age 13.5 to 14 years. As with the care of adolescents ≥16 years of age, we recommend that an expert multidisciplinary team of medical and MHPs manage this treatment. (1 ⊕○○○)
- 2.6. We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment. (2 ⊕⊕○○)

3.0 Hormonal therapy for transgender adults

- 3.1. We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and

the criteria for the endocrine phase of gender transition before beginning treatment. (1 ⊕⊕⊕○)

- 3.2. We recommend that clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment. (1 ⊕⊕⊕○)
- 3.3. We suggest that clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender. (2 ⊕⊕○○)
- 3.4. We suggest that endocrinologists provide education to transgender individuals undergoing treatment about the onset and time course of physical changes induced by sex hormone treatment. (2 ⊕○○○)

4.0 Adverse outcome prevention and long-term care

- 4.1. We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every 3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly. (2 ⊕⊕○○)
- 4.2. We suggest periodically monitoring prolactin levels in transgender females treated with estrogens. (2 ⊕⊕○○)
- 4.3. We suggest that clinicians evaluate transgender persons treated with hormones for cardiovascular risk factors using fasting lipid profiles, diabetes screening, and/or other diagnostic tools. (2 ⊕⊕○○)
- 4.4. We recommend that clinicians obtain bone mineral density (BMD) measurements when risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. (1 ⊕⊕○○)
- 4.5. We suggest that transgender females with no known increased risk of breast cancer follow breast-screening guidelines recommended for non-transgender females. (2 ⊕⊕○○)
- 4.6. We suggest that transgender females treated with estrogens follow individualized screening according to personal risk for prostatic disease and prostate cancer. (2 ⊕○○○)
- 4.7. We advise that clinicians determine the medical necessity of including a total hysterectomy and oophorectomy as part of gender-affirming surgery. (Ungraded Good Practice Statement)

5.0 Surgery for sex reassignment and gender confirmation

- 5.1. We recommend that a patient pursue genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically necessary and would benefit the patient's overall health and/or well-being. (1 ⊕⊕○○)
- 5.2. We advise that clinicians approve genital gender-affirming surgery only after completion of at least 1 year of consistent and compliant hormone treatment, unless hormone therapy is not desired or medically contraindicated. (Ungraded Good Practice Statement)
- 5.3. We advise that the clinician responsible for endocrine treatment and the primary care provider ensure appropriate medical clearance of transgender individuals for genital gender-affirming surgery and collaborate with the surgeon regarding hormone use during and after surgery. (Ungraded Good Practice Statement)
- 5.4. We recommend that clinicians refer hormone-treated transgender individuals for genital surgery when: (1) the individual has had a satisfactory social role change, (2) the individual is satisfied about the hormonal effects, and (3) the individual desires definitive surgical changes. (1 ⊕○○○)
- 5.5. We suggest that clinicians delay gender-affirming genital surgery involving gonadectomy and/or hysterectomy until the patient is at least 18 years old or legal age of majority in his or her country. (2 ⊕⊕○○)
- 5.6. We suggest that clinicians determine the timing of breast surgery for transgender males based upon the physical and mental health status of the individual. There is insufficient evidence to recommend a specific age requirement. (2 ⊕○○○)

Changes Since the Previous Guideline

Both the current guideline and the one published in 2009 contain similar sections. Listed here are the sections contained in the current guideline and the corresponding number of recommendations: Introduction, Evaluation of Youth and Adults (5), Treatment of Adolescents (6), Hormonal Therapy for Transgender Adults (4), Adverse Outcomes Prevention and Long-term Care (7), and Surgery for Sex Reassignment and Gender Confirmation (6). The current introduction updates the diagnostic classification of “gender dysphoria/gender incongruence.” It also reviews the development of “gender identity” and summarizes its natural development. The section on

clinical evaluation of both youth and adults, defines in detail the professional qualifications required of those who diagnose and treat both adolescents and adults. We advise that decisions regarding the social transition of prepubertal youth are made with the assistance of a mental health professional or similarly experienced professional. We recommend against puberty blocking followed by gender-affirming hormone treatment of prepubertal children. Clinicians should inform pubertal children, adolescents, and adults seeking gender-confirming treatment of their options for fertility preservation. Prior to treatment, clinicians should evaluate the presence of medical conditions that may be worsened by hormone depletion and/or treatment. A multidisciplinary team, preferably composed of medical and mental health professionals, should monitor treatments. Clinicians evaluating transgender adults for endocrine treatment should confirm the diagnosis of persistent gender dysphoria/gender incongruence. Physicians should educate transgender persons regarding the time course of steroid-induced physical changes. Treatment should include periodic monitoring of hormone levels and metabolic parameters, as well as assessments of bone density and the impact upon prostate, gonads, and uterus. We also make recommendations for transgender persons who plan genital gender-affirming surgery.

Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee (CGS) of the Endocrine Society deemed the diagnosis and treatment of individuals with GD/gender incongruence a priority area for revision and appointed a task force to formulate evidence-based recommendations. The task force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation group, an international group with expertise in the development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The task force used the best available research evidence to develop the recommendations. The task force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase “we recommend” and the number 1, and weak recommendations use the phrase “we suggest” and the number 2. Cross-filled circles indicate the quality of the evidence, such that ⊕○○○ denotes very low-quality evidence; ⊕⊕○○, low quality; ⊕⊕⊕○, moderate quality; and ⊕⊕⊕⊕, high quality. The task force has confidence that persons who receive care according to the strong recommendations will derive, on average, more benefit than harm. Weak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence and the

values that the task force considered in making the recommendation. In some instances, there are remarks in which the task force offers technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the task force and their preferences; therefore, one should consider these remarks as suggestions.

In this guideline, the task force made several statements to emphasize the importance of shared decision-making, general preventive care measures, and basic principles of the treatment of transgender persons. They labeled these “Ungraded Good Practice Statement.” Direct evidence for these statements was either unavailable or not systematically appraised and considered out of the scope of this guideline. The intention of these statements is to draw attention to these principles.

The Endocrine Society maintains a rigorous conflict-of-interest review process for developing clinical practice guidelines. All task force members must declare any potential conflicts of interest by completing a conflict-of-interest form. The CGS reviews all conflicts of interest before the Society’s Council approves the members to participate on the task force and periodically during the development of the guideline. All others participating in the guideline’s development must also disclose any conflicts of interest in the matter under study, and most of these participants must be without any conflicts of interest. The CGS and the task force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined as remuneration in any amount from commercial interests; grants; research support; consulting fees; salary; ownership interests [e.g., stocks and stock options (excluding diversified mutual funds)]; honoraria and other payments for participation in speakers’ bureaus, advisory boards, or boards of directors; and all other financial benefits. Completed forms are available through the Endocrine Society office.

The Endocrine Society provided the funding for this guideline; the task force received no funding or remuneration from commercial or other entities.

Commissioned Systematic Review

The task force commissioned two systematic reviews to support this guideline. The first one aimed to summarize the available evidence on the effect of sex steroid use in transgender individuals on lipids and cardiovascular outcomes. The review identified 29 eligible studies at moderate risk of bias. In transgender males (female to male), sex steroid therapy was associated with a statistically significant increase in serum triglycerides and low-density lipoprotein cholesterol levels. High-density lipoprotein cholesterol levels decreased significantly across all follow-up time periods. In transgender females (male to female), serum triglycerides were significantly higher without any changes in other parameters. Few myocardial infarction, stroke, venous thromboembolism (VTE), and death events were reported. These events were more frequent in transgender females. However, the

quality of the evidence was low. The second review summarized the available evidence regarding the effect of sex steroids on bone health in transgender individuals and identified 13 studies. In transgender males, there was no statistically significant difference in the lumbar spine, femoral neck, or total hip BMD at 12 and 24 months compared with baseline values before initiating masculinizing hormone therapy. In transgender females, there was a statistically significant increase in lumbar spine BMD at 12 months and 24 months compared with baseline values before initiation of feminizing hormone therapy. There was minimal information on fracture rates. The quality of evidence was also low.

Introduction

Throughout recorded history (in the absence of an endocrine disorder) some men and women have experienced confusion and anguish resulting from rigid, forced conformity to sexual dimorphism. In modern history, there have been numerous ongoing biological, psychological, cultural, political, and sociological debates over various aspects of gender variance. The 20th century marked the emergence of a social awakening for men and women with the belief that they are “trapped” in the wrong body (3). Magnus Hirschfeld and Harry Benjamin, among others, pioneered the medical responses to those who sought relief from and a resolution to their profound discomfort. Although the term transsexual became widely known after Benjamin wrote “The Transsexual Phenomenon” (4), it was Hirschfeld who coined the term “transsexual” in 1923 to describe people who want to live a life that corresponds with their experienced gender vs their designated gender (5). Magnus Hirschfeld (6) and others (4, 7) have described other types of trans phenomena besides transsexualism. These early researchers proposed that the gender identity of these people was located somewhere along a unidimensional continuum. This continuum ranged from all male through “something in between” to all female. Yet such a classification does not take into account that people may have gender identities outside this continuum. For instance, some experience themselves as having both a male and female gender identity, whereas others completely renounce any gender classification (8, 9). There are also reports of individuals experiencing a continuous and rapid involuntary alternation between a male and female identity (10) or men who do not experience themselves as men but do not want to live as women (11, 12). In some countries, (e.g., Nepal, Bangladesh, and Australia), these nonmale or nonfemale genders are officially recognized (13). Specific treatment protocols, however, have not yet been developed for these groups.

Instead of the term transsexualism, the current classification system of the American Psychiatric Association uses the term gender dysphoria in its diagnosis of persons who are not satisfied with their designated gender (14). The current version of the World Health Organization's ICD-10 still uses the term transsexualism when diagnosing adolescents and adults. However, for the ICD-11, the World Health Organization has proposed using the term "gender incongruence" (15).

Treating persons with GD/gender incongruence (15) was previously limited to relatively ineffective elixirs or creams. However, more effective endocrinology-based treatments became possible with the availability of testosterone in 1935 and diethylstilbestrol in 1938. Reports of individuals with GD/gender incongruence who were treated with hormones and gender-affirming surgery appeared in the press during the second half of the 20th century. The Harry Benjamin International Gender Dysphoria Association was founded in September 1979 and is now called the World Professional Association for Transgender Health (WPATH). WPATH published its first Standards of Care in 1979. These standards have since been regularly updated, providing guidance for treating persons with GD/gender incongruence (16).

Prior to 1975, few peer-reviewed articles were published concerning endocrine treatment of transgender persons. Since then, more than two thousand articles about various aspects of transgender care have appeared.

It is the purpose of this guideline to make detailed recommendations and suggestions, based on existing medical literature and clinical experience, that will enable treating physicians to maximize benefit and minimize risk when caring for individuals diagnosed with GD/gender incongruence.

In the future, we need more rigorous evaluations of the effectiveness and safety of endocrine and surgical protocols. Specifically, endocrine treatment protocols for GD/gender incongruence should include the careful assessment of the following: (1) the effects of prolonged delay of puberty in adolescents on bone health, gonadal function, and the brain (including effects on cognitive, emotional, social, and sexual development); (2) the effects of treatment in adults on sex hormone levels; (3) the requirement for and the effects of progestins and other agents used to suppress endogenous sex steroids during treatment; and (4) the risks and benefits of gender-affirming hormone treatment in older transgender people.

To successfully establish and enact these protocols, a commitment of mental health and endocrine investigators is required to collaborate in long-term, large-scale

studies across countries that use the same diagnostic and inclusion criteria, medications, assay methods, and response assessment tools (*e.g.*, the European Network for the Investigation of Gender Incongruence) (17, 18).

Terminology and its use vary and continue to evolve. Table 1 contains the definitions of terms as they are used throughout this guideline.

Biological Determinants of Gender Identity Development

One's self-awareness as male or female changes gradually during infant life and childhood. This process of cognitive and affective learning evolves with interactions with parents, peers, and environment. A fairly accurate timetable exists outlining the steps in this process (19). Normative psychological literature, however, does not address if and when gender identity becomes crystallized and what factors contribute to the development of a gender identity that is not congruent with the gender of rearing. Results of studies from a variety of biomedical disciplines—genetic, endocrine, and neuroanatomic—support the concept that gender identity and/or gender expression (20) likely reflect a complex interplay of biological, environmental, and cultural factors (21, 22).

With respect to endocrine considerations, studies have failed to find differences in circulating levels of sex steroids between transgender and nontransgender individuals (23). However, studies in individuals with a disorder/difference of sex development (DSD) have informed our understanding of the role that hormones may play in gender identity outcome, even though most persons with GD/gender incongruence do not have a DSD. For example, although most 46,XX adult individuals with virilizing congenital adrenal hyperplasia caused by mutations in *CYP21A2* reported a female gender identity, the prevalence of GD/gender incongruence was much greater in this group than in the general population without a DSD. This supports the concept that there is a role for prenatal/postnatal androgens in gender development (24–26), although some studies indicate that prenatal androgens are more likely to affect gender behavior and sexual orientation rather than gender identity *per se* (27, 28).

Researchers have made similar observations regarding the potential role of androgens in the development of gender identity in other individuals with DSD. For example, a review of two groups of 46,XY persons, each with androgen synthesis deficiencies and female raised, reported transgender male (female-to-male) gender role changes in 56% to 63% and 39% to 64% of patients, respectively (29). Also, in 46,XY female-raised individuals with cloacal

Table 1. Definitions of Terms Used in This Guideline

<i>Biological sex, biological male or female:</i> These terms refer to physical aspects of maleness and femaleness. As these may not be in line with each other (e.g., a person with XY chromosomes may have female-appearing genitalia), the terms biological sex and biological male or female are imprecise and should be avoided.
<i>Cisgender:</i> This means not transgender. An alternative way to describe individuals who are not transgender is “non-transgender people.”
<i>Gender-affirming (hormone) treatment:</i> See “gender reassignment”
<i>Gender dysphoria:</i> This is the distress and unease experienced if gender identity and designated gender are not completely congruent (see Table 2). In 2013, the American Psychiatric Association released the fifth edition of the DSM-5, which replaced “gender identity disorder” with “gender dysphoria” and changed the criteria for diagnosis.
<i>Gender expression:</i> This refers to external manifestations of gender, expressed through one’s name, pronouns, clothing, haircut, behavior, voice, or body characteristics. Typically, transgender people seek to make their gender expression align with their gender identity, rather than their designated gender.
<i>Gender identity/experienced gender:</i> This refers to one’s internal, deeply held sense of gender. For transgender people, their gender identity does not match their sex designated at birth. Most people have a gender identity of man or woman (or boy or girl). For some people, their gender identity does not fit neatly into one of those two choices. Unlike gender expression (see below), gender identity is not visible to others.
<i>Gender identity disorder:</i> This is the term used for GD/gender incongruence in previous versions of DSM (see “gender dysphoria”). The ICD-10 still uses the term for diagnosing child diagnoses, but the upcoming ICD-11 has proposed using “gender incongruence of childhood.”
<i>Gender incongruence:</i> This is an umbrella term used when the gender identity and/or gender expression differs from what is typically associated with the designated gender. Gender incongruence is also the proposed name of the gender identity–related diagnoses in ICD-11. Not all individuals with gender incongruence have gender dysphoria or seek treatment.
<i>Gender variance:</i> See “gender incongruence”
<i>Gender reassignment:</i> This refers to the treatment procedure for those who want to adapt their bodies to the experienced gender by means of hormones and/or surgery. This is also called gender-confirming or gender-affirming treatment.
<i>Gender-reassignment surgery (gender-confirming/gender-affirming surgery):</i> These terms refer only to the surgical part of gender-confirming/gender-affirming treatment.
<i>Gender role:</i> This refers to behaviors, attitudes, and personality traits that a society (in a given culture and historical period) designates as masculine or feminine and/or that society associates with or considers typical of the social role of men or women.
<i>Sex designated at birth:</i> This refers to sex assigned at birth, usually based on genital anatomy.
<i>Sex:</i> This refers to attributes that characterize biological maleness or femaleness. The best known attributes include the sex-determining genes, the sex chromosomes, the H-Y antigen, the gonads, sex hormones, internal and external genitalia, and secondary sex characteristics.
<i>Sexual orientation:</i> This term describes an individual’s enduring physical and emotional attraction to another person. Gender identity and sexual orientation are not the same. Irrespective of their gender identity, transgender people may be attracted to women (gynephilic), attracted to men (androphilic), bisexual, asexual, or queer.
<i>Transgender:</i> This is an umbrella term for people whose gender identity and/or gender expression differs from what is typically associated with their sex designated at birth. Not all transgender individuals seek treatment.
<i>Transgender male (also: trans man, female-to-male, transgender male):</i> This refers to individuals assigned female at birth but who identify and live as men.
<i>Transgender woman (also: trans woman, male-to-female, transgender female):</i> This refers to individuals assigned male at birth but who identify and live as women.
<i>Transition:</i> This refers to the process during which transgender persons change their physical, social, and/or legal characteristics consistent with the affirmed gender identity. Prepubertal children may choose to transition socially.
<i>Transsexual:</i> This is an older term that originated in the medical and psychological communities to refer to individuals who have permanently transitioned through medical interventions or desired to do so.

exstrophy and penile agenesis, the occurrence of transgender male changes was significantly more prevalent than in the general population (30, 31). However, the fact that a high percentage of individuals with the same conditions did not change gender suggests that cultural factors may play a role as well.

With respect to genetics and gender identity, several studies have suggested heritability of GD/gender incongruence (32, 33). In particular, a study by Heylens *et al.* (33) demonstrated a 39.1% concordance rate for gender identity disorder (based on the DSM-IV criteria) in 23 monozygotic twin pairs but no concordance in 21 same-sex dizygotic or seven opposite-sex twin pairs. Although numerous investigators have sought to identify

specific genes associated with GD/gender incongruence, such studies have been inconsistent and without strong statistical significance (34–38).

Studies focusing on brain structure suggest that the brain phenotypes of people with GD/gender incongruence differ in various ways from control males and females, but that there is not a complete sex reversal in brain structures (39).

In summary, although there is much that is still unknown with respect to gender identity and its expression, compelling studies support the concept that biologic factors, in addition to environmental factors, contribute to this fundamental aspect of human development.

Natural History of Children With GD/Gender Incongruence

With current knowledge, we cannot predict the psychosexual outcome for any specific child. Prospective follow-up studies show that childhood GD/gender incongruence does not invariably persist into adolescence and adulthood (so-called “desisters”). Combining all outcome studies to date, the GD/gender incongruence of a minority of prepubertal children appears to persist in adolescence (20, 40). In adolescence, a significant number of these desisters identify as homosexual or bisexual. It may be that children who only showed some gender nonconforming characteristics have been included in the follow-up studies, because the DSM-IV text revision criteria for a diagnosis were rather broad. However, the persistence of GD/gender incongruence into adolescence is more likely if it had been extreme in childhood (41, 42). With the newer, stricter criteria of the DSM-5 (Table 2), persistence rates may well be different in future studies.

1.0 Evaluation of Youth and Adults

Gender-affirming treatment is a multidisciplinary effort. After evaluation, education, and diagnosis, treatment may include mental health care, hormone therapy, and/or surgical therapy. Together with an MHP, hormone-prescribing clinicians should examine the psychosocial impact of the potential changes on people’s lives, including mental health, friends, family, jobs, and their role in society. Transgender individuals should be encouraged to experience living in the new gender role and assess whether

this improves their quality of life. Although the focus of this guideline is gender-affirming hormone therapy, collaboration with appropriate professionals responsible for each aspect of treatment maximizes a successful outcome.

Diagnostic assessment and mental health care

GD/gender incongruence may be accompanied with psychological or psychiatric problems (43–51). It is therefore necessary that clinicians who prescribe hormones and are involved in diagnosis and psychosocial assessment meet the following criteria: (1) are competent in using the DSM and/or the ICD for diagnostic purposes, (2) are able to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) are trained in diagnosing psychiatric conditions, (4) undertake or refer for appropriate treatment, (5) are able to do a psychosocial assessment of the patient’s understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) regularly attend relevant professional meetings.

Because of the psychological vulnerability of many individuals with GD/gender incongruence, it is important that mental health care is available before, during, and sometimes also after transitioning. For children and adolescents, an MHP who has training/experience in child and adolescent gender development (as well as child and adolescent psychopathology) should make the diagnosis, because assessing GD/gender incongruence in children and adolescents is often extremely complex.

During assessment, the clinician obtains information from the individual seeking gender-affirming treatment. In the case

Table 2. DSM-5 Criteria for Gender Dysphoria in Adolescents and Adults

- A. A marked incongruence between one’s experienced/expressed gender and natal gender of at least 6 mo in duration, as manifested by at least two of the following:
 1. A marked incongruence between one’s experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)
 2. A strong desire to be rid of one’s primary and/or secondary sex characteristics because of a marked incongruence with one’s experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)
 3. A strong desire for the primary and/or secondary sex characteristics of the other gender
 4. A strong desire to be of the other gender (or some alternative gender different from one’s designated gender)
 5. A strong desire to be treated as the other gender (or some alternative gender different from one’s designated gender)
 6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one’s designated gender)
 - B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- Specify if:
1. The condition exists with a disorder of sex development.
 2. The condition is posttransitional, in that the individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one sex-related medical procedure or treatment regimen—namely, regular sex hormone treatment or gender reassignment surgery confirming the desired gender (*e.g.*, penectomy, vaginoplasty in natal males; mastectomy or phalloplasty in natal females).

of adolescents, the clinician also obtains information from the parents or guardians regarding various aspects of the child's general and psychosexual development and current functioning. On the basis of this information, the clinician:

- decides whether the individual fulfills criteria for treatment (see Tables 2 and 3) for GD/gender incongruence (DSM-5) or transsexualism (DSM-5 and/or ICD-10);
- informs the individual about the possibilities and limitations of various kinds of treatment (hormonal/surgical and nonhormonal), and if medical treatment is desired, provides correct information to prevent unrealistically high expectations;
- assesses whether medical interventions may result in unfavorable psychological and social outcomes.

In cases in which severe psychopathology, circumstances, or both seriously interfere with the diagnostic work or make satisfactory treatment unlikely, clinicians should assist the adolescent in managing these other issues. Literature on postoperative regret suggests that besides poor quality of surgery, severe psychiatric comorbidity and lack of support may interfere with positive outcomes (52–56).

For adolescents, the diagnostic procedure usually includes a complete psychodiagnostic assessment (57) and an assessment of the decision-making capability of the youth. An evaluation to assess the family's ability to endure stress, give support, and deal with the complexities of the adolescent's situation should be part of the diagnostic phase (58).

Social transitioning

A change in gender expression and role (which may involve living part time or full time in another gender role that is consistent with one's gender identity) may test the person's resolve, the capacity to function in the affirmed gender, and the adequacy of social, economic, and psychological supports. It assists both the individual and the clinician in their judgments about how to proceed (16). During social transitioning, the person's feelings about the social transformation (including coping with the responses of others) is a major focus of the counseling. The optimal timing for social transitioning may differ between individuals. Sometimes people wait until they

start gender-affirming hormone treatment to make social transitioning easier, but individuals increasingly start social transitioning long before they receive medically supervised, gender-affirming hormone treatment.

Criteria

Adolescents and adults seeking gender-affirming hormone treatment and surgery should satisfy certain criteria before proceeding (16). Criteria for gender-affirming hormone therapy for adults are in Table 4, and criteria for gender-affirming hormone therapy for adolescents are in Table 5. Follow-up studies in adults meeting these criteria indicate a high satisfaction rate with treatment (59). However, the quality of evidence is usually low. A few follow-up studies on adolescents who fulfilled these criteria also indicated good treatment results (60–63).

Recommendations for Those Involved in the Gender-Affirming Hormone Treatment of Individuals With GD/Gender Incongruence

- 1.1. We advise that only trained MHPs who meet the following criteria should diagnose GD/gender incongruence in adults: (1) competence in using the DSM and/or the ICD for diagnostic purposes, (2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings. (Ungraded Good Practice Statement)
- 1.2. We advise that only MHPs who meet the following criteria should diagnose GD/gender incongruence in children and adolescents: (1) training in child and adolescent developmental psychology and psychopathology, (2) competence in using the DSM and/or ICD for diagnostic

Table 3. ICD-10 Criteria for Transsexualism

Transsexualism (F64.0) has three criteria:

1. The desire to live and be accepted as a member of the opposite sex, usually accompanied by the wish to make his or her body as congruent as possible with the preferred sex through surgery and hormone treatments.
2. The transsexual identity has been present persistently for at least 2 y.
3. The disorder is not a symptom of another mental disorder or a genetic, DSD, or chromosomal abnormality.

Table 4. Criteria for Gender-Affirming Hormone Therapy for Adults

1. Persistent, well-documented gender dysphoria/gender incongruence
2. The capacity to make a fully informed decision and to consent for treatment
3. The age of majority in a given country (if younger, follow the criteria for adolescents)
4. Mental health concerns, if present, must be reasonably well controlled

Reproduced from World Professional Association for Transgender Health (16).

purposes, (3) the ability to make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (4) training in diagnosing psychiatric conditions, (5) the ability to undertake or refer for appropriate treatment, (6) the ability to psychosocially assess the person's understanding and social conditions that can impact gender-affirming hormone therapy, (7) a practice of regularly attending relevant professional meetings, and (8) knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents. (Ungraded Good Practice Statement)

Evidence

Individuals with gender identity issues may have psychological or psychiatric problems (43–48, 50, 51, 64, 65). It is therefore necessary that clinicians making the diagnosis are able to make a distinction between GD/gender incongruence and conditions that have similar features. Examples of conditions with similar features are body dysmorphic disorder, body identity integrity disorder (a condition in which individuals have a sense that their anatomical configuration as an able-bodied person is somehow wrong or inappropriate) (66), or certain forms of eunuchism (in which a person is preoccupied with or engages in castration and/or penectomy for

Table 5. Criteria for Gender-Affirming Hormone Therapy for Adolescents

Adolescents are eligible for GnRH agonist treatment if:

1. A qualified MHP has confirmed that:
 - the adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed),
 - gender dysphoria worsened with the onset of puberty,
 - any coexisting psychological, medical, or social problems that could interfere with treatment (*e.g.*, that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment,
 - the adolescent has sufficient mental capacity to give informed consent to this (reversible) treatment,
2. And the adolescent:
 - has been informed of the effects and side effects of treatment (including potential loss of fertility if the individual subsequently continues with sex hormone treatment) and options to preserve fertility,
 - has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,
3. And a pediatric endocrinologist or other clinician experienced in pubertal assessment
 - agrees with the indication for GnRH agonist treatment,
 - has confirmed that puberty has started in the adolescent (Tanner stage $\geq$ G2/B2),
 - has confirmed that there are no medical contraindications to GnRH agonist treatment.

Adolescents are eligible for subsequent sex hormone treatment if:

1. A qualified MHP has confirmed:
 - the persistence of gender dysphoria,
 - any coexisting psychological, medical, or social problems that could interfere with treatment (*e.g.*, that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start sex hormone treatment,
 - the adolescent has sufficient mental capacity (which most adolescents have by age 16 years) to estimate the consequences of this (partly) irreversible treatment, weigh the benefits and risks, and give informed consent to this (partly) irreversible treatment,
2. And the adolescent:
 - has been informed of the (irreversible) effects and side effects of treatment (including potential loss of fertility and options to preserve fertility),
 - has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,
3. And a pediatric endocrinologist or other clinician experienced in pubertal induction:
 - agrees with the indication for sex hormone treatment,
 - has confirmed that there are no medical contraindications to sex hormone treatment.

Reproduced from World Professional Association for Transgender Health (16).

reasons that are not gender identity related) (11). Clinicians should also be able to diagnose psychiatric conditions accurately and ensure that these conditions are treated appropriately, particularly when the conditions may complicate treatment, affect the outcome of gender-affirming treatment, or be affected by hormone use.

Values and preferences

The task force placed a very high value on avoiding harm from hormone treatment in individuals who have conditions other than GD/gender incongruence and who may not benefit from the physical changes associated with this treatment and placed a low value on any potential benefit these persons believe they may derive from hormone treatment. This justifies the good practice statement.

- 1.3. We advise that decisions regarding the social transition of prepubertal youths with GD/gender incongruence are made with the assistance of an MHP or another experienced professional. (Ungraded Good Practice Statement).
- 1.4. We recommend against puberty blocking and gender-affirming hormone treatment in prepubertal children with GD/gender incongruence. (1 ⊕⊕○○)

Evidence

In most children diagnosed with GD/gender incongruence, it did not persist into adolescence. The percentages differed among studies, probably dependent on which version of the DSM clinicians used, the patient's age, the recruitment criteria, and perhaps cultural factors. However, the large majority (about 85%) of prepubertal children with a childhood diagnosis did not remain GD/gender incongruent in adolescence (20). If children have completely socially transitioned, they may have great difficulty in returning to the original gender role upon entering puberty (40). Social transition is associated with the persistence of GD/gender incongruence as a child progresses into adolescence. It may be that the presence of GD/gender incongruence in prepubertal children is the earliest sign that a child is destined to be transgender as an adolescent/adult (20). However, social transition (in addition to GD/gender incongruence) has been found to contribute to the likelihood of persistence.

This recommendation, however, does not imply that children should be discouraged from showing gender-variant behaviors or should be punished for exhibiting such behaviors. In individual cases, an early complete social transition may result in a more favorable outcome, but there are currently no criteria to identify the

GD/gender-incongruent children to whom this applies. At the present time, clinical experience suggests that persistence of GD/gender incongruence can only be reliably assessed after the first signs of puberty.

Values and preferences

The task force placed a high value on avoiding harm with gender-affirming hormone therapy in prepubertal children with GD/gender incongruence. This justifies the strong recommendation in the face of low-quality evidence.

- 1.5. We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults. (1 ⊕⊕⊕○)

Remarks

Persons considering hormone use for gender affirmation need adequate information about this treatment in general and about fertility effects of hormone treatment in particular to make an informed and balanced decision (67, 68). Because young adolescents may not feel qualified to make decisions about fertility and may not fully understand the potential effects of hormonal interventions, consent and protocol education should include parents, the referring MHP(s), and other members of the adolescent's support group. To our knowledge, there are no formally evaluated decision aids available to assist in the discussion and decision regarding the future fertility of adolescents or adults beginning gender-affirming treatment.

Treating early pubertal youth with GnRH analogs will temporarily impair spermatogenesis and oocyte maturation. Given that an increasing number of transgender youth want to preserve fertility potential, delaying or temporarily discontinuing GnRH analogs to promote gamete maturation is an option. This option is often not preferred, because mature sperm production is associated with later stages of puberty and with the significant development of secondary sex characteristics.

For those designated male at birth with GD/gender incongruence and who are in early puberty, sperm production and the development of the reproductive tract are insufficient for the cryopreservation of sperm. However, prolonged pubertal suppression using GnRH analogs is reversible and clinicians should inform these individuals that sperm production can be initiated following prolonged gonadotropin suppression. This can be accomplished by spontaneous gonadotropin recovery after

cessation of GnRH analogs or by gonadotropin treatment and will probably be associated with physical manifestations of testosterone production, as stated above. Note that there are no data in this population concerning the time required for sufficient spermatogenesis to collect enough sperm for later fertility. In males treated for precocious puberty, spermatogenesis was reported 0.7 to 3 years after cessation of GnRH analogs (69). In adult men with gonadotropin deficiency, sperm are noted in seminal fluid by 6 to 12 months of gonadotropin treatment. However, sperm numbers when partners of these patients conceive are far below the “normal range” (70, 71).

In girls, no studies have reported long-term, adverse effects of pubertal suppression on ovarian function after treatment cessation (72, 73). Clinicians should inform adolescents that no data are available regarding either time to spontaneous ovulation after cessation of GnRH analogs or the response to ovulation induction following prolonged gonadotropin suppression.

In males with GD/gender incongruence, when medical treatment is started in a later phase of puberty or in adulthood, spermatogenesis is sufficient for cryopreservation and storage of sperm. *In vitro* spermatogenesis is currently under investigation. Restoration of spermatogenesis after prolonged estrogen treatment has not been studied.

In females with GD/gender incongruence, the effect of prolonged treatment with exogenous testosterone on ovarian function is uncertain. There have been reports of an increased incidence of polycystic ovaries in transgender males, both prior to and as a result of androgen treatment (74–77), although these reports were not confirmed by others (78). Pregnancy has been reported in transgender males who have had prolonged androgen treatment and have discontinued testosterone but have not had genital surgery (79, 80). A reproductive endocrine gynecologist can counsel patients before gender-affirming hormone treatment or surgery regarding potential fertility options (81). Techniques for cryopreservation of oocytes, embryos, and ovarian tissue continue to improve, and oocyte maturation of immature tissue is being studied (82).

2.0 Treatment of Adolescents

During the past decade, clinicians have progressively acknowledged the suffering of young adolescents with GD/gender incongruence. In some forms of GD/gender incongruence, psychological interventions may be useful and sufficient. However, for many adolescents with GD/gender incongruence, the pubertal physical changes are unbearable. As early medical intervention may prevent

psychological harm, various clinics have decided to start treating young adolescents with GD/gender incongruence with puberty-suppressing medication (a GnRH analog). As compared with starting gender-affirming treatment long after the first phases of puberty, a benefit of pubertal suppression at early puberty may be a better psychological and physical outcome.

In girls, the first physical sign of puberty is the budding of the breasts followed by an increase in breast and fat tissue. Breast development is also associated with the pubertal growth spurt, and menarche occurs ~2 years later. In boys, the first physical change is testicular growth. A testicular volume ≥ 4 mL is seen as consistent with the initiation of physical puberty. At the beginning of puberty, estradiol and testosterone levels are still low and are best measured in the early morning with an ultrasensitive assay. From a testicular volume of 10 mL, daytime testosterone levels increase, leading to virilization (83). Note that pubic hair and/or axillary hair/odor may not reflect the onset of gonadarche; instead, it may reflect adrenarche alone.

- 2.1. We suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment (Table 5), and are requesting treatment should initially undergo treatment to suppress pubertal development. (2 $\oplus\oplus\oplus\oplus$)
- 2.2. We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty (Tanner stages G2/B2). (2 $\oplus\oplus\oplus\oplus$)

Evidence

Pubertal suppression can expand the diagnostic phase by a long period, giving the subject more time to explore options and to live in the experienced gender before making a decision to proceed with gender-affirming sex hormone treatments and/or surgery, some of which is irreversible (84, 85). Pubertal suppression is fully reversible, enabling full pubertal development in the natal gender, after cessation of treatment, if appropriate. The experience of full endogenous puberty is an undesirable condition for the GD/gender-incongruent individual and may seriously interfere with healthy psychological functioning and well-being. Treating GD/gender-incongruent adolescents entering puberty with GnRH analogs has been shown to improve psychological functioning in several domains (86).

Another reason to start blocking pubertal hormones early in puberty is that the physical outcome is improved compared with initiating physical transition after puberty has been completed (60, 62). Looking like a man or woman when living as the opposite sex creates difficult

barriers with enormous life-long disadvantages. We therefore advise starting suppression in early puberty to prevent the irreversible development of undesirable secondary sex characteristics. However, adolescents with GD/gender incongruence should experience the first changes of their endogenous spontaneous puberty, because their emotional reaction to these first physical changes has diagnostic value in establishing the persistence of GD/gender incongruence (85). Thus, Tanner stage 2 is the optimal time to start pubertal suppression. However, pubertal suppression treatment in early puberty will limit the growth of the penis and scrotum, which will have a potential effect on future surgical treatments (87).

Clinicians can also use pubertal suppression in adolescents in later pubertal stages to stop menses in transgender males and prevent facial hair growth in transgender females. However, in contrast to the effects in early pubertal adolescents, physical sex characteristics (such as more advanced breast development in transgender boys and lowering of the voice and outgrowth of the jaw and brow in transgender girls) are not reversible.

Values and preferences

These recommendations place a high value on avoiding an unsatisfactory physical outcome when secondary sex characteristics have become manifest and irreversible, a higher value on psychological well-being, and a lower value on avoiding potential harm from early pubertal suppression.

Remarks

Table 6 lists the Tanner stages of breast and male genital development. Careful documentation of hallmarks of pubertal development will ensure precise timing when initiating pubertal suppression once puberty has started. Clinicians can use pubertal LH and sex steroid levels to confirm that puberty has progressed sufficiently before starting pubertal suppression (88). Reference

ranges for sex steroids by Tanner stage may vary depending on the assay used. Ultrasensitive sex steroid and gonadotropin assays will help clinicians document early pubertal changes.

Irreversible and, for GD/gender-incongruent adolescents, undesirable sex characteristics in female puberty are breasts, female body habitus, and, in some cases, relative short stature. In male puberty, they are a prominent Adam's apple; low voice; male bone configuration, such as a large jaw, big feet and hands, and tall stature; and male hair pattern on the face and extremities.

- 2.3. We recommend that, where indicated, GnRH analogues are used to suppress pubertal hormones. (1 ⊕ ⊕ ⊕ ⊕)

Evidence

Clinicians can suppress pubertal development and gonadal function most effectively via gonadotropin suppression using GnRH analogs. GnRH analogs are long-acting agonists that suppress gonadotropins by GnRH receptor desensitization after an initial increase of gonadotropins during ~10 days after the first and (to a lesser degree) the second injection (89). Antagonists immediately suppress pituitary gonadotropin secretion (90, 91). Long-acting GnRH analogs are the currently preferred treatment option. Clinicians may consider long-acting GnRH antagonists when evidence on their safety and efficacy in adolescents becomes available.

During GnRH analog treatment, slight development of secondary sex characteristics may regress, and in a later phase of pubertal development, it will stop. In girls, breast tissue will become atrophic, and menses will stop. In boys, virilization will stop, and testicular volume may decrease (92).

An advantage of using GnRH analogs is the reversibility of the intervention. If, after extensive exploration of his/her transition wish, the individual no longer desires transition, they can discontinue pubertal suppression. In subjects with

Table 6. Tanner Stages of Breast Development and Male External Genitalia

The description of Tanner stages for breast development:

1. Prepubertal
2. Breast and papilla elevated as small mound; areolar diameter increased
3. Breast and areola enlarged, no contour separation
4. Areola and papilla form secondary mound
5. Mature; nipple projects, areola part of general breast contour

For penis and testes:

1. Prepubertal, testicular volume <4 mL
2. Slight enlargement of penis; enlarged scrotum, pink, texture altered, testes 4–6 mL
3. Penis longer, testes larger (8–12 mL)
4. Penis and glans larger, including increase in breadth; testes larger (12–15 mL), scrotum dark
5. Penis adult size; testicular volume > 15 mL

Adapted from Lawrence (56).

precocious puberty, spontaneous pubertal development has been shown to resume after patients discontinue taking GnRH analogs (93).

Recommendations 2.1 to 2.3 are supported by a prospective follow-up study from The Netherlands. This report assessed mental health outcomes in 55 transgender adolescents/young adults (22 transgender females and 33 transgender males) at three time points: (1) before the start of GnRH agonist (average age of 14.8 years at start of treatment), (2) at initiation of gender-affirming hormones (average age of 16.7 years at start of treatment), and (3) 1 year after “gender-reassignment surgery” (average age of 20.7 years) (63). Despite a decrease in depression and an improvement in general mental health functioning, GD/gender incongruence persisted through pubertal suppression, as previously reported (86). However, following sex hormone treatment and gender-reassignment surgery, GD/gender incongruence was resolved and psychological functioning steadily improved (63). Furthermore, well-being was similar to or better than that reported by age-matched young adults from the general population, and none of the study participants regretted treatment. This study represents the first long-term follow-up of individuals managed according to currently existing clinical practice guidelines for transgender youth, and it underscores the benefit of the multidisciplinary approach pioneered in The Netherlands; however, further studies are needed.

Side effects

The primary risks of pubertal suppression in GD/gender-incongruent adolescents may include adverse effects on bone mineralization (which can theoretically be reversed with sex hormone treatment), compromised fertility if the person subsequently is treated with sex hormones, and unknown effects on brain development. Few data are available on the effect of GnRH analogs on BMD in adolescents with GD/gender incongruence. Initial data in GD/gender-incongruent subjects demonstrated no change of absolute areal BMD during 2 years of GnRH analog therapy but a decrease in BMD z scores (85). A recent study also suggested suboptimal bone mineral accrual during GnRH analog treatment. The study reported a decrease in areal BMD z scores and of bone mineral apparent density z scores (which takes the size of the bone into account) in 19 transgender males treated with GnRH analogs from a mean age of 15.0 years (standard deviation = 2.0 years) for a median duration of 1.5 years (0.3 to 5.2 years) and in 15 transgender females treated from 14.9 (± 1.9) years for 1.3 years (0.5 to 3.8 years), although not all changes were statistically significant (94). There was incomplete catch-up at age 22 years after sex hormone treatment from age 16.6 (± 1.4)

years for a median duration of 5.8 years (3.0 to 8.0 years) in transgender females and from age 16.4 (± 2.3) years for 5.4 years (2.8 to 7.8 years) in transgender males. Little is known about more prolonged use of GnRH analogs. Researchers reported normal BMD z scores at age 35 years in one individual who used GnRH analogs from age 13.7 years until age 18.6 years before initiating sex hormone treatment (65).

Additional data are available from individuals with late puberty or GnRH analog treatment of other indications. Some studies reported that men with constitutionally delayed puberty have decreased BMD in adulthood (95). However, other studies reported that these men have normal BMD (96, 97). Treating adults with GnRH analogs results in a decrease of BMD (98). In children with central precocious puberty, treatment with GnRH analogs has been found to result in a decrease of BMD during treatment by some (99) but not others (100). Studies have reported normal BMD after discontinuing therapy (69, 72, 73, 101, 102). In adolescents treated with growth hormone who are small for gestational age and have normal pubertal timing, 2-year GnRH analog treatments did not adversely affect BMD (103). Calcium supplementation may be beneficial in optimizing bone health in GnRH analog-treated individuals (104). There are no studies of vitamin D supplementation in this context, but clinicians should offer supplements to vitamin D-deficient adolescents. Physical activity, especially during growth, is important for bone mass in healthy individuals (103) and is therefore likely to be beneficial for bone health in GnRH analog-treated subjects.

GnRH analogs did not induce a change in body mass index standard deviation score in GD/gender-incongruent adolescents (94) but caused an increase in fat mass and decrease in lean body mass percentage (92). Studies in girls treated for precocious puberty also reported a stable body mass index standard deviation score during treatment (72) and body mass index and body composition comparable to controls after treatment (73).

Arterial hypertension has been reported as an adverse effect in a few girls treated with GnRH analogs for precocious/early puberty (105, 106). Blood pressure monitoring before and during treatment is recommended.

Individuals may also experience hot flashes, fatigue, and mood alterations as a consequence of pubertal suppression. There is no consensus on treatment of these side effects in this context.

It is recommended that any use of pubertal blockers (and subsequent use of sex hormones, as detailed below) include a discussion about implications for fertility (see recommendation 1.3). Transgender adolescents may

want to preserve fertility, which may be otherwise compromised if puberty is suppressed at an early stage and the individual completes phenotypic transition with the use of sex hormones.

Limited data are available regarding the effects of GnRH analogs on brain development. A single cross-sectional study demonstrated no compromise of executive function (107), but animal data suggest there may be an effect of GnRH analogs on cognitive function (108).

Values and preferences

Our recommendation of GnRH analogs places a higher value on the superior efficacy, safety, and reversibility of the pubertal hormone suppression achieved (as compared with the alternatives) and a relatively lower value on limiting the cost of therapy. Of the available alternatives, depot and oral progestin preparations are effective. Experience with this treatment dates back prior to the emergence of GnRH analogs for treating precocious puberty in papers from the 1960s and early 1970s (109–112). These compounds are usually safe, but some side effects have been reported (113–115). Only two recent studies involved transgender youth (116, 117). One of these studies described the use of oral lynestrenol monotherapy followed by the addition of testosterone treatment in transgender boys who were at Tanner stage B4 or further at the start of treatment (117). They found lynestrenol safe, but gonadotropins were not fully suppressed. The study reported metrorrhagia in approximately half of the individuals, mainly in the first 6 months. Acne, headache, hot flashes, and fatigue were other frequent side effects. Another progestin that has been studied in the United States is medroxyprogesterone. This agent is not as effective as GnRH analogs in lowering endogenous sex hormones either and may be associated with other side effects (116). Progestin preparations may be an acceptable treatment for persons without access to GnRH analogs or with a needle phobia. If GnRH analog treatment is not available (insurance denial, prohibitive cost, or other reasons), postpubertal, transgender female adolescents may be treated with an antiandrogen that directly suppresses androgen synthesis or action (see adult section).

Remarks

Measurements of gonadotropin and sex steroid levels give precise information about gonadal axis suppression, although there is insufficient evidence for any specific short-term monitoring scheme in children treated with GnRH analogs (88). If the gonadal axis is not completely suppressed—as evidenced by (for example) menses, erections, or progressive hair growth—the interval of GnRH analog treatment can be shortened or the dose increased. During treatment, adolescents should be monitored for negative effects of delaying puberty, including a halted growth spurt and impaired bone mineral accretion. Table 7 illustrates a suggested clinical protocol.

Anthropometric measurements and X-rays of the left hand to monitor bone age are informative for evaluating growth. To assess BMD, clinicians can perform dual-energy X-ray absorptiometry scans.

- 2.4. In adolescents who request sex hormone treatment (given this is a partly irreversible treatment), we recommend initiating treatment using a gradually increasing dose schedule (see Table 8) after a multidisciplinary team of medical and MHPs has confirmed the persistence of GD/gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years (Table 5). (1 ⊕⊕○○)
- 2.5. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to the age of 16 years in some adolescents with GD/gender incongruence, even though there are minimal published studies of gender-affirming hormone treatments administered before age 13.5 to 14 years. As with the care of adolescents ≥16 years of age, we recommend that an expert multidisciplinary team of medical and MHPs manage this treatment. (1 ⊕○○○)
- 2.6. We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment (Table 9). (2 ⊕⊕○○)

Table 7. Baseline and Follow-Up Protocol During Suppression of Puberty

Every 3–6 mo
Anthropometry: height, weight, sitting height, blood pressure, Tanner stages
Every 6–12 mo
Laboratory: LH, FSH, E2/T, 25OH vitamin D
Every 1–2 y
Bone density using DXA
Bone age on X-ray of the left hand (if clinically indicated)

Adapted from Hembree *et al.* (118).

Abbreviations: DXA, dual-energy X-ray absorptiometry; E2, estradiol; FSH, follicle stimulating hormone; LH, luteinizing hormone; T, testosterone;

Table 8. Protocol Induction of Puberty

Induction of female puberty with oral 17β -estradiol, increasing the dose every 6 mo:

5 $\mu\text{g/kg/d}$

10 $\mu\text{g/kg/d}$

15 $\mu\text{g/kg/d}$

20 $\mu\text{g/kg/d}$

Adult dose = 2–6 mg/d

In postpubertal transgender female adolescents, the dose of 17β -estradiol can be increased more rapidly:

1 mg/d for 6 mo

2 mg/d

Induction of female puberty with transdermal 17β -estradiol, increasing the dose every 6 mo (new patch is placed every 3.5 d):

6.25–12.5 $\mu\text{g/24 h}$ (cut 25- μg patch into quarters, then halves)

25 $\mu\text{g/24 h}$

37.5 $\mu\text{g/24 h}$

Adult dose = 50–200 $\mu\text{g/24 h}$

For alternatives once at adult dose, see Table 11.

Adjust maintenance dose to mimic physiological estradiol levels (see Table 15).

Induction of male puberty with testosterone esters increasing the dose every 6 mo (IM or SC):

25 $\text{mg/m}^2/2 \text{ wk}$ (or alternatively, half this dose weekly, or double the dose every 4 wk)

50 $\text{mg/m}^2/2 \text{ wk}$

75 $\text{mg/m}^2/2 \text{ wk}$

100 $\text{mg/m}^2/2 \text{ wk}$

Adult dose = 100–200 mg every 2 wk

In postpubertal transgender male adolescents the dose of testosterone esters can be increased more rapidly:

75 mg/2 wk for 6 mo

125 mg/2 wk

For alternatives once at adult dose, see Table 11.

Adjust maintenance dose to mimic physiological testosterone levels (see Table 14).

Adapted from Hembree et al. (118).

Abbreviations: IM, intramuscularly; SC, subcutaneously.

Evidence

Adolescents develop competence in decision making at their own pace. Ideally, the supervising medical professionals should individually assess this competence, although no objective tools to make such an assessment are currently available.

Many adolescents have achieved a reasonable level of competence by age 15 to 16 years (119), and in many countries 16-year-olds are legally competent with regard to medical decision making (120). However, others believe that although some capacities are generally achieved before age 16 years, other abilities (such as good risk

assessment) do not develop until well after 18 years (121). They suggest that health care procedures should be divided along a matrix of relative risk, so that younger adolescents can be allowed to decide about low-risk procedures, such as most diagnostic tests and common therapies, but not about high-risk procedures, such as most surgical procedures (121).

Currently available data from transgender adolescents support treatment with sex hormones starting at age 16 years (63, 122). However, some patients may incur potential risks by waiting until age 16 years. These include the potential risk to bone health if puberty is suppressed

Table 9. Baseline and Follow-up Protocol During Induction of Puberty

Every 3–6 mo

•Anthropometry: height, weight, sitting height, blood pressure, Tanner stages

Every 6–12 mo

•In transgender males: hemoglobin/hematocrit, lipids, testosterone, 25OH vitamin D

•In transgender females: prolactin, estradiol, 25OH vitamin D

Every 1–2 y

•BMD using DXA

•Bone age on X-ray of the left hand (if clinically indicated)

BMD should be monitored into adulthood (until the age of 25–30 y or until peak bone mass has been reached).

For recommendations on monitoring once pubertal induction has been completed, see Tables 14 and 15.

Adapted from Hembree et al. (118).

Abbreviation: DXA, dual-energy X-ray absorptiometry.

for 6 to 7 years before initiating sex hormones (*e.g.*, if someone reached Tanner stage 2 at age 9-10 years old). Additionally, there may be concerns about inappropriate height and potential harm to mental health (emotional and social isolation) if initiation of secondary sex characteristics must wait until the person has reached 16 years of age. However, only minimal data supporting earlier use of gender-affirming hormones in transgender adolescents currently exist (63). Clearly, long-term studies are needed to determine the optimal age of sex hormone treatment in GD/gender-incongruent adolescents.

The MHP who has followed the adolescent during GnRH analog treatment plays an essential role in assessing whether the adolescent is eligible to start sex hormone therapy and capable of consenting to this treatment (Table 5). Support of the family/environment is essential. Prior to the start of sex hormones, clinicians should discuss the implications for fertility (see recommendation 1.5). Throughout pubertal induction, an MHP and a pediatric endocrinologist (or other clinician competent in the evaluation and induction of pubertal development) should monitor the adolescent. In addition to monitoring therapy, it is also important to pay attention to general adolescent health issues, including healthy life style choices, such as not smoking, contraception, and appropriate vaccinations (*e.g.*, human papillomavirus).

For the induction of puberty, clinicians can use a similar dose scheme for hypogonadal adolescents with GD/gender incongruence as they use in other individuals with hypogonadism, carefully monitoring for desired and undesired effects (Table 8). In transgender female adolescents, transdermal 17β -estradiol may be an alternative for oral 17β -estradiol. It is increasingly used for pubertal induction in hypogonadal females. However, the absence of low-dose estrogen patches may be a problem. As a result, individuals may need to cut patches to size themselves to achieve appropriate dosing (123). In transgender male adolescents, clinicians can give testosterone injections intramuscularly or subcutaneously (124, 125).

When puberty is initiated with a gradually increasing schedule of sex steroid doses, the initial levels will not be high enough to suppress endogenous sex steroid secretion. Gonadotropin secretion and endogenous production of testosterone may resume and interfere with the effectiveness of estrogen treatment, in transgender female adolescents (126, 127). Therefore, continuation of GnRH analog treatment is advised until gonadectomy. Given that GD/gender-incongruent adolescents may opt not to have gonadectomy, long-term studies are necessary to examine the potential risks of prolonged GnRH analog treatment. Alternatively, in transgender male adolescents, GnRH analog treatment can be discontinued once an

adult dose of testosterone has been reached and the individual is well virilized. If uterine bleeding occurs, a progestin can be added. However, the combined use of a GnRH analog (for ovarian suppression) and testosterone may enable phenotypic transition with a lower dose of testosterone in comparison with testosterone alone. If there is a wish or need to discontinue GnRH analog treatment in transgender female adolescents, they may be treated with an antiandrogen that directly suppresses androgen synthesis or action (see section 3.0 “Hormonal Therapy for Transgender Adults”).

Values and preferences

The recommendation to initiate pubertal induction only when the individual has sufficient mental capacity (roughly age 16 years) to give informed consent for this partly irreversible treatment places a higher value on the ability of the adolescent to fully understand and oversee the partially irreversible consequences of sex hormone treatment and to give informed consent. It places a lower value on the possible negative effects of delayed puberty. We may not currently have the means to weigh adequately the potential benefits of waiting until around age 16 years to initiate sex hormones vs the potential risks/harm to BMD and the sense of social isolation from having the timing of puberty be so out of sync with peers (128).

Remarks

Before starting sex hormone treatment, effects on fertility and options for fertility preservation should be discussed. Adult height may be a concern in transgender adolescents. In a transgender female adolescent, clinicians may consider higher doses of estrogen or a more rapid tempo of dose escalation during pubertal induction. There are no established treatments yet to augment adult height in a transgender male adolescent with open epiphyses during pubertal induction. It is not uncommon for transgender adolescents to present for clinical services after having completed or nearly completed puberty. In such cases, induction of puberty with sex hormones can be done more rapidly (see Table 8). Additionally, an adult dose of testosterone in transgender male adolescents may suffice to suppress the gonadal axis without the need to use a separate agent. At the appropriate time, the multidisciplinary team should adequately prepare the adolescent for transition to adult care.

3.0 Hormonal Therapy for Transgender Adults

The two major goals of hormonal therapy are (1) to reduce endogenous sex hormone levels, and thus reduce

the secondary sex characteristics of the individual's designated gender, and (2) to replace endogenous sex hormone levels consistent with the individual's gender identity by using the principles of hormone replacement treatment of hypogonadal patients. The timing of these two goals and the age at which to begin treatment with the sex hormones of the chosen gender is codetermined in collaboration with both the person pursuing transition and the health care providers. The treatment team should include a medical provider knowledgeable in transgender hormone therapy, an MHP knowledgeable in GD/gender incongruence and the mental health concerns of transition, and a primary care provider able to provide care appropriate for transgender individuals. The physical changes induced by this sex hormone transition are usually accompanied by an improvement in mental well-being (129, 130).

- 3.1. We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and the criteria for the endocrine phase of gender transition before beginning treatment. (1 ⊕⊕⊕⊕)
- 3.2. We recommend that clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment (Table 10). (1 ⊕⊕⊕⊕)
- 3.3. We suggest that clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender. (2 ⊕⊕⊕⊕)

Evidence

It is the responsibility of the treating clinician to confirm that the person fulfills criteria for treatment. The treating clinician should become familiar with the terms and criteria presented in Tables 1–5 and take a thorough history from the patient in collaboration with the other members of the treatment team. The treating clinician must ensure that the desire for transition is appropriate; the consequences, risks, and benefits of treatment are well understood; and the desire for transition persists. They also need to discuss fertility preservation options (see recommendation 1.3) (67, 68).

Transgender males

Clinical studies have demonstrated the efficacy of several different androgen preparations to induce masculinization in transgender males (Appendix A) (113, 114, 131–134). Regimens to change secondary sex characteristics follow the general principle of hormone replacement treatment of male hypogonadism (135). Clinicians can use either parenteral or transdermal preparations to achieve testosterone values in the normal male range (this is dependent on the specific assay, but is typically 320 to 1000 ng/dL) (Table 11) (136). Sustained supraphysiologic levels of testosterone increase the risk of adverse reactions (see section 4.0 “Adverse Outcome Prevention and Long-Term Care”) and should be avoided.

Similar to androgen therapy in hypogonadal men, testosterone treatment in transgender males results in increased muscle mass and decreased fat mass, increased facial hair and acne, male pattern baldness in those genetically predisposed, and increased sexual desire (137).

Table 10. Medical Risks Associated With Sex Hormone Therapy

Transgender female: estrogen

Very high risk of adverse outcomes:

- Thromboembolic disease

Moderate risk of adverse outcomes:

- Macroprolactinoma
- Breast cancer
- Coronary artery disease
- Cerebrovascular disease
- Cholelithiasis
- Hypertriglyceridemia

Transgender male: testosterone

Very high risk of adverse outcomes:

- Erythrocytosis (hematocrit > 50%)

Moderate risk of adverse outcomes:

- Severe liver dysfunction (transaminases > threefold upper limit of normal)
- Coronary artery disease
- Cerebrovascular disease
- Hypertension
- Breast or uterine cancer

Table 11. Hormone Regimens in Transgender Persons

Transgender females ^a	
Estrogen	
Oral	
Estradiol	2.0–6.0 mg/d
Transdermal	
Estradiol transdermal patch	0.025–0.2 mg/d
(New patch placed every 3–5 d)	
Parenteral	
Estradiol valerate or cypionate	5–30 mg IM every 2 wk 2–10 mg IM every week
Anti-androgens	
Spironolactone	100–300 mg/d
Cyproterone acetate ^b	25–50 mg/d
GnRH agonist	3.75 mg SQ (SC) monthly 11.25 mg SQ (SC) 3-monthly
Transgender males	
Testosterone	
Parenteral testosterone	
Testosterone enanthate or cypionate	100–200 mg SQ (IM) every 2 wk or SQ (SC) 50% per week
Testosterone undecanoate ^c	1000 mg every 12 wk
Transdermal testosterone	
Testosterone gel 1.6% ^d	50–100 mg/d
Testosterone transdermal patch	2.5–7.5 mg/d

Abbreviations: IM, intramuscularly; SQ, sequentially; SC, subcutaneously.

^aEstrogens used with or without antiandrogens or GnRH agonist.

^bNot available in the United States.

^cOne thousand milligrams initially followed by an injection at 6 wk then at 12-wk intervals.

^dAvoid cutaneous transfer to other individuals.

In transgender males, testosterone will result in clitoromegaly, temporary or permanent decreased fertility, deepening of the voice, cessation of menses (usually), and a significant increase in body hair, particularly on the face, chest, and abdomen. Cessation of menses may occur within a few months with testosterone treatment alone, although high doses of testosterone may be required. If uterine bleeding continues, clinicians may consider the addition of a progestational agent or endometrial ablation (138). Clinicians may also administer GnRH analogs or depot medroxyprogesterone to stop menses prior to testosterone treatment.

Transgender females

The hormone regimen for transgender females is more complex than the transgender male regimen (Appendix B). Treatment with physiologic doses of estrogen alone is insufficient to suppress testosterone levels into the normal range for females (139). Most published clinical studies report the need for adjunctive therapy to achieve testosterone levels in the female range (21, 113, 114, 132–134, 139, 140).

Multiple adjunctive medications are available, such as progestins with antiandrogen activity and GnRH agonists (141). Spironolactone works by directly blocking androgens during their interaction with the androgen

receptor (114, 133, 142). It may also have estrogenic activity (143). Cyproterone acetate, a progestational compound with antiandrogenic properties (113, 132, 144), is widely used in Europe. 5 α -Reductase inhibitors do not reduce testosterone levels and have adverse effects (145).

Dittrich *et al.* (141) reported that monthly doses of the GnRH agonist goserelin acetate in combination with estrogen were effective in reducing testosterone levels with a low incidence of adverse reactions in 60 transgender females. Leuprolide and transdermal estrogen were as effective as cyproterone and transdermal estrogen in a comparative retrospective study (146).

Patients can take estrogen as oral conjugated estrogens, oral 17 β -estradiol, or transdermal 17 β -estradiol. Among estrogen options, the increased risk of thromboembolic events associated with estrogens in general seems most concerning with ethinyl estradiol specifically (134, 140, 141), which is why we specifically suggest that it not be used in any transgender treatment plan. Data distinguishing among other estrogen options are less well established although there is some thought that oral routes of administration are more thrombogenic due to the “first pass effect” than are transdermal and parenteral routes, and that the risk of thromboembolic events is dose-dependent. Injectable estrogen and sublingual

estrogen may benefit from avoiding the first pass effect, but they can result in more rapid peaks with greater overall periodicity and thus are more difficult to monitor (147, 148). However, there are no data demonstrating that increased periodicity is harmful otherwise.

Clinicians can use serum estradiol levels to monitor oral, transdermal, and intramuscular estradiol. Blood tests cannot monitor conjugated estrogens or synthetic estrogen use. Clinicians should measure serum estradiol and serum testosterone and maintain them at the level for premenopausal females (100 to 200 pg/mL and <50 ng/dL, respectively). The transdermal preparations and injectable estradiol cypionate or valerate preparations may confer an advantage in older transgender females who may be at higher risk for thromboembolic disease (149).

Values

Our recommendation to maintain levels of gender-affirming hormones in the normal adult range places a high value on the avoidance of the long-term complications of pharmacologic doses. Those patients receiving endocrine treatment who have relative contraindications to hormones should have an in-depth discussion with their physician to balance the risks and benefits of therapy.

Remarks

Clinicians should inform all endocrine-treated individuals of all risks and benefits of gender-affirming hormones prior to initiating therapy. Clinicians should strongly encourage tobacco use cessation in transgender females to avoid increased risk of VTE and cardiovascular complications. We strongly discourage the unsupervised use of hormone therapy (150).

Not all individuals with GD/gender incongruence seek treatment as described (e.g., male-to-eunuchs and individuals seeking partial transition). Tailoring current protocols to the individual may be done within the context of accepted safety guidelines using a multidisciplinary approach including mental health. No evidence-based protocols are available for these groups (151). We need prospective studies to better understand treatment options for these persons.

- 3.4. We suggest that endocrinologists provide education to transgender individuals undergoing treatment about the onset and time course of physical changes induced by sex hormone treatment. (2 ⊕○○○)

Evidence

Transgender males

Physical changes that are expected to occur during the first 1 to 6 months of testosterone therapy include

cessation of menses, increased sexual desire, increased facial and body hair, increased oiliness of skin, increased muscle, and redistribution of fat mass. Changes that occur within the first year of testosterone therapy include deepening of the voice (152, 153), clitoromegaly, and male pattern hair loss (in some cases) (114, 144, 154, 155) (Table 12).

Transgender females

Physical changes that may occur in transgender females in the first 3 to 12 months of estrogen and anti-androgen therapy include decreased sexual desire, decreased spontaneous erections, decreased facial and body hair (usually mild), decreased oiliness of skin, increased breast tissue growth, and redistribution of fat mass (114, 139, 149, 154, 155, 161) (Table 13). Breast development is generally maximal at 2 years after initiating hormones (114, 139, 149, 155). Over a long period of time, the prostate gland and testicles will undergo atrophy.

Although the time course of breast development in transgender females has been studied (150), precise information about other changes induced by sex hormones is lacking (141). There is a great deal of variability among individuals, as evidenced during pubertal development. We all know that a major concern for transgender females is breast development. If we work with estrogens, the result will be often not what the transgender female expects.

Alternatively, there are transgender females who report an anecdotal improved breast development, mood, or sexual desire with the use of progestogens. However, there have been no well-designed studies of the role of progestogens in feminizing hormone regimens, so the question is still open.

Our knowledge concerning the natural history and effects of different cross-sex hormone therapies on breast

Table 12. Masculinizing Effects in Transgender Males

Effect	Onset	Maximum
Skin oiliness/acne	1–6 mo	1–2 y
Facial/body hair growth	6–12 mo	4–5 y
Scalp hair loss	6–12 mo	— ^a
Increased muscle mass/strength	6–12 mo	2–5 y
Fat redistribution	1–6 mo	2–5 y
Cessation of menses	1–6 mo	— ^b
Clitoral enlargement	1–6 mo	1–2 y
Vaginal atrophy	1–6 mo	1–2 y
Deepening of voice	6–12 mo	1–2 y

Estimates represent clinical observations: Toorians *et al.* (149), Assche-man *et al.* (156), Gooren *et al.* (157), Wierckx *et al.* (158).

^aPrevention and treatment as recommended for biological men.

^bMenorrhagia requires diagnosis and treatment by a gynecologist.

Table 13. Feminizing Effects in Transgender Females

Effect	Onset	Maximum
Redistribution of body fat	3–6 mo	2–3 y
Decrease in muscle mass and strength	3–6 mo	1–2 y
Softening of skin/decreased oiliness	3–6 mo	Unknown
Decreased sexual desire	1–3 mo	3–6 mo
Decreased spontaneous erections	1–3 mo	3–6 mo
Male sexual dysfunction	Variable	Variable
Breast growth	3–6 mo	2–3 y
Decreased testicular volume	3–6 mo	2–3 y
Decreased sperm production	Unknown	>3 y
Decreased terminal hair growth	6–12 mo	>3 y ^a
Scalp hair	Variable	— ^b
Voice changes	None	— ^c

Estimates represent clinical observations: Toorians *et al.* (149), Asscheman *et al.* (156), Gooren *et al.* (157).

^aComplete removal of male sexual hair requires electrolysis or laser treatment or both.

^bFamilial scalp hair loss may occur if estrogens are stopped.

^cTreatment by speech pathologists for voice training is most effective.

development in transgender females is extremely sparse and based on the low quality of evidence. Current evidence does not indicate that progestogens enhance breast development in transgender females, nor does evidence prove the absence of such an effect. This prevents us from drawing any firm conclusion at this moment and demonstrates the need for further research to clarify these important clinical questions (162).

Values and preferences

Transgender persons have very high expectations regarding the physical changes of hormone treatment and are aware that body changes can be enhanced by surgical procedures (*e.g.*, breast, face, and body habitus). Clear expectations for the extent and timing of sex hormone-induced changes may prevent the potential harm and expense of unnecessary procedures.

4.0 Adverse Outcome Prevention and Long-Term Care

Hormone therapy for transgender males and females confers many of the same risks associated with sex hormone replacement therapy in nontransgender persons. The risks arise from and are worsened by inadvertent or intentional use of supraphysiologic doses of sex hormones, as well as use of inadequate doses of sex hormones to maintain normal physiology (131, 139).

- 4.1. We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every

3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly. (2 ⊕⊕○○)

Evidence

Pretreatment screening and appropriate regular medical monitoring are recommended for both transgender males and females during the endocrine transition and periodically thereafter (26, 155). Clinicians should monitor weight and blood pressure, conduct physical exams, and assess routine health questions, such as tobacco use, symptoms of depression, and risk of adverse events such as deep vein thrombosis/pulmonary embolism and other adverse effects of sex steroids.

Transgender males

Table 14 contains a standard monitoring plan for transgender males on testosterone therapy (154, 159). Key issues include maintaining testosterone levels in the physiologic normal male range and avoiding adverse events resulting from excess testosterone therapy, particularly erythrocytosis, sleep apnea, hypertension, excessive weight gain, salt retention, lipid changes, and excessive or cystic acne (135).

Because oral 17-alkylated testosterone is not recommended, serious hepatic toxicity is not anticipated with parenteral or transdermal testosterone use (163, 164). Past concerns regarding liver toxicity with testosterone have been alleviated with subsequent reports that indicate the risk of serious liver disease is minimal (144, 165, 166).

Transgender females

Table 15 contains a standard monitoring plan for transgender females on estrogens, gonadotropin suppression, or antiandrogens (160). Key issues include avoiding supraphysiologic doses or blood levels of estrogen that may lead to increased risk for thromboembolic disease, liver dysfunction, and hypertension. Clinicians should monitor serum estradiol levels using laboratories participating in external quality control, as measurements of estradiol in blood can be very challenging (167).

VTE may be a serious complication. A study reported a 20-fold increase in venous thromboembolic disease in a large cohort of Dutch transgender subjects (161). This increase may have been associated with the use of the synthetic estrogen, ethinyl estradiol (149). The incidence decreased when clinicians stopped administering ethinyl estradiol (161). Thus, the use of synthetic estrogens and conjugated estrogens is undesirable because of the inability to regulate doses by measuring serum levels and the risk of thromboembolic disease. In a German gender clinic, deep vein thrombosis occurred in 1 of 60 of transgender females treated with a GnRH analog and oral

Table 14. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Male

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of virilization and for development of adverse reactions.
2. Measure serum testosterone every 3 mo until levels are in the normal physiologic male range:^a
 - a. For testosterone enanthate/cypionate injections, the testosterone level should be measured midway between injections. The target level is 400–700 ng/dL to 400 ng/dL. Alternatively, measure peak and trough levels to ensure levels remain in the normal male range.
 - b. For parenteral testosterone undecanoate, testosterone should be measured just before the following injection. If the level is <400 ng/dL, adjust dosing interval.
 - c. For transdermal testosterone, the testosterone level can be measured no sooner than after 1 wk of daily application (at least 2 h after application).
3. Measure hematocrit or hemoglobin at baseline and every 3 mo for the first year and then one to two times a year. Monitor weight, blood pressure, and lipids at regular intervals.
4. Screening for osteoporosis should be conducted in those who stop testosterone treatment, are not compliant with hormone therapy, or who develop risks for bone loss.
5. If cervical tissue is present, monitoring as recommended by the American College of Obstetricians and Gynecologists.
6. Ovariectomy can be considered after completion of hormone transition.
7. Conduct sub- and periareolar annual breast examinations if mastectomy performed. If mastectomy is not performed, then consider mammograms as recommended by the American Cancer Society.

^aAdapted from Lapauw *et al.* (154) and Ott *et al.* (159).

estradiol (141). The patient who developed a deep vein thrombosis was found to have a homozygous C677 T mutation in the methylenetetrahydrofolate reductase gene. In an Austrian gender clinic, administering gender-affirming hormones to 162 transgender females and 89 transgender males was not associated with VTE, despite an 8.0% and 5.6% incidence of thrombophilia (159). A more recent multinational study reported only 10 cases of VTE from a cohort of 1073 subjects (168). Thrombophilia screening of transgender persons initiating hormone treatment should be restricted to those with a personal or family history of VTE (159). Monitoring D-dimer levels during treatment is not recommended (169).

- 4.2. We suggest periodically monitoring prolactin levels in transgender females treated with estrogens. (2 ⊕⊕○○)

Evidence

Estrogen therapy can increase the growth of pituitary lactotroph cells. There have been several reports of prolactinomas occurring after long-term, high-dose

estrogen therapy (170–173). Up to 20% of transgender females treated with estrogens may have elevations in prolactin levels associated with enlargement of the pituitary gland (156). In most cases, the serum prolactin levels will return to the normal range with a reduction or discontinuation of the estrogen therapy or discontinuation of cyproterone acetate (157, 174, 175).

The onset and time course of hyperprolactinemia during estrogen treatment are not known. Clinicians should measure prolactin levels at baseline and then at least annually during the transition period and every 2 years thereafter. Given that only a few case studies reported prolactinomas, and prolactinomas were not reported in large cohorts of estrogen-treated persons, the risk is likely to be very low. Because the major presenting findings of microprolactinomas (hypogonadism and sometimes gynecomastia) are not apparent in transgender females, clinicians may perform radiologic examinations of the pituitary in those patients whose prolactin levels persistently increase despite stable or reduced estrogen levels. Some transgender individuals receive psychotropic medications that can increase prolactin levels (174).

Table 15. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Female

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of feminization and for development of adverse reactions.
2. Measure serum testosterone and estradiol every 3 mo.
 - a. Serum testosterone levels should be <50 ng/dL.
 - b. Serum estradiol should not exceed the peak physiologic range: 100–200 pg/mL.
3. For individuals on spironolactone, serum electrolytes, particularly potassium, should be monitored every 3 mo in the first year and annually thereafter.
4. Routine cancer screening is recommended, as in nontransgender individuals (all tissues present).
5. Consider BMD testing at baseline (160). In individuals at low risk, screening for osteoporosis should be conducted at age 60 years or in those who are not compliant with hormone therapy.

This table presents strong recommendations and does not include lower level recommendations.

- 4.3. We suggest that clinicians evaluate transgender persons treated with hormones for cardiovascular risk factors using fasting lipid profiles, diabetes screening, and/or other diagnostic tools. (2 ⊕⊕○○)

Evidence

Transgender males

Administering testosterone to transgender males results in a more atherogenic lipid profile with lowered high-density lipoprotein cholesterol and higher triglyceride and low-density lipoprotein cholesterol values (176–179). Studies of the effect of testosterone on insulin sensitivity have mixed results (178, 180). A randomized, open-label uncontrolled safety study of transgender males treated with testosterone undecanoate demonstrated no insulin resistance after 1 year (181, 182). Numerous studies have demonstrated the effects of sex hormone treatment on the cardiovascular system (160, 179, 183, 184). Long-term studies from The Netherlands found no increased risk for cardiovascular mortality (161). Likewise, a meta-analysis of 19 randomized trials in nontransgender males on testosterone replacement showed no increased incidence of cardiovascular events (185). A systematic review of the literature found that data were insufficient (due to very low-quality evidence) to allow a meaningful assessment of patient-important outcomes, such as death, stroke, myocardial infarction, or VTE in transgender males (176). Future research is needed to ascertain the potential harm of hormonal therapies (176). Clinicians should manage cardiovascular risk factors as they emerge according to established guidelines (186).

Transgender females

A prospective study of transgender females found favorable changes in lipid parameters with increased high-density lipoprotein and decreased low-density lipoprotein concentrations (178). However, increased weight, blood pressure, and markers of insulin resistance attenuated these favorable lipid changes. In a meta-analysis, only serum triglycerides were higher at ≥ 24 months without changes in other parameters (187). The largest cohort of transgender females (mean age 41 years, followed for a mean of 10 years) showed no increase in cardiovascular mortality despite a 32% rate of tobacco use (161).

Thus, there is limited evidence to determine whether estrogen is protective or detrimental on lipid and glucose metabolism in transgender females (176). With aging, there is usually an increase of body weight. Therefore, as with nontransgender individuals, clinicians should

monitor and manage glucose and lipid metabolism and blood pressure regularly according to established guidelines (186).

- 4.4. We recommend that clinicians obtain BMD measurements when risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. (1 ⊕⊕○○)

Evidence

Transgender males

Baseline bone mineral measurements in transgender males are generally in the expected range for their pre-treatment gender (188). However, adequate dosing of testosterone is important to maintain bone mass in transgender males (189, 190). In one study (190), serum LH levels were inversely related to BMD, suggesting that low levels of sex hormones were associated with bone loss. Thus, LH levels in the normal range may serve as an indicator of the adequacy of sex steroid administration to preserve bone mass. The protective effect of testosterone may be mediated by peripheral conversion to estradiol, both systemically and locally in the bone.

Transgender females

A baseline study of BMD reported T scores less than -2.5 in 16% of transgender females (191). In aging males, studies suggest that serum estradiol more positively correlates with BMD than does testosterone (192, 193) and is more important for peak bone mass (194). Estrogen preserves BMD in transgender females who continue on estrogen and antiandrogen therapies (188, 190, 191, 195, 196).

Fracture data in transgender males and females are not available. Transgender persons who have undergone gonadectomy may choose not to continue consistent sex steroid treatment after hormonal and surgical sex reassignment, thereby becoming at risk for bone loss. There have been no studies to determine whether clinicians should use the sex assigned at birth or affirmed gender for assessing osteoporosis (e.g., when using the FRAX tool). Although some researchers use the sex assigned at birth (with the assumption that bone mass has usually peaked for transgender people who initiate hormones in early adulthood), this should be assessed on a case-by-case basis until there are more data available. This assumption will be further complicated by the increasing prevalence of transgender people who undergo hormonal transition at a pubertal age or soon after puberty. Sex for comparison within risk assessment tools may be based on the age at which hormones were initiated and the length of exposure to hormones. In some cases, it may be

reasonable to assess risk using both the male and female calculators and using an intermediate value. Because all subjects underwent normal pubertal development, with known effects on bone size, reference values for birth sex were used for all participants (154).

- 4.5. We suggest that transgender females with no known increased risk of breast cancer follow breast-screening guidelines recommended for those designated female at birth. (2 ⊕⊕○○)
- 4.6. We suggest that transgender females treated with estrogens follow individualized screening according to personal risk for prostatic disease and prostate cancer. (2 ⊕○○○)

Evidence

Studies have reported a few cases of breast cancer in transgender females (197–200). A Dutch study of 1800 transgender females followed for a mean of 15 years (range of 1–30 years) found one case of breast cancer. The Women's Health Initiative study reported that females taking conjugated equine estrogen without progesterone for 7 years did not have an increased risk of breast cancer as compared with females taking placebo (137).

In transgender males, a large retrospective study conducted at the U.S. Veterans Affairs medical health system identified seven breast cancers (194). The authors reported that this was not above the expected rate of breast cancers in cisgender females in this cohort. Furthermore, they did report one breast cancer that developed in a transgender male patient after mastectomy, supporting the fact that breast cancer can occur even after mastectomy. Indeed, there have been case reports of breast cancer developing in subareolar tissue in transgender males, which occurred after mastectomy (201, 202).

Women with primary hypogonadism (Turner syndrome) treated with estrogen replacement exhibited a significantly decreased incidence of breast cancer as compared with national standardized incidence ratios (203, 204). These studies suggest that estrogen therapy does not increase the risk of breast cancer in the short term (<20 to 30 years). We need long-term studies to determine the actual risk, as well as the role of screening mammograms. Regular examinations and gynecologic advice should determine monitoring for breast cancer.

Prostate cancer is very rare before the age of 40, especially with androgen deprivation therapy (205). Childhood or pubertal castration results in regression of the prostate and adult castration reverses benign prostate hypertrophy (206). Although van Kesteren *et al.* (207) reported that estrogen therapy does not induce hypertrophy or premalignant changes in the prostates of

transgender females, studies have reported cases of benign prostatic hyperplasia in transgender females treated with estrogens for 20 to 25 years (208, 209). Studies have also reported a few cases of prostate carcinoma in transgender females (210–214).

Transgender females may feel uncomfortable scheduling regular prostate examinations. Gynecologists are not trained to screen for prostate cancer or to monitor prostate growth. Thus, it may be reasonable for transgender females who transitioned after age 20 years to have annual screening digital rectal examinations after age 50 years and prostate-specific antigen tests consistent with U.S. Preventive Services Task Force Guidelines (215).

- 4.7. We advise that clinicians determine the medical necessity of including a total hysterectomy and oophorectomy as part of gender-affirming surgery. (Ungraded Good Practice Statement)

Evidence

Although aromatization of testosterone to estradiol in transgender males has been suggested as a risk factor for endometrial cancer (216), no cases have been reported. When transgender males undergo hysterectomy, the uterus is small and there is endometrial atrophy (217, 218). Studies have reported cases of ovarian cancer (219, 220). Although there is limited evidence for increased risk of reproductive tract cancers in transgender males, health care providers should determine the medical necessity of a laparoscopic total hysterectomy as part of a gender-affirming surgery to prevent reproductive tract cancer (221).

Values

Given the discomfort that transgender males experience accessing gynecologic care, our recommendation for the medical necessity of total hysterectomy and oophorectomy places a high value on eliminating the risks of female reproductive tract disease and cancer and a lower value on avoiding the risks of these surgical procedures (related to the surgery and to the potential undesirable health consequences of oophorectomy) and their associated costs.

Remarks

The sexual orientation and type of sexual practices will determine the need and types of gynecologic care required following transition. Additionally, in certain countries, the approval required to change the sex in a birth certificate for transgender males may be dependent on having a complete hysterectomy. Clinicians should help patients research nonmedical administrative criteria and

provide counseling. If individuals decide not to undergo hysterectomy, screening for cervical cancer is the same as all other females.

5.0 Surgery for Sex Reassignment and Gender Confirmation

For many transgender adults, genital gender-affirming surgery may be the necessary step toward achieving their ultimate goal of living successfully in their desired gender role. The type of surgery falls into two main categories: (1) those that directly affect fertility and (2) those that do not. Those that change fertility (previously called sex reassignment surgery) include genital surgery to remove the penis and gonads in the male and removal of the uterus and gonads in the female. The surgeries that effect fertility are often governed by the legal system of the state or country in which they are performed. Other gender-conforming surgeries that do not directly affect fertility are not so tightly governed.

Gender-affirming surgical techniques have improved markedly during the past 10 years. Reconstructive genital surgery that preserves neurologic sensation is now the standard. The satisfaction rate with surgical reassignment of sex is now very high (187). Additionally, the mental health of the individual seems to be improved by participating in a treatment program that defines a pathway of gender-affirming treatment that includes hormones and surgery (130, 144) (Table 16).

Surgery that affects fertility is irreversible. The World Professional Association for Transgender Health Standards of Care (222) emphasizes that the “threshold of 18 should not be seen as an indication in itself for active intervention.” If the social transition has not been satisfactory, if the person is not satisfied with or is ambivalent about the effects of sex hormone treatment, or if the person is ambivalent about surgery then the individual should not be referred for surgery (223, 224).

Gender-affirming genital surgeries for transgender females that affect fertility include gonadectomy, penectomy, and creation of a neovagina (225, 226). Surgeons often invert the skin of the penis to form the wall of the vagina, and several literatures reviews have

reported on outcomes (227). Sometimes there is inadequate tissue to form a full neovagina, so clinicians have revisited using intestine and found it to be successful (87, 228, 229). Some newer vaginoplasty techniques may involve autologous oral epithelial cells (230, 231).

The scrotum becomes the labia majora. Surgeons use reconstructive surgery to fashion the clitoris and its hood, preserving the neurovascular bundle at the tip of the penis as the neurosensory supply to the clitoris. Some surgeons are also creating a sensate pedicled-spot adding a G spot to the neovagina to increase sensation (232). Most recently, plastic surgeons have developed techniques to fashion labia minora. To further complete the feminization, uterine transplants have been proposed and even attempted (233).

Neovaginal prolapse, rectovaginal fistula, delayed healing, vaginal stenosis, and other complications do sometimes occur (234, 235). Clinicians should strongly remind the transgender person to use their dilators to maintain the depth and width of the vagina throughout the postoperative period. Genital sexual responsivity and other aspects of sexual function are usually preserved following genital gender-affirming surgery (236, 237).

Ancillary surgeries for more feminine or masculine appearance are not within the scope of this guideline. Voice therapy by a speech language pathologist is available to transform speech patterns to the affirmed gender (148). Spontaneous voice deepening occurs during testosterone treatment of transgender males (152, 238). No studies have compared the effectiveness of speech therapy, laryngeal surgery, or combined treatment.

Breast surgery is a good example of gender-confirming surgery that does not affect fertility. In all females, breast size exhibits a very broad spectrum. For transgender females to make the best informed decision, clinicians should delay breast augmentation surgery until the patient has completed at least 2 years of estrogen therapy, because the breasts continue to grow during that time (141, 155).

Another major procedure is the removal of facial and masculine-appearing body hair using either electrolysis or

Table 16. Criteria for Gender-Affirming Surgery, Which Affects Fertility

1. Persistent, well-documented gender dysphoria
2. Legal age of majority in the given country
3. Having continuously and responsibly used gender-affirming hormones for 12 mo (if there is no medical contraindication to receiving such therapy)
4. Successful continuous full-time living in the new gender role for 12 mo
5. If significant medical or mental health concerns are present, they must be well controlled
6. Demonstrable knowledge of all practical aspects of surgery (e.g., cost, required lengths of hospitalizations, likely complications, postsurgical rehabilitation)

laser treatments. Other feminizing surgeries, such as that to feminize the face, are now becoming more popular (239–241).

In transgender males, clinicians usually delay gender-affirming genital surgeries until after a few years of androgen therapy. Those surgeries that affect fertility in this group include oophorectomy, vaginectomy, and complete hysterectomy. Surgeons can safely perform them vaginally with laparoscopy. These are sometimes done in conjunction with the creation of a neopenis. The cosmetic appearance of a neopenis is now very good, but the surgery is multistage and very expensive (242, 243). Radial forearm flap seems to be the most satisfactory procedure (228, 244). Other flaps also exist (245). Surgeons can make neopenile erections possible by reinnervation of the flap and subsequent contraction of the muscle, leading to stiffening of the neopenis (246, 247), but results are inconsistent (248). Surgeons can also stiffen the penis by imbedding some mechanical device (*e.g.*, a rod or some inflatable apparatus) (249, 250). Because of these limitations, the creation of a neopenis has often been less than satisfactory. Recently, penis transplants are being proposed (233).

In fact, most transgender males do not have any external genital surgery because of the lack of access, high cost, and significant potential complications. Some choose a metaoidioplasty that brings forward the clitoris, thereby allowing them to void in a standing position without wetting themselves (251, 252). Surgeons can create the scrotum from the labia majora with good cosmetic effect and can implant testicular prostheses (253).

The most important masculinizing surgery for the transgender male is mastectomy, and it does not affect fertility. Breast size only partially regresses with androgen therapy (155). In adults, discussions about mastectomy usually take place after androgen therapy has started. Because some transgender male adolescents present after significant breast development has occurred, they may also consider mastectomy 2 years after they begin androgen therapy and before age 18 years. Clinicians should individualize treatment based on the physical and mental health status of the individual. There are now newer approaches to mastectomy with better outcomes (254, 255). These often involve chest contouring (256). Mastectomy is often necessary for living comfortably in the new gender (256).

- 5.1. We recommend that a patient pursue genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically

necessary and would benefit the patient's overall health and/or well-being. (1 ⊕⊕○○)

- 5.2. We advise that clinicians approve genital gender-affirming surgery only after completion of at least 1 year of consistent and compliant hormone treatment, unless hormone therapy is not desired or medically contraindicated. (Ungraded Good Practice Statement)
- 5.3. We advise that the clinician responsible for endocrine treatment and the primary care provider ensure appropriate medical clearance of transgender individuals for genital gender-affirming surgery and collaborate with the surgeon regarding hormone use during and after surgery. (Ungraded Good Practice Statement)
- 5.4. We recommend that clinicians refer hormone-treated transgender individuals for genital surgery when: (1) the individual has had a satisfactory social role change, (2) the individual is satisfied about the hormonal effects, and (3) the individual desires definitive surgical changes. (1 ⊕○○○)
- 5.5. We suggest that clinicians delay gender-affirming genital surgery involving gonadectomy and/or hysterectomy until the patient is at least 18 years old or legal age of majority in his or her country. (2 ⊕⊕○○)
- 5.6. We suggest that clinicians determine the timing of breast surgery for transgender males based upon the physical and mental health status of the individual. There is insufficient evidence to recommend a specific age requirement. (2 ⊕○○○)

Evidence

Owing to the lack of controlled studies, incomplete follow-up, and lack of valid assessment measures, evaluating various surgical approaches and techniques is difficult. However, one systematic review including a large numbers of studies reported satisfactory cosmetic and functional results for vaginoplasty/neovagina construction (257). For transgender males, the outcomes are less certain. However, the problems are now better understood (258). Several postoperative studies report significant long-term psychological and psychiatric pathology (259–261). One study showed satisfaction with breasts, genitals, and femininity increased significantly and showed the importance of surgical treatment as a key therapeutic option for transgender females (262). Another analysis demonstrated that, despite the young average age at death following surgery and the relatively larger number of individuals with somatic morbidity, the study does not allow for determination of

causal relationships between, for example, specific types of hormonal or surgical treatment received and somatic morbidity and mortality (263). Reversal surgery in regretful male-to-female transsexuals after sexual reassignment surgery represents a complex, multistage procedure with satisfactory outcomes. Further insight into the characteristics of persons who regret their decision postoperatively would facilitate better future selection of applicants eligible for sexual reassignment surgery. We need more studies with appropriate controls that examine long-term quality of life, psychosocial outcomes, and psychiatric outcomes to determine the long-term benefits of surgical treatment.

When a transgender individual decides to have gender-affirming surgery, both the hormone prescribing clinician and the MHP must certify that the patient satisfies criteria for gender-affirming surgery (Table 16).

There is some concern that estrogen therapy may cause an increased risk for venous thrombosis during or following surgery (176). For this reason, the surgeon and the hormone-prescribing clinician should collaborate in making a decision about the use of hormones before and following surgery. One study suggests that preoperative factors (such as compliance) are less important for patient satisfaction than are the physical postoperative results (56). However, other studies and clinical experience dictate that individuals who do not follow medical instructions and do not work with their physicians toward a common goal do not achieve treatment goals (264) and experience higher rates of postoperative infections and other complications (265, 266). It is also important that the person requesting surgery feels comfortable with the anatomical changes that have occurred during hormone therapy. Dissatisfaction with social and physical outcomes during the hormone transition may be a contraindication to surgery (223).

An endocrinologist or experienced medical provider should monitor transgender individuals after surgery. Those who undergo gonadectomy will require hormone replacement therapy, surveillance, or both to prevent adverse effects of chronic hormone deficiency.

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Guidelines for Psychological Practice With Transgender and Gender Nonconforming People

American Psychological Association

Transgender and gender nonconforming¹ (TGNC) people are those who have a gender identity that is not fully aligned with their sex assigned at birth. The existence of TGNC people has been documented in a range of historical cultures (Coleman, Colgan, & Gooren, 1992; Feinberg, 1996; Miller & Nichols, 2012; Schmidt, 2003). Current population estimates of TGNC people have ranged from 0.17 to 1,333 per 100,000 (Meier & Labuski, 2013). The Massachusetts Behavioral Risk Factor Surveillance Survey found 0.5% of the adult population aged 18 to 64 years identified as TGNC between 2009 and 2011 (Conron, Scott, Stowell, & Landers, 2012). However, population estimates likely underreport the true number of TGNC people, given difficulties in collecting comprehensive demographic information about this group (Meier & Labuski, 2013). Within the last two decades, there has been a significant increase in research about TGNC people. This increase in knowledge, informed by the TGNC community, has resulted in the development of progressively more trans-affirmative practice across the multiple health disciplines involved in the care of TGNC people (Bockting, Knudson, & Goldberg, 2006; Coleman et al., 2012). Research has documented the extensive experiences of stigma and discrimination reported by TGNC people (Grant et al., 2011) and the mental health consequences of these experiences across the life span (Bockting, Miner, Swinburne Romine, Hamilton, & Coleman, 2013), including increased rates of depression (Fredriksen-Goldsen et al., 2014) and suicidality (Clements-Nolle, Marx, & Katz, 2006). TGNC people's lack of access to trans-affirmative mental and physical health care is a common barrier (Fredriksen-Goldsen et al., 2014; Garofalo, Deleon, Osmer, Doll, & Harper, 2006; Grossman & D'Augelli, 2006), with TGNC people sometimes being denied care because of their gender identity (Xavier et al., 2012).

In 2009, the American Psychological Association (APA) Task Force on Gender Identity and Gender Variance (TFGIGV) survey found that less than 30% of psychologist and graduate student participants reported familiarity with issues that TGNC people experience (APA TFGIGV, 2009). Psychologists and other mental health professionals who have limited training and experience in TGNC-affirmative care may cause harm to TGNC people (Mikalson, Pardo, & Green, 2012; Xavier et al., 2012). The significant level of societal stigma and discrimination that TGNC people face, the associated mental health consequences, and psychologists' lack of familiarity with trans-affirmative care led the APA Task Force to recommend that psycho-

logical practice guidelines be developed to help psychologists maximize the effectiveness of services offered and avoid harm when working with TGNC people and their families.

Purpose

The purpose of the *Guidelines for Psychological Practice with Transgender and Gender Nonconforming People* (hereafter *Guidelines*) is to assist psychologists in the provision of culturally competent, developmentally appropriate, and trans-affirmative psychological practice with TGNC people. Trans-affirmative practice is the provision

The American Psychological Association's (APA's) Task Force on Guidelines for Psychological Practice with Transgender and Gender Nonconforming People developed these guidelines. Lore M. Dickey, Louisiana Tech University, and Anneliese A. Singh, The University of Georgia, served as chairs of the Task Force. The members of the Task Force included Walter O. Bockting, Columbia University; Sand Chang, Independent Practice; Kelly Ducheny, Howard Brown Health Center; Laura Edwards-Leeper, Pacific University; Randall D. Ehrbar, Whitman Walker Health Center; Max Fuentes Fuhrmann, Independent Practice; Michael L. Hendricks, Washington Psychological Center, P.C.; and Ellen Magalhaes, Center for Psychological Studies at Nova Southeastern University and California School of Professional Psychology at Alliant International University.

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This document will expire as APA policy in 2022. After this date, users should contact the APA Public Interest Directorate to determine whether the guidelines in this document remain in effect as APA policy.

Correspondence concerning this article should be addressed to the Public Interest Directorate, American Psychological Association, 750 First Street, NE, Washington, DC 20002.

¹ For the purposes of these guidelines, we use the term *transgender and gender nonconforming* (TGNC). We intend for the term to be as broadly inclusive as possible, and recognize that some TGNC people do not ascribe to these terms. Readers are referred to [Appendix A](#) for a listing of terms that include various TGNC identity labels.

EXHIBIT

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of care that is respectful, aware, and supportive of the identities and life experiences of TGNC people (Korell & Lorah, 2007). The *Guidelines* are an introductory resource for psychologists who will encounter TGNC people in their practice, but can also be useful for psychologists with expertise in this area of practice to improve the care already offered to TGNC people. The *Guidelines* include a set of definitions for readers who may be less familiar with language used when discussing gender identity and TGNC populations (see Appendix A). Distinct from TGNC, the term “cisgender” is used to refer to people whose sex assigned at birth is aligned with their gender identity (E. R. Green, 2006; Serano, 2006).

Given the added complexity of working with TGNC and gender-questioning youth² and the limitations of the available research, the *Guidelines* focus primarily, though not exclusively, on TGNC adults. Future revisions of the *Guidelines* will deepen a focus on TGNC and gender-questioning children and adolescents. The *Guidelines* address the strengths of TGNC people, the challenges they face, ethical and legal issues, life span considerations, research, education, training, and health care. Because issues of gender identity are often conflated with issues of gender expression or sexual orientation, psychological practice with the TGNC population warrants the acquisition of specific knowledge about concerns unique to TGNC people that are not addressed by other practice guidelines (APA, 2012). It is important to note that these *Guidelines* are not intended to address some of the conflicts that cisgender people may experience due to societal expectations regarding gender roles (Butler, 1990), nor are they intended to address intersex people (Dreger, 1999; Preves, 2003).

Documentation of Need

In 2005, the APA Council of Representatives authorized the creation of the Task Force on Gender Identity and Gender Variance (TFGIGV), charging the Task Force to review APA policies related to TGNC people and to offer recommendations for APA to best meet the needs of TGNC people (APA TFGIGV, 2009). In 2009, the APA Council of Representatives adopted the Resolution on Transgender, Gender Identity, & Gender Expression Non-Discrimination, which calls upon psychologists in their professional roles to provide appropriate, nondiscriminatory treatment; encourages psychologists to take a leadership role in working against discrimination; supports the provision of adequate and necessary mental and medical health care; recognizes the efficacy, benefit, and medical necessity of gender transition; supports access to appropriate treatment in institutional settings; and supports the creation of educational resources for all psychologists (Anton, 2009). In 2009, in an extensive report on the current state of psychological practice with TGNC people, the TFGIGV determined that there was sufficient knowledge and expertise in the field to warrant the development of practice guidelines for TGNC populations (APA TFGIGV, 2009). The report identified that TGNC people constituted a population with

unique needs and that the creation of practice guidelines would be a valuable resource for the field (APA TFGIGV, 2009). Psychologists’ relative lack of knowledge about TGNC people and trans-affirmative care, the level of societal stigma and discrimination that TGNC people face, and the significant mental health consequences that TGNC people experience as a result offer a compelling need for psychological practice guidelines for this population.

Users

The intended audience for these *Guidelines* includes psychologists who provide clinical care, conduct research, or provide education or training. Given that gender identity issues can arise at any stage in a TGNC person’s life (Lev, 2004), clinicians can encounter a TGNC person in practice or have a client’s presenting problem evolve into an issue related to gender identity and gender expression. Researchers, educators, and trainers will benefit from use of these *Guidelines* to inform their work, even when not specifically focused on TGNC populations. Psychologists who focus on TGNC populations in their clinical practice, research, or educational and training activities will also benefit from the use of these *Guidelines*.

Distinction Between Standards and Guidelines

When using these *Guidelines*, psychologists should be aware that APA has made an important distinction between *standards* and *guidelines* (Reed, McLaughlin, & Newman, 2002). Standards are mandates to which all psychologists must adhere (e.g., the *Ethical Principles of Psychologists and Code of Conduct*; APA, 2010), whereas guidelines are aspirational. Psychologists are encouraged to use these *Guidelines* in tandem with the *Ethical Principles of Psychologists and Code of Conduct*, and should be aware that state and federal laws may override these *Guidelines* (APA, 2010).

In addition, these *Guidelines* refer to psychological practice (e.g., clinical work, consultation, education, research, and training) rather than treatment. Practice guidelines are practitioner-focused and provide guidance for professionals regarding “conduct and the issues to be considered in particular areas of clinical practice” (Reed et al., 2002, p. 1044). Treatment guidelines are client-focused and address intervention-specific recommendations for a clinical population or condition (Reed et al., 2002). The current *Guidelines* are intended to complement treatment guidelines for TGNC people seeking mental health services, such as those set forth by the World Professional Association for Transgender Health Standards of Care (Coleman et al., 2012) and the Endocrine Society (Hembree et al., 2009).

² For the purposes of these guidelines, “youth” refers to both children and adolescents under the age of 18.

Compatibility

These *Guidelines* are consistent with the APA *Ethical Principles of Psychologists and Code of Conduct* (APA, 2010), the *Standards of Accreditation for Health Service Psychology* (APA, 2015), the APA TFGIGV (2009) report, and the APA Council of Representatives Resolution on Transgender, Gender Identity, & Gender Expression Non-Discrimination (Anton, 2009).

Practice Guidelines Development Process

To address one of the recommendations of the APA TFGIGV (2009), the APA Committee on Sexual Orientation and Gender Diversity (CSOGD; then the Committee on Lesbian, Gay, Bisexual, and Transgender Concerns) and Division 44 (the Society for the Psychological Study of Lesbian, Gay, Bisexual and Transgender Issues) initiated a joint Task Force on Psychological Practice Guidelines with Transgender and Gender Nonconforming People in 2011. Task Force members were selected through an application and review process conducted by the leadership of CSOGD and Division 44. The Task Force included 10 members who had substantial psychological practice expertise with TGNC people. Of the 10 task force members, five individuals identified as TGNC with a range of gender identities and five identified as cisgender. In terms of race/ethnicity, six of the task force members identified as White and four identified as people of color (one Indian American, one Chinese American, one Latina American, and one mixed race).

The Task Force conducted a comprehensive review of the extant scholarship, identified content most pertinent to the practice of psychology with TGNC people, and evaluated the level of evidence to support guidance within each guideline. To ensure the accuracy and comprehensiveness of these *Guidelines*, Task Force members met with TGNC community members and groups and consulted with subject matter experts within and outside of psychology. When the Task Force discovered a lack of professional consensus, every effort was made to include divergent opinions in the field relevant to that issue. When this occurred, the Task Force described the various approaches documented in the literature. Additionally, these *Guidelines* were informed by comments received at multiple presentations held at professional conferences and comments obtained through two cycles of open public comment on earlier *Guideline* drafts.

This document contains 16 guidelines for TGNC psychological practice. Each guideline includes a Rationale section, which reviews relevant scholarship supporting the need for the guideline, and an Application section, which describes how the particular guideline may be applied in psychological practice. The *Guidelines* are organized into five clusters: (a) foundational knowledge and awareness; (b) stigma, discrimination, and barriers to care; (c) life span development; (d) assessment, therapy, and intervention; and (e) research, education, and training.

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Selection of Evidence

Although the number of publications on the topic of TGNC-affirmative practice has been increasing, this is still an emerging area of scholarly literature and research. When possible, the Task Force relied on peer-reviewed publications, but books, chapters, and reports that do not typically receive a high level of peer review have also been cited when appropriate. These sources are from a diverse range of fields addressing mental health, including psychology, counseling, social work, and psychiatry. Some studies of TGNC people utilize small sample sizes, which limits the generalizability of results. Few studies of TGNC people utilize probability samples or randomized control groups (e.g., Conron et al., 2012; Dhejne et al., 2011). As a result, the Task Force relied primarily on studies using convenience samples, which limits the generalizability of results to the population as a whole, but can be adequate for describing issues and situations that arise within the population.

Foundational Knowledge and Awareness

Guideline 1. Psychologists understand that gender is a nonbinary construct that allows for a range of gender identities and that a person's gender identity may not align with sex assigned at birth.

Rationale. Gender identity is defined as a person's deeply felt, inherent sense of being a girl, woman, or female; a boy, a man, or male; a blend of male or female; or an alternative gender (Bethea & McCollum, 2013; Institute of Medicine [IOM], 2011). In many cultures and religious traditions, gender has been perceived as a binary construct, with mutually exclusive categories of male or female, boy or girl, man or woman (Benjamin, 1966; Mollenkott, 2001; Tanis, 2003). These mutually exclusive categories include an assumption that gender identity is always in alignment with sex assigned at birth (Bethea & McCollum, 2013). For TGNC people, gender identity differs from sex assigned at birth to varying degrees, and may be experienced and expressed outside of the gender binary (Harrison, Grant, & Herman, 2012; Kuper, Nussbaum, & Mustanski, 2012).

Gender as a nonbinary construct has been described and studied for decades (Benjamin, 1966; Herdt, 1994; Kulick, 1998). There is historical evidence of recognition, societal acceptance, and sometimes reverence of diversity in gender identity and gender expression in several different cultures (Coleman et al., 1992; Feinberg, 1996; Miller

& Nichols, 2012; Schmidt, 2003). Many cultures in which gender nonconforming persons and groups were visible were diminished by westernization, colonialism, and systemic inequity (Nanda, 1999). In the 20th century, TGNC expression became medicalized (Hirschfeld, 1910/1991), and medical interventions to treat discordance between a person's sex assigned at birth, secondary sex characteristics, and gender identity became available (Meyerowitz, 2002).

As early as the 1950s, research found variability in how an individual described their³ gender, with some participants reporting a gender identity different from the culturally defined, mutually exclusive categories of "man" or "woman" (Benjamin, 1966). In several recent large online studies of the TGNC population in the United States, 30% to 40% of participants identified their gender identity as other than man or woman (Harrison et al., 2012; Kuper et al., 2012). Although some studies have cultivated a broader understanding of gender (Conron, Scout, & Austin, 2008), the majority of research has required a forced choice between man and woman, thus failing to represent or depict those with different gender identities (IOM, 2011). Research over the last two decades has demonstrated the existence of a wide spectrum of gender identity and gender expression (Bockting, 2008; Harrison et al., 2012; Kuper et al., 2012), which includes people who identify as either man or woman, neither man nor woman, a blend of man and woman, or a unique gender identity. A person's identification as TGNC can be healthy and self-affirming, and is not inherently pathological (Coleman et al., 2012). However, people may experience distress associated with discordance between their gender identity and their body or sex assigned at birth, as well as societal stigma and discrimination (Coleman et al., 2012).

Between the late 1960s and the early 1990s, health care to alleviate gender dysphoria largely reinforced a binary conceptualization of gender (APA TFGIGV, 2009; Bolin, 1994; Hastings, 1974). At that time, it was considered an ideal outcome for TGNC people to conform to an identity that aligned with either sex assigned at birth or, if not possible, with the "opposite" sex, with a heavy emphasis on blending into the cisgender population or "passing" (APA TFGIGV, 2009; Bolin, 1994; Hastings, 1974). Variance from these options could raise concern for health care providers about a TGNC person's ability to transition successfully. These concerns could act as a barrier to accessing surgery or hormone therapy because medical and mental health care provider endorsement was required before surgery or hormones could be accessed (Berger et al., 1979). Largely because of self-advocacy of TGNC individuals and communities in the 1990s, combined with advances in research and models of trans-affirmative care, there is greater recognition and acknowledgment of a spectrum of gender diversity and corresponding individualized, TGNC-specific health care (Bockting et al., 2006; Coleman et al., 2012).

Application. A nonbinary understanding of gender is fundamental to the provision of affirmative care for TGNC people. Psychologists are encouraged to adapt or

modify their understanding of gender, broadening the range of variation viewed as healthy and normative. By understanding the spectrum of gender identities and gender expressions that exist, and that a person's gender identity may not be in full alignment with sex assigned at birth, psychologists can increase their capacity to assist TGNC people, their families, and their communities (Lev, 2004). Respecting and supporting TGNC people in authentically articulating their gender identity and gender expression, as well as their lived experience, can improve TGNC people's health, well-being, and quality of life (Witten, 2003).

Some TGNC people may have limited access to visible, positive TGNC role models. As a result, many TGNC people are isolated and must cope with the stigma of gender nonconformity without guidance or support, worsening the negative effect of stigma on mental health (Fredriksen-Goldsen et al., 2014; Singh, Hays, & Watson, 2011). Psychologists may assist TGNC people in challenging gender norms and stereotypes, and in exploring their unique gender identity and gender expression. TGNC people, partners, families, friends, and communities can benefit from education about the healthy variation of gender identity and gender expression, and the incorrect assumption that gender identity automatically aligns with sex assigned at birth.

Psychologists may model an acceptance of ambiguity as TGNC people develop and explore aspects of their gender, especially in childhood and adolescence. A non-judgmental stance toward gender nonconformity can help to counteract the pervasive stigma faced by many TGNC people and provide a safe environment to explore gender identity and make informed decisions about gender expression.

Guideline 2. Psychologists understand that gender identity and sexual orientation are distinct but interrelated constructs.

Rationale. The constructs of gender identity and sexual orientation are theoretically and clinically distinct, even though professionals and nonprofessionals frequently conflate them. Although some research suggests a potential link in the development of gender identity and sexual orientation, the mechanisms of such a relationship are unknown (Adelson & American Academy of Child and Adolescent Psychiatry [AACAP] Committee on Quality Issues [CQI], 2012; APA TFGIGV, 2009; A. H. Devor, 2004; Drescher & Byne, 2013). *Sexual orientation* is defined as a person's sexual and/or emotional attraction to another person (Shively & De Cecco, 1977), compared with *gender identity*, which is defined by a person's felt, inherent sense of gender. For most people, gender identity develops earlier than sexual orientation. Gender identity is often established in young toddlerhood (Adelson & AACAP CQI, 2012; Kohlberg, 1966), compared with aware-

³ The third person plural pronouns "they," "them," and "their" in some instances function in these guidelines as third-person singular pronouns to model a common technique used to avoid the use of gendered pronouns when speaking to or about TGNC people.

ness of same-sex attraction, which often emerges in early adolescence (Adelson & AACAP CQI, 2012; D'Augelli & Hershberger, 1993; Herdt & Boxer, 1993; Ryan, 2009; Savin-Williams & Diamond, 2000). Although gender identity is usually established in childhood, individuals may become aware that their gender identity is not in full alignment with sex assigned at birth in childhood, adolescence, or adulthood. The developmental pathway of gender identity typically includes a progression through multiple stages of awareness, exploration, expression, and identity integration (Bockting & Coleman, 2007; A. H. Devor, 2004; Vanderburgh, 2007). Similarly, a person's sexual orientation may progress through multiple stages of awareness, exploration, and identity through adolescence and into adulthood (Bilodeau & Renn, 2005). Just as some people experience their sexual orientation as being fluid or variable (L. M. Diamond, 2013), some people also experience their gender identity as fluid (Lev, 2004).

The experience of questioning one's gender can create significant confusion for some TGNC people, especially for those who are unfamiliar with the range of gender identities that exist. To explain any discordance they may experience between their sex assigned at birth, related societal expectations, patterns of sexual and romantic attraction, and/or gender role nonconformity and gender identity, some TGNC people may assume that they must be gay, lesbian, bisexual, or queer (Bockting, Benner, & Coleman, 2009). Focusing solely on sexual orientation as the cause for discordance may obscure awareness of a TGNC identity. It can be very important to include sexual orientation and gender identity in the process of identity exploration as well as in the associated decisions about which options will work best for any particular person. In addition, many TGNC adults have disguised or rejected their experience of gender incongruence in childhood or adolescence to conform to societal expectations and minimize their fear of difference (Bockting & Coleman, 2007; Byne et al., 2012).

Because gender and patterns of attraction are used to identify a person's sexual orientation, the articulation of sexual orientation is made more complex when sex assigned at birth is not aligned with gender identity. A person's sexual orientation identity cannot be determined by simply examining external appearance or behavior, but must incorporate a person's identity and self-identification (Broido, 2000).

Application. Psychologists may assist people in differentiating gender identity and sexual orientation. As clients become aware of previously hidden or constrained aspects of their gender identity or sexuality, psychologists may provide acceptance, support, and understanding without making assumptions or imposing a specific sexual orientation or gender identity outcome (APA TFGIGV, 2009). Because of their roles in assessment, treatment, and prevention, psychologists are in a unique position to help TGNC people better understand and integrate the various aspects of their identities. Psychologists may assist TGNC people by introducing and normalizing differences in gender identity and expression. As a TGNC person finds a

comfortable way to actualize and express their gender identity, psychologists may notice that previously incongruent aspects of their sexual orientation may become more salient, better integrated, or increasingly egosyntonic (Bockting et al., 2009; H. Devor, 1993; Schleifer, 2006). This process may allow TGNC people the comfort and opportunity to explore attractions or aspects of their sexual orientation that previously had been repressed, hidden, or in conflict with their identity. TGNC people may experience a renewed exploration of their sexual orientation, a widened spectrum of attraction, or a shift in how they identify their sexual orientation in the context of a developing TGNC identity (Coleman, Bockting, & Gooren, 1993; Meier, Pardo, Labuski, & Babcock, 2013; Samons, 2008).

Psychologists may need to provide TGNC people with information about TGNC identities, offering language to describe the discordance and confusion TGNC people may be experiencing. To facilitate TGNC people's learning, psychologists may introduce some of the narratives written by TGNC people that reflect a range of outcomes and developmental processes in exploring and affirming gender identity (e.g., Bornstein & Bergman, 2010; Boylan, 2013; J. Green, 2004; Krieger, 2011; Lawrence, 2014). These resources may potentially aid TGNC people in distinguishing between issues of sexual orientation and gender identity and in locating themselves on the gender spectrum. Psychologists may also educate families and broader community systems (e.g., schools, medical systems) to better understand how gender identity and sexual orientation are different but related; this may be particularly useful when working with youth (Singh & Burnes, 2009; Whitman, 2013). Because gender identity and sexual orientation are often conflated, even by professionals, psychologists are encouraged to carefully examine resources that claim to provide affirmative services for lesbian, gay, bisexual, transgender, and queer (LGBTQ) people, and to confirm which are knowledgeable about and inclusive of the needs of TGNC people before offering referrals or recommendations to TGNC people and their families.

Guideline 3. Psychologists seek to understand how gender identity intersects with the other cultural identities of TGNC people.

Rationale. Gender identity and gender expression may have profound intersections with other aspects of identity (Collins, 2000; Warner, 2008). These aspects may include, but are not limited to, race/ethnicity, age, education, socioeconomic status, immigration status, occupation, disability status, HIV status, sexual orientation, relational status, and religion and/or spiritual affiliation. Whereas some of these aspects of identity may afford privilege, others may create stigma and hinder empowerment (Burnes & Chen, 2012; K. M. de Vries, 2015). In addition, TGNC people who transition may not be prepared for changes in privilege or societal treatment based on gender identity and gender expression. To illustrate, an African American trans man may gain male privilege, but may face racism and

societal stigma particular to African American men. An Asian American/Pacific Islander trans woman may experience the benefit of being perceived as a cisgender woman, but may also experience sexism, misogyny, and objectification particular to Asian American/Pacific Islander cisgender women.

The intersection of multiple identities within TGNC people's lives is complex and may obstruct or facilitate access to necessary support (A. Daley, Solomon, Newman, & Mishna, 2008). TGNC people with less privilege and/or multiple oppressed identities may experience greater stress and restricted access to resources. They may also develop resilience and strength in coping with disadvantages, or may locate community-based resources available to specific groups (e.g., for people living with HIV; Singh et al., 2011). Gender identity affirmation may conflict with religious beliefs or traditions (Bockting & Cesaretti, 2001). Finding an affirmative expression of their religious and spiritual beliefs and traditions, including positive relationships with religious leaders, can be an important resource for TGNC people (Glaser, 2008; Porter, Ronneberg, & Witten, 2013; Xavier, 2000).

Application. In practice, psychologists strive to recognize the salient multiple and intersecting identities of TGNC people that influence coping, discrimination, and resilience (Burnes & Chen, 2012). Improved rapport and therapeutic alliance are likely to develop when psychologists avoid overemphasizing gender identity and gender expression when not directly relevant to TGNC people's needs and concerns. Even when gender identity is the main focus of care, psychologists are encouraged to understand that a TGNC person's experience of gender may also be shaped by other important aspects of identity (e.g., age, race/ethnicity, sexual orientation), and that the salience of different aspects of identity may evolve as the person continues psychosocial development across the life span, regardless of whether they complete a social or medical transition.

At times, a TGNC person's intersection of identities may result in conflict, such as a person's struggle to integrate gender identity with religious and/or spiritual upbringing and beliefs (Kidd & Witten, 2008; Levy & Lo, 2013; Rodriguez & Follins, 2012). Psychologists may aid TGNC people in understanding and integrating identities that may be differently privileged within systems of power and systemic inequity (Burnes & Chen, 2012). Psychologists may also highlight and strengthen the development of TGNC people's competencies and resilience as they learn to manage the intersection of stigmatized identities (Singh, 2012).

Guideline 4. Psychologists are aware of how their attitudes about and knowledge of gender identity and gender expression may affect the quality of care they provide to TGNC people and their families.

Rationale. Psychologists, like other members of society, come to their personal understanding and acceptance of different aspects of human diversity through a

process of socialization. Psychologists' cultural biases, as well as the cultural differences between psychologists and their clients, have a clinical impact (Israel, Gorcheva, Burnes, & Walther, 2008; Vasquez, 2007). The assumptions, biases, and attitudes psychologists hold regarding TGNC people and gender identity and/or gender expression can affect the quality of services psychologists provide and their ability to develop an effective therapeutic alliance (Bess & Stabb, 2009; Rachlin, 2002). In addition, a lack of knowledge or training in providing affirmative care to TGNC people can limit a psychologist's effectiveness and perpetuate barriers to care (Bess & Stabb, 2009; Rachlin, 2002). Psychologists experienced with lesbian, gay, or bisexual (LGB) people may not be familiar with the unique needs of TGNC people (Israel, 2005; Israel et al., 2008). In community surveys, TGNC people have reported that many mental health care providers lack basic knowledge and skills relevant to care of TGNC people (Bradford, Xavier, Hendricks, Rives, & Honnold, 2007; Xavier, Bobbin, Singer, & Budd, 2005) and receive little training to prepare them to work with TGNC people (APA TFGIGV, 2009; Lurie, 2005). The National Transgender Discrimination Survey (Grant et al., 2011) reported that 50% of TGNC respondents shared that they had to educate their health care providers about TGNC care, 28% postponed seeking medical care due to antitrans bias, and 19% were refused care due to discrimination.

The APA ethics code (APA, 2010) specifies that psychologists practice in areas only within the boundaries of their competence (Standard 2.01), participate in proactive and consistent ways to enhance their competence (Standard 2.03), and base their work upon established scientific and professional knowledge (Standard 2.04). Competence in working with TGNC people can be developed through a range of activities, such as education, training, supervised experience, consultation, study, or professional experience.

Application. Psychologists may engage in practice with TGNC people in various ways; therefore, the depth and level of knowledge and competence required by a psychologist depends on the type and complexity of service offered to TGNC people. Services that psychologists provide to TGNC people require a basic understanding of the population and its needs, as well as the ability to respectfully interact in a trans-affirmative manner (L. Carroll, 2010).

APA emphasizes the use of evidence-based practice (APA Presidential Task Force on Evidence-Based Practice, 2006). Given how easily assumptions or stereotypes could influence treatment, evidence-based practice may be especially relevant to psychological practice with TGNC people. Until evidence-based practices are developed specifically for TGNC people, psychologists are encouraged to utilize existing evidence-based practices in the care they provide. APA also promotes collaboration with clients concerning clinical decisions, including issues related to costs, potential benefits, and the existing options and resources related to treatment (APA Presidential Task Force on Evidence-Based Practice, 2006). TGNC people could benefit from such collaboration and active engagement in decision

making, given the historical disenfranchisement and disempowerment of TGNC people in health care.

In an effort to develop competence in working with TGNC people, psychologists are encouraged to examine their personal beliefs regarding gender and sexuality, gender stereotypes, and TGNC identities, in addition to identifying gaps in their own knowledge, understanding, and acceptance (American Counseling Association [ACA], 2010). This examination may include exploring one's own gender identity and gendered experiences related to privilege, power, or marginalization, as well as seeking consultation and training with psychologists who have expertise in working with TGNC people and communities.

Psychologists are further encouraged to develop competence in working with TGNC people and their families by seeking up-to-date basic knowledge and understanding of gender identity and expression, and learning how to interact with TGNC people and their families respectfully and without judgment. Competence in working with TGNC people may be achieved and maintained in formal and informal ways, ranging from exposure in the curriculum of training programs for future psychologists and continuing education at professional conferences, to affirmative involvement as allies in the TGNC community. Beyond acquiring general competence, psychologists who choose to specialize in working with TGNC people presenting with gender-identity-related concerns are strongly encouraged to obtain advanced training, consultation, and professional experience (ACA, 2010; Coleman et al., 2012).

Psychologists may gain knowledge about the TGNC community and become more familiar with the complex social issues that affect the lives of TGNC people through first-hand experiences (e.g., attending community meetings and conferences, reading narratives written by TGNC people). If psychologists have not yet developed competence in working with TGNC people, it is recommended that they refer TGNC people to other psychologists or providers who are knowledgeable and able to provide trans-affirmative care.

Stigma, Discrimination, and Barriers to Care

Guideline 5. Psychologists recognize how stigma, prejudice, discrimination, and violence affect the health and well-being of TGNC people.

Rationale. Many TGNC people experience discrimination, ranging from subtle to severe, when accessing housing, health care, employment, education, public assistance, and other social services (Bazargan & Galvan, 2012; Bradford, Reisner, Honnold, & Xavier, 2013; Dispenza, Watson, Chung, & Brack, 2012; Grant et al., 2011). Discrimination can include assuming a person's assigned sex at birth is fully aligned with that person's gender identity, not using a person's preferred name or pronoun, asking TGNC people inappropriate questions about their bodies, or making the assumption that psychopathology exists given a specific gender identity or gender expression (Na-

dal, Rivera, & Corpus, 2010; Nadal, Skolnik, & Wong, 2012). Discrimination may also include refusing access to housing or employment or extreme acts of violence (e.g., sexual assault, murder). TGNC people who hold multiple marginalized identities are more vulnerable to discrimination and violence. TGNC women and people of color disproportionately experience severe forms of violence and discrimination, including police violence, and are less likely to receive help from law enforcement (Edelman, 2011; National Coalition of Anti-Violence Programs, 2011; Saffin, 2011).

TGNC people are at risk of experiencing antitrans prejudice and discrimination in educational settings. In a national representative sample of 7,898 LGBT youth in K-12 settings, 55.2% of participants reported verbal harassment, 22.7% reported physical harassment, and 11.4% reported physical assault based on their gender expression (Kosciw, Greytak, Palmer, & Boesen, 2014). In a national community survey of TGNC adults, 15% reported prematurely leaving educational settings ranging from kindergarten through college as a result of harassment (Grant et al., 2011). Many schools do not include gender identity and gender expression in their school nondiscrimination policies; this leaves TGNC youth without needed protections from bullying and aggression in schools (Singh & Jackson, 2012). TGNC youth in rural settings may be even more vulnerable to bullying and hostility in their school environments due to antitrans prejudice (Kosciw et al., 2014).

Inequities in educational settings and other forms of TGNC-related discrimination may contribute to the significant economic disparities TGNC people have reported. Grant and colleagues (2011) found that TGNC people were four times more likely to have a household income of less than \$10,000 compared with cisgender people, and almost half of a sample of TGNC older adults reported a household income at or below 200% of poverty (Fredriksen-Goldsen et al., 2014). TGNC people often face workplace discrimination both when seeking and maintaining employment (Brewster, Velez, Mennicke, & Tebbe, 2014; Dispenza et al., 2012; Mizock & Mueser, 2014). In a nonrepresentative national study of TGNC people, 90% reported having "directly experienced harassment or mistreatment at work and felt forced to take protective actions that negatively impacted their careers or their well-being, such as hiding who they were to avoid workplace repercussions" (Grant et al., 2011, p. 56). In addition, 78% of respondents reported experiencing some kind of direct mistreatment or discrimination at work (Grant et al., 2011). Employment discrimination may be related to stigma based on a TGNC person's appearance, discrepancies in identity documentation, or being unable to provide job references linked to that person's pretransition name or gender presentation (Bender-Baird, 2011).

Issues of employment discrimination and workplace harassment are particularly salient for TGNC military personnel and veterans. Currently, TGNC people cannot serve openly in the U.S. military. Military regulations cite "transsexualism" as a medical exclusion from service (Department of Defense, 2011; Elders & Steinman, 2014). When

enlisted, TGNC military personnel are faced with very difficult decisions related to coming out, transition, and seeking appropriate medical and mental health care, which may significantly impact or end their military careers. Not surprisingly, research documents very high rates of suicidal ideation and behavior among TGNC military and veteran populations (Blosnich et al., 2013; Matarazzo et al., 2014). Being open about their TGNC identity with health care providers can carry risk for TGNC military personnel (Out-Serve-Servicemembers Legal Defense Network, n.d.). Barriers to accessing health care noted by TGNC veterans include viewing the VA health care system as an extension of the military, perceiving the VA as an unwelcoming environment, and fearing providers' negative reactions to their identity (Sherman, Kauth, Shipherd, & Street, 2014; Shipherd, Mizock, Maguen, & Green, 2012). A recent study shows 28% of LGBT veterans perceived their VA as welcoming and one third as unwelcoming (Sherman et al., 2014). Multiple initiatives are underway throughout the VA system to improve the quality and sensitivity of services to LGBT veterans.

Given widespread workplace discrimination and possible dismissal following transition, TGNC people may engage in sex work or survival sex (e.g., trading sex for food), or sell drugs to generate income (Grant et al., 2011; Hwang & Nuttbrock, 2007; Operario, Soma, & Underhill, 2008; Stanley, 2011). This increases the potential for negative interactions with the legal system, such as harassment by the police, bribery, extortion, and arrest (Edelman, 2011; Testa et al., 2012), as well as increased likelihood of mental health symptoms and greater health risks, such as higher incidence of sexually transmitted infections, including HIV (Nemoto, Operario, Keatley, & Villegas, 2004).

Incarcerated TGNC people report harassment, isolation, forced sex, and physical assault, both by prison personnel and other inmates (American Civil Liberties Union National Prison Project, 2005; Brothman, 2013; C. Daley, 2005). In sex-segregated facilities, TGNC people may be subjected to involuntary solitary confinement (also called "administrative segregation"), which can lead to severe negative mental and physical health consequences and may block access to services (Gallagher, 2014; National Center for Transgender Equality, 2012). Another area of concern is for TGNC immigrants and refugees. TGNC people in detention centers may not be granted access to necessary care and experience significant rates of assault and violence in these facilities (Gruberg, 2013). TGNC people may seek asylum in the United States to escape danger as a direct result of lack of protections in their country of origin (APA Presidential Task Force on Immigration, 2012; Cerezo, Morales, Quintero, & Rothman, 2014; Morales, 2013).

TGNC people have difficulty accessing necessary health care (Fredriksen-Goldsen et al., 2014; Lambda Legal, 2012) and often feel unsafe sharing their gender identity or their experiences of antitrans prejudice and discrimination due to historical and current discrimination from health care providers (Grant et al., 2011; Lurie, 2005; Singh & McKleroy, 2011). Even when TGNC people have health insurance, plans may explicitly exclude coverage

related to gender transition (e.g., hormone therapy, surgery). TGNC people may also have difficulty accessing trans-affirmative primary health care if coverage for procedures is denied based on gender. For example, trans men may be excluded from necessary gynecological care based on the assumption that men do not need these services. These barriers often lead to a lack of preventive health care for TGNC people (Fredriksen-Goldsen et al., 2014; Lambda Legal, 2012). Although the landscape is beginning to change with the recent revision of Medicare policy (National Center for Transgender Equality, 2014) and changes to state laws (Transgender Law Center, n.d.), many TGNC people are still likely to have little to no access to TGNC-related health care as a result of the exclusions in their insurance.

Application. Awareness of and sensitivity to the effects of antitrans prejudice and discrimination can assist psychologists in assessing, treating, and advocating for their TGNC clients. When a TGNC person faces discrimination based on gender identity or gender expression, psychologists may facilitate emotional processing of these experiences and work with the person to identify supportive resources and possible courses of action. Specific needs of TGNC people might vary from developing self-advocacy strategies, to navigating public spaces, to seeking legal recourse for harassment and discrimination in social services and other systems. Additionally, TGNC people who have been traumatized by physical or emotional violence may need therapeutic support.

Psychologists may be able to assist TGNC people in accessing relevant social service systems. For example, psychologists may be able to assist in identifying health care providers and housing resources that are affirming and affordable, or locating affirming religious and spiritual communities (Glaser, 2008; Porter et al., 2013). Psychologists may also assist in furnishing documentation or official correspondence that affirms gender identity for the purpose of accessing appropriate public accommodations, such as bathroom use or housing (Lev, 2009; W. J. Meyer, 2009).

Additionally, psychologists may identify appropriate resources, information, and services to help TGNC people in addressing workplace discrimination, including strategies during a social and/or medical transition for identity disclosure at work. For those who are seeking employment, psychologists may help strategize about how and whether to share information about gender history. Psychologists may also work with employers to develop supportive policies for workplace gender transition or to develop training to help employees adjust to the transition of a coworker.

For TGNC military and veteran populations, psychologists may help to address the emotional impact of navigating TGNC identity development in the military system. Psychologists are encouraged to be aware that issues of confidentiality may be particularly sensitive with active duty or reserve status service members, as the consequences of being identified as TGNC may prevent the client's disclosure of gender identity in treatment.

In educational settings, psychologists may advocate for TGNC youth on a number of levels (APA & National

Association of School Psychologists, 2014; Boulder Valley School District, 2012). Psychologists may consult with administrators, teachers, and school counselors to provide resources and trainings on antitrans prejudice and developing safer school environments for TGNC students (Singh & Burnes, 2009). Peer support from other TGNC people has been shown to buffer the negative effect of stigma on mental health (Bockting et al., 2013). As such, psychologists may consider and develop peer-based interventions to facilitate greater understanding and respectful treatment of TGNC youth by cisgender peers (Case & Meier, 2014). Psychologists may work with TGNC youth and their families to identify relevant resources, such as school policies that protect gender identity and gender expression (APA & National Association of School Psychologists, 2014; Gonzalez & McNulty, 2010), referrals to TGNC-affirmative organizations, and online resources, which may be especially helpful for TGNC youth in rural settings.

Guideline 6. Psychologists strive to recognize the influence of institutional barriers on the lives of TGNC people and to assist in developing TGNC-affirmative environments.

Rationale. Antitrans prejudice and the adherence of mainstream society to the gender binary adversely affect TGNC people within their families, schools, health care, legal systems, workplaces, religious traditions, and communities (American Civil Liberties Union National Prison Project, 2005; Bradford et al., 2013; Brewster et al., 2014; Levy & Lo, 2013; McGuire, Anderson, & Toomey, 2010). TGNC people face challenges accessing gender-inclusive restrooms, which may result in discomfort when being forced to use a men's or women's restroom (Transgender Law Center, 2005). In addition to the emotional distress the forced binary choice that public restrooms may create for some, TGNC people are frequently concerned with others' reactions to their presence in public restrooms, including potential discrimination, harassment, and violence (Herman, 2013).

Many TGNC people may be distrustful of care providers due to previous experiences of being pathologized (Benson, 2013). Experiences of discrimination and prejudice with health care providers may be complicated by power differentials within the therapeutic relationship that may greatly affect or complicate the care that TGNC people experience. TGNC people have routinely been asked to obtain an endorsement letter from a psychologist attesting to the stability of their gender identity as a prerequisite to access an endocrinologist, surgeon, or legal institution (e.g., driver's license bureau; Lev, 2009). The need for such required documentation from a psychologist may influence rapport, resulting in TGNC people fearing prejudicial treatment in which this documentation is withheld or delayed by the treating provider (Bouman et al., 2014). Whether a TGNC person has personally experienced interactions with providers as disempowering or has learned from community members to expect such a dynamic, psychologists are encouraged to be prepared for TGNC people to be very cautious when entering into a therapeutic rela-

tionship. When TGNC people feel validated and empowered within the environment in which a psychologist practices, the therapeutic relationship will benefit and the person may be more willing to explore their authentic selves and share uncertainties and ambiguities that are a common part of TGNC identity development.

Application. Because many TGNC people experience antitrans prejudice or discrimination, psychologists are encouraged to ensure that their work settings are welcoming and respectful of TGNC people, and to be mindful of what TGNC people may perceive as unwelcoming. To do so, psychologists may educate themselves about the many ways that cisgender privilege and antitrans prejudice may be expressed. Psychologists may also have specific conversations with TGNC people about their experiences of the mental health system and implement feedback to foster TGNC-affirmative environments. As a result, when TGNC people access various treatment settings and public spaces, they may experience less harm, disempowerment, or pathologization, and thus will be more likely to avail themselves of resources and support.

Psychologists are encouraged to be proactive in considering how overt or subtle cues in their workplaces and other environments may affect the comfort and safety of TGNC people. To increase the comfort of TGNC people, psychologists are encouraged to display TGNC-affirmative resources in waiting areas and to avoid the display of items that reflect antitrans attitudes (Lev, 2009). Psychologists are encouraged to examine how their language (e.g., use of incorrect pronouns and names) may reinforce the gender binary in overt or subtle and unintentional ways (Smith, Shin, & Officer, 2012). It may be helpful for psychologists to provide training for support staff on how to respectfully interact with TGNC people. A psychologist may consider making changes to paperwork, forms, or outreach materials to ensure that these materials are more inclusive of TGNC people (Spade, 2011b). For example, demographic questionnaires can communicate respect through the use of inclusive language and the inclusion of a range of gender identities. In addition, psychologists may also work within their institutions to advocate for restrooms that are inclusive and accessible for people of all gender identities and/or gender expressions.

When working with TGNC people in a variety of care and institutional settings (e.g., inpatient medical and psychiatric hospitals, substance abuse treatment settings, nursing homes, foster care, religious communities, military and VA health care settings, and prisons), psychologists may become liaisons and advocates for TGNC people's mental health needs and for respectful treatment that addresses their gender identity in an affirming manner. In playing this role, psychologists may find guidance and best practices that have been published for particular institutional contexts to be helpful (e.g., Department of Veterans Affairs, Veterans' Health Administration, 2013; Glezer, McNeil, & Binder, 2013; Merksamer, 2011).

Guideline 7: Psychologists understand the need to promote social change that reduces the negative effects of stigma on the health and well-being of TGNC people.

Rationale. The lack of public policy that addresses the needs of TGNC people creates significant hardships for them (Taylor, 2007). Although there have been major advances in legal protections for TGNC people in recent years (Buzuvis, 2013; Harvard Law Review Association, 2013), many TGNC people are still not afforded protections from discrimination on the basis of gender identity or expression (National LGBTQ Task Force, 2013; Taylor, 2007). For instance, in many states, TGNC people do not have employment or housing protections and may be fired or lose their housing based on their gender identity. Many policies that protect the rights of cisgender people, including LGB people, do not protect the rights of TGNC people (Currah, & Minter, 2000; Spade, 2011a).

TGNC people can experience challenges obtaining gender-affirming identity documentation (e.g., birth certificate, passport, social security card, driver's license). For TGNC people experiencing poverty or economic hardship, requirements for obtaining this documentation may be impossible to meet, in part due to the difficulty of securing employment without identity documentation that aligns with their gender identity and gender expression (Sheridan, 2009). Additionally, systemic barriers related to binary gender identification systems prevent some TGNC people from changing their documents, including those who are incarcerated, undocumented immigrants, and people who live in jurisdictions that explicitly forbid such changes (Spade, 2006). Documentation requirements can also assume a universal TGNC experience that marginalizes some TGNC people, especially those who do not undergo a medical transition. This may affect a TGNC person's social and psychological well-being and interfere with accessing employment, education, housing and shelter, health care, public benefits, and basic life management resources (e.g., opening a bank account).

Application. Psychologists are encouraged to inform public policy to reduce negative systemic impact on TGNC people and to promote positive social change. Psychologists are encouraged to identify and improve systems that permit violence; educational, employment, and housing discrimination; lack of access to health care; unequal access to other vital resources; and other instances of systemic inequity that TGNC people experience (ACA, 2010). Many TGNC people experience stressors from constant barriers, inequitable treatment, and forced release of sensitive and private information about their bodies and their lives (Hendricks & Testa, 2012). To obtain proper identity documentation, TGNC people may be required to provide court orders, proof of having had surgery, and documentation of psychotherapy or a psychiatric diagnosis. Psychologists may assist TGNC people by normalizing their reactions of fatigue and traumatization while interacting with legal systems and requirements; TGNC people may also benefit from guidance about alternate avenues of

recourse, self-advocacy, or appeal. When TGNC people feel that it is unsafe to advocate for themselves, psychologists may work with their clients to access appropriate resources in the community.

Psychologists are encouraged to be sensitive to the challenges of attaining gender-affirming identity documentation and how the receipt or denial of such documentation may affect social and psychological well-being, the person's ability to obtain education and employment, find safe housing, access public benefits, obtain student loans, and access health insurance. It may be of significant assistance for psychologists to understand and offer information about the process of a legal name change, gender marker change on identification, or the process for accessing other gender-affirming documents. Psychologists may consult the National Center for Transgender Equality, the Sylvia Rivera Law Project, or the Transgender Law Center for additional information on identity documentation for TGNC people.

Psychologists may choose to become involved with an organization that seeks to revise law and public policy to better protect the rights and dignities of TGNC people. Psychologists may participate at the local, state, or national level to support TGNC-affirmative health care accessibility, human rights in sex-segregated facilities, or policy change regarding gender-affirming identity documentation. Psychologists working in institutional settings may also expand their roles to work as collaborative advocates for TGNC people (Gonzalez & McNulty, 2010). Psychologists are encouraged to provide written affirmations supporting TGNC people and their gender identity so that they may access necessary services (e.g., hormone therapy).

Life Span Development

Guideline 8. Psychologists working with gender-questioning⁴ and TGNC youth understand the different developmental needs of children and adolescents, and that not all youth will persist in a TGNC identity into adulthood.

Rationale. Many children develop stability (constancy across time) in their gender identity between Ages 3 to 4 (Kohlberg, 1966), although gender consistency (recognition that gender remains the same across situations) often does not occur until Ages 4 to 7 (Siegal & Robinson, 1987). Children who demonstrate gender nonconformity in preschool and early elementary years may not follow this trajectory (Zucker & Bradley, 1995). Existing research suggests that between 12% and 50% of children diagnosed with gender dysphoria may persist in their identification with a gender different than sex assigned at birth into late adolescence and young adulthood (Drummond, Bradley,

⁴ Gender-questioning youth are differentiated from TGNC youth in this section of the guidelines. Gender-questioning youth may be questioning or exploring their gender identity but have not yet developed a TGNC identity. As such, they may not be eligible for some services that would be offered to TGNC youth. Gender-questioning youth are included here because gender questioning may lead to a TGNC identity.

Peterson-Badaali, & Zucker, 2008; Steensma, McGuire, Kreukels, Beekman, & Cohen-Kettenis, 2013; Wallien & Cohen-Kettenis, 2008). However, several research studies categorized 30% to 62% of youth who did not return to the clinic for medical intervention after initial assessment, and whose gender identity may be unknown, as “desisters” who no longer identified with a gender different than sex assigned at birth (Steensma et al., 2013; Wallien & Cohen-Kettenis, 2008; Zucker, 2008a). As a result, this research runs a strong risk of inflating estimates of the number of youth who do not persist with a TGNC identity. Research has suggested that children who identify more intensely with a gender different than sex assigned at birth are more likely to persist in this gender identification into adolescence (Steensma et al., 2013), and that when gender dysphoria persists through childhood and intensifies into adolescence, the likelihood of long-term TGNC identification increases (A. L. de Vries, Steensma, Doreleijers, & Cohen-Kettenis, 2011; Steensma et al., 2013; Wallien & Cohen-Kettenis, 2008; Zucker, 2008b). Gender-questioning children who do not persist may be more likely to later identify as gay or lesbian than non-gender-questioning children (Bailey & Zucker, 1995; Drescher, 2014; Wallien & Cohen-Kettenis, 2008).

A clear distinction between care of TGNC and gender-questioning children and adolescents exists in the literature. Due to the evidence that not all children persist in a TGNC identity into adolescence or adulthood, and because no approach to working with TGNC children has been adequately, empirically validated, consensus does not exist regarding best practice with prepubertal children. Lack of consensus about the preferred approach to treatment may be due in part to divergent ideas regarding what constitutes optimal treatment outcomes for TGNC and gender-questioning youth (Hembree et al., 2009). Two distinct approaches exist to address gender identity concerns in children (Hill, Menvielle, Sica, & Johnson, 2010; Wallace & Russell, 2013), with some authors subdividing one of the approaches to suggest three (Byne et al., 2012; Drescher, 2014; Stein, 2012).

One approach encourages an affirmation and acceptance of children’s expressed gender identity. This may include assisting children to socially transition and to begin medical transition when their bodies have physically developed, or allowing a child’s gender identity to unfold without expectation of a specific outcome (A. L. de Vries & Cohen-Kettenis, 2012; Edwards-Leeper & Spack, 2012; Ehrensaft, 2012; Hidalgo et al., 2013; Tishelman et al., 2015). Clinicians using this approach believe that an open exploration and affirmation will assist children to develop coping strategies and emotional tools to integrate a positive TGNC identity should gender questioning persist (Edwards-Leeper & Spack, 2012).

In the second approach, children are encouraged to embrace their given bodies and to align with their assigned gender roles. This includes endorsing and supporting behaviors and attitudes that align with the child’s sex assigned at birth prior to the onset of puberty (Zucker, 2008a; Zucker, Wood, Singh, & Bradley, 2012). Clinicians using

this approach believe that undergoing multiple medical interventions and living as a TGNC person in a world that stigmatizes gender nonconformity is a less desirable outcome than one in which children may be assisted to happily align with their sex assigned at birth (Zucker et al., 2012). Consensus does not exist regarding whether this approach may provide benefit (Zucker, 2008a; Zucker et al., 2012) or may cause harm or lead to psychosocial adversities (Hill et al., 2010; Pyne, 2014; Travers et al., 2012; Wallace & Russell, 2013). When addressing psychological interventions for children and adolescents, the World Professional Association for Transgender Health Standards of Care identify interventions “aimed at trying to change gender identity and expression to become more congruent with sex assigned at birth” as unethical (Coleman et al., 2012, p. 175). It is hoped that future research will offer improved guidance in this area of practice (Adelson & AACAP CQI, 2012; Malpas, 2011).

Much greater consensus exists regarding practice with adolescents. Adolescents presenting with gender identity concerns bring their own set of unique challenges. This may include having a late-onset (i.e., postpubertal) presentation of gender nonconforming identification, with no history of gender role nonconformity or gender questioning in childhood (Edwards-Leeper & Spack, 2012). Complicating their clinical presentation, many gender-questioning adolescents also present with co-occurring psychological concerns, such as suicidal ideation, self-injurious behaviors (Liu & Mustanski, 2012; Mustanski, Garofalo, & Emerson, 2010), drug and alcohol use (Garofalo et al., 2006), and autism spectrum disorders (A. L. de Vries, Noens, Cohen-Kettenis, van Berckelaer-Onnes, & Doreleijers, 2010; Jones et al., 2012). Additionally, adolescents can become intensely focused on their immediate desires, resulting in outward displays of frustration and resentment when faced with any delay in receiving the medical treatment from which they feel they would benefit and to which they feel entitled (Angello, 2013; Edwards-Leeper & Spack, 2012). This intense focus on immediate needs may create challenges in assuring that adolescents are cognitively and emotionally able to make life-altering decisions to change their name or gender marker, begin hormone therapy (which may affect fertility), or pursue surgery.

Nonetheless, there is greater consensus that treatment approaches for adolescents affirm an adolescents’ gender identity (Coleman et al., 2012). Treatment options for adolescents extend beyond social approaches to include medical approaches. One particular medical intervention involves the use of puberty-suppressing medication or “blockers” (GnRH analogue), which is a reversible medical intervention used to delay puberty for appropriately screened adolescents with gender dysphoria (Coleman et al., 2012; A. L. C. de Vries et al., 2014; Edwards-Leeper, & Spack, 2012). Because of their age, other medical interventions may also become available to adolescents, and psychologists are frequently consulted to provide an assessment of whether such procedures would be advisable (Coleman et al., 2012).

Application. Psychologists working with TGNC and gender-questioning youth are encouraged to regularly review the most current literature in this area, recognizing the limited available research regarding the potential benefits and risks of different treatment approaches for children and for adolescents. Psychologists are encouraged to offer parents and guardians clear information about available treatment approaches, regardless of the specific approach chosen by the psychologist. Psychologists are encouraged to provide psychological service to TGNC and gender-questioning children and adolescents that draws from empirically validated literature when available, recognizing the influence psychologists' values and beliefs may have on the treatment approaches they select (Ehrbar & Gorton, 2010). Psychologists are also encouraged to remain aware that what one youth and/or parent may be seeking in a therapeutic relationship may not coincide with a clinician's approach (Brill & Pepper, 2008). In cases in which a youth and/or parent identify different preferred treatment outcomes than a clinician, it may not be clinically appropriate for the clinician to continue working with the youth and family, and alternative options, including referral, might be considered. Psychologists may also find themselves navigating family systems in which youth and their caregivers are seeking different treatment outcomes (Edwards-Leeper & Spack, 2012). Psychologists are encouraged to carefully reflect on their personal values and beliefs about gender identity development in conjunction with the available research, and to keep the best interest of the child or adolescent at the forefront of their clinical decisions at all times.

Because gender nonconformity may be transient for younger children in particular, the psychologist's role may be to help support children and their families through the process of exploration and self-identification (Ehrensaft, 2012). Additionally, psychologists may provide parents with information about possible long-term trajectories children may take in regard to their gender identity, along with the available medical interventions for adolescents whose TGNC identification persists (Edwards-Leeper & Spack, 2012).

When working with adolescents, psychologists are encouraged to recognize that some TGNC adolescents will not have a strong history of childhood gender role nonconformity or gender dysphoria either by self-report or family observation (Edwards-Leeper & Spack, 2012). Some of these adolescents may have withheld their feelings of gender nonconformity out of a fear of rejection, confusion, conflating gender identity and sexual orientation, or a lack of awareness of the option to identify as TGNC. Parents of these adolescents may need additional assistance in understanding and supporting their youth, given that late-onset gender dysphoria and TGNC identification may come as a significant surprise. Moving more slowly and cautiously in these cases is often advisable (Edwards-Leeper & Spack, 2012). Given the possibility of adolescents' intense focus on immediate desires and strong reactions to perceived delays or barriers, psychologists are encouraged to validate these concerns and the desire to move through the process

quickly while also remaining thoughtful and deliberate in treatment. Adolescents and their families may need support in tolerating ambiguity and uncertainty with regard to gender identity and its development (Brill & Pepper, 2008). It is encouraged that care should be taken not to foreclose this process.

For adolescents who exhibit a long history of gender nonconformity, psychologists may inform parents that the adolescent's self-affirmed gender identity is most likely stable (A. L. de Vries et al., 2011). The clinical needs of these adolescents may be different than those who are in the initial phases of exploring or questioning their gender identity. Psychologists are encouraged to complete a comprehensive evaluation and ensure the adolescent's and family's readiness to progress while also avoiding unnecessary delay for those who are ready to move forward.

Psychologists working with TGNC and gender-questioning youth are encouraged to become familiar with medical treatment options for adolescents (e.g., puberty-suppressing medication, hormone therapy) and work collaboratively with medical providers to provide appropriate care to clients. Because the ongoing involvement of a knowledgeable mental health provider is encouraged due to the psychosocial implications, and is often also a required part of the medical treatment regimen that may be offered to TGNC adolescents (Coleman et al., 2012; Hembree et al., 2009), psychologists often play an essential role in assisting in this process.

Psychologists may encourage parents and caregivers to involve youth in developmentally appropriate decision making about their education, health care, and peer networks, as these relate to children's and adolescents' gender identity and gender expression (Ryan, Russell, Huebner, Diaz, & Sanchez, 2010). Psychologists are also encouraged to educate themselves about the advantages and disadvantages of social transition during childhood and adolescence, and to discuss these factors with both their young clients and clients' parents. Emphasizing to parents the importance of allowing their child the freedom to return to a gender identity that aligns with sex assigned at birth or another gender identity at any point cannot be overstated, particularly given the research that suggests that not all young gender nonconforming children will ultimately express a gender identity different from that assigned at birth (Wallien, & Cohen-Kettenis, 2008; Zucker & Bradley, 1995). Psychologists are encouraged to acknowledge and explore the fear and burden of responsibility that parents and caregivers may feel as they make decisions about the health of their child or adolescent (Grossman, D'Augelli, Howell, & Hubbard, 2006). Parents and caregivers may benefit from a supportive environment to discuss feelings of isolation, explore loss and grief they may experience, vent anger and frustration at systems that disrespect or discriminate against them and their youth, and learn how to communicate with others about their child's or adolescent's gender identity or gender expression (Brill & Pepper, 2008).

Guideline 9. Psychologists strive to understand both the particular challenges that TGNC elders experience and the resilience they can develop.

Rationale. Little research has been conducted about TGNC elders, leaving much to be discovered about this life stage for TGNC people (Auldrige, Tamar-Mattis, Kennedy, Ames, & Tobin, 2012). Socialization into gender role behaviors and expectations based on sex assigned at birth, as well as the extent to which TGNC people adhere to these societal standards, is influenced by the chronological age at which a person self-identifies as TGNC, the age at which a person comes out or socially and/or medically transitions (Birren & Schaie, 2006; Bockting & Coleman, 2007; Cavanaugh & Blanchard-Fields, 2010; Nuttbrock et al., 2010; Wahl, Iwarsson, & Oswald, 2012), and a person's generational cohort (e.g., 1950 vs. 2010; Fredriksen-Goldsen et al., 2011).

Even decades after a medical or social transition, TGNC elders may still subscribe to the predominant gender role expectations that existed at the time of their transition (Knochel, Croghan, Moore, & Quam, 2011). Prior to the 1980s, TGNC people who transitioned were strongly encouraged by providers to pass in society as cisgender and heterosexual and to avoid associating with other TGNC people (Benjamin, 1966; R. Green & Money, 1969; Hastings, 1974; Hastings & Markland, 1978). Even TGNC elders who were comfortable telling others about their TGNC identity when they were younger may choose not to reveal their identity at a later stage of life (Ekins & King, 2005; Ippolito & Witten, 2014). Elders' unwillingness to disclose their TGNC identity can result from feelings of physical vulnerability or increased reliance on others who may discriminate against them or treat them poorly as a result of their gender identity (Bockting & Coleman, 2007), especially if the elder resides in an institutionalized setting (i.e., nursing home, assisted living facility) and relies on others for many daily needs (Auldrige et al., 2012). TGNC elders are also at a heightened risk for depression, suicidal ideation, and loneliness compared with LGB elders (Auldrige et al., 2012; Fredriksen-Goldsen et al., 2011).

A Transgender Law Center survey found that TGNC and LGB elders had less financial well-being than their younger cohorts, despite having a higher than average educational level for their age group compared with the general population (Hartzell, Frazer, Wertz, & Davis, 2009). Survey research has also revealed that TGNC elders experience underemployment and gaps in employment, often due to discrimination (Auldrige et al., 2012; Beemyn & Rankin, 2011; Factor & Rothblum, 2007). In the past, some TGNC people with established careers may have been encouraged by service providers to find new careers or jobs to avoid undergoing a gender transition at work or being identified as TGNC, potentially leading to a significant loss of income and occupational identity (Cook-Daniels, 2006). Obstacles to employment can increase economic disparities that result in increased needs for supportive housing and other social services (National Center for

Transgender Equality, 2012; Services and Advocacy for GLBT Elders & National Center for Transgender Equality, 2012).

TGNC elders may face obstacles to seeking or accessing resources that support their physical, financial, or emotional well-being. For instance, they may be concerned about applying for social security benefits, fearing that their TGNC identity may become known (Hartzell et al., 2009). A TGNC elder may avoid medical care, increasing the likelihood of later needing a higher level of medical care (e.g., home-based care, assisted living, or nursing home) than their same-age cisgender peers (Hartzell et al., 2009; Ippolito & Witten, 2014; Mikalson et al., 2012). Nursing homes and assisted living facilities are rarely sensitive to the unique medical needs of TGNC elders (National Senior Citizens Law Center, 2011). Some TGNC individuals who enter congregate housing, assisted living, or long-term care settings may feel the need to reverse their transition to align with sex assigned at birth to avoid discrimination and persecution by other residents and staff (Ippolito & Witten, 2014).

Older age may both facilitate and complicate medical treatment related to gender transition. TGNC people who begin hormone therapy later in life may have a smoother transition due to waning hormone levels that are a natural part of aging (Witten & Eyler, 2012). Age may also influence the decisions TGNC elders make regarding sex-affirmation surgeries, especially if physical conditions exist that could significantly increase risks associated with surgery or recovery.

Much has been written about the resilience of elders who have endured trauma (Fuhrmann & Shevlowitz, 2006; Hardy, Concato, & Gill, 2004; Mlinac, Sheeran, Blissmer, Lees, & Martins, 2011; Rodin & Stewart, 2012). Although some TGNC elders have experienced significant psychological trauma related to their gender identity, some also have developed resilience and effective ways of coping with adversity (Fruhauf & Orel, 2015). Despite the limited availability of LGBTQ-affirmative religious organizations in many local communities, TGNC elders make greater use of these resources than their cisgender peers (Porter et al., 2013).

Application. Psychologists are encouraged to seek information about the biopsychosocial needs of TGNC elders to inform case conceptualization and treatment planning to address psychological, social, and medical concerns. Many TGNC elders are socially isolated. Isolation can occur as a result of a loss of social networks through death or through disclosure of a TGNC identity. Psychologists may assist TGNC elders in establishing new social networks that support and value their TGNC identity, while also working to strengthen existing family and friend networks after a TGNC identity has been disclosed. TGNC elders may find special value in relationships with others in their generational cohort or those who may have similar coming-out experiences. Psychologists may encourage TGNC elders to identify ways they can mentor and improve the resilience of younger TGNC generations, creating a sense of generativity (Erikson, 1968) and contribu-

tion while building new supportive relationships. Psychologists working with TGNC elders may help them recognize the sources of their resilience and encourage them to connect with and be active in their communities (Fuhrmann & Craffey, 2014).

For TGNC elders who have chosen not to disclose their gender identity, psychologists may provide support to address shame, guilt, or internalized antitrans prejudice, and validate each person's freedom to choose their pattern of disclosure. Clinicians may also provide validation and empathy when TGNC elders have chosen a model of transition that avoids any disclosure of gender identity and is heavily focused on passing as cisgender.

TGNC elders who choose to undergo a medical or social transition in older adulthood may experience antitrans prejudice from people who question the value of transition at an older age or who believe that these elders are not truly invested in their transition or in a TGNC identity given the length of time they have waited (Auldridge et al., 2012). Some TGNC elders may also grieve lost time and missed opportunities. Psychologists may validate elders' choices to come out, transition, or evolve their gender identity or gender expression at any age, recognizing that such choices may have been much less accessible or viable at earlier stages of TGNC elders' lives.

Psychologists may assist congregating housing, assisted living, or long-term care settings to best meet TGNC elders' needs through respectful communication and affirmation of each person's gender identity and gender expression. Psychologists may work with TGNC people in hospice care systems to develop an end-of-life plan that respects the person's wishes about disclosure of gender identity during and after death.

Assessment, Therapy, and Intervention

Guideline 10. Psychologists strive to understand how mental health concerns may or may not be related to a TGNC person's gender identity and the psychological effects of minority stress.

Rationale. TGNC people may seek assistance from psychologists in addressing gender-related concerns, other mental health issues, or both. Mental health problems experienced by a TGNC person may or may not be related to that person's gender identity and/or may complicate assessment and intervention of gender-related concerns. In some cases, there may not be a relationship between a person's gender identity and a co-occurring condition (e.g., depression, PTSD, substance abuse). In other cases, having a TGNC identity may lead or contribute to a co-occurring mental health condition, either directly by way of gender dysphoria, or indirectly by way of minority stress and oppression (Hendricks & Testa, 2012; I. H. Meyer, 1995, 2003). In extremely rare cases, a co-occurring condition can mimic gender dysphoria (i.e., a psychotic process that distorts the perception of one's gender; Baltieri & De

Andrade, 2009; Hepp, Kraemer, Schnyder, Miller, & Designore, 2004).

Regardless of the presence or absence of an etiological link, gender identity may affect how a TGNC person experiences a co-occurring mental health condition, and/or a co-occurring mental health condition may complicate the person's gender expression or gender identity. For example, an eating disorder may be influenced by a TGNC person's gender expression (e.g., rigid eating patterns used to manage body shape or menstruation may be related to gender identity or gender dysphoria; Ålgars, Alanko, Santtila, & Sandnabba, 2012; Murray, Boon, & Touyz, 2013). In addition, the presence of autism spectrum disorder may complicate a TGNC person's articulation and exploration of gender identity (Jones et al., 2012). In cases in which gender dysphoria is contributing to other mental health concerns, treatment of gender dysphoria may be helpful in alleviating those concerns as well (Keo-Meier et al., 2015).

A relationship also exists between mental health conditions and the psychological sequelae of minority stress that TGNC people can experience. Given that TGNC people experience physical and sexual violence (Clements-Nolle et al., 2006; Kenagy & Bostwick, 2005; Lombardi, Wilchins, Priesing, & Malouf, 2001; Xavier et al., 2005), general harassment and discrimination (Beemyn & Rankin, 2011; Factor & Rothblum, 2007), and employment and housing discrimination (Bradford et al., 2007), they are likely to experience significant levels of minority stress. Studies have demonstrated the disproportionately high levels of negative psychological sequelae related to minority stress, including suicidal ideation and suicide attempts (Center for Substance Abuse Treatment, 2012; Clements-Nolle et al., 2006; Cochran & Cauce, 2006; Nuttbrock et al., 2010; Xavier et al., 2005) and completed suicides (Dhejne et al., 2011; van Kesteren, Asscheman, Megens, & Gooren, 1997). Recent studies have begun to demonstrate an association between sources of external stress and psychological distress (Bockting et al., 2013; Nuttbrock et al., 2010), including suicidal ideation and attempts and self-injurious behavior (Dickey, Reisner, & Juntunen, 2015; Goldblum et al., 2012; Testa et al., 2012).

The minority stress model accounts for both the negative mental health effects of stigma-related stress and the processes by which members of the minority group may develop resilience and resistance to the negative effects of stress (I. H. Meyer, 1995, 2003). Although the minority stress model was developed as a theory of the relationship between sexual orientation and mental disorders, the model has been adapted to TGNC populations (Hendricks & Testa, 2012).

Application. Because of the increased risk of stress-related mental health conditions, psychologists are encouraged to conduct a careful diagnostic assessment, including a differential diagnosis, when working with TGNC people (Coleman et al., 2012). Taking into account the intricate interplay between the effects of mental health symptoms and gender identity and gender expression, psychologists are encouraged to neither ignore mental health problems a TGNC person is experiencing, nor erroneously

assume that those mental health problems are a result of the person's gender identity or gender expression. Psychologists are strongly encouraged to be cautious before determining that gender nonconformity or dysphoria is due to an underlying psychotic process, as this type of causal relationship is rare.

When TGNC people seek to access transition-related health care, a psychosocial assessment is often part of this process (Coleman et al., 2012). A comprehensive and balanced assessment typically includes not only information about a person's past experiences of antitrans prejudice or discrimination, internalized messages related to these experiences, and anticipation of future victimization or rejection (Coolhart, Provancher, Hager, & Wang, 2008), but also coping strategies and sources of resilience (Hendricks & Testa, 2012; Singh et al., 2011). Gathering information about negative life events directly related to a TGNC person's gender identity and gender expression may assist psychologists in understanding the sequelae of stress and discrimination, distinguishing them from concurrent and potentially unrelated mental health problems. Similarly, when a TGNC person has a primary presenting concern that is not gender focused, a comprehensive assessment takes into account that person's experience relative to gender identity and gender expression, including any discrimination, just as it would include assessing other potential trauma history, medical concerns, previous experience with helping professionals, important future goals, and important aspects of identity. Strategies a TGNC person uses to navigate antitrans discrimination could be sources of strength to deal with life challenges or sources of distress that increase challenges and barriers.

Psychologists are encouraged to help TGNC people understand the pervasive influence of minority stress and discrimination that may exist in their lives, potentially including internalized negative attitudes about themselves and their TGNC identity (Hendricks & Testa, 2012). With this support, clients can better understand the origins of their mental health symptoms and normalize their reactions when faced with TGNC-related inequities and discrimination. Minority stress models also identify potentially important sources of resilience. TGNC people can develop resilience when they connect with other TGNC people who provide information on how to navigate antitrans prejudice and increase access to necessary care and resources (Singh et al., 2011). TGNC people may need help developing social support systems to nurture their resilience and bolster their ability to cope with the adverse effects of antitrans prejudice and/or discrimination (Singh & McKleroy, 2011).

Feminizing or masculinizing hormone therapy can positively or negatively affect existing mood disorders (Coleman et al., 2012). Psychologists may also help TGNC people who are in the initial stages of hormone therapy adjust to normal changes in how they experience emotions. For example, trans women who begin estrogens and anti-androgens may experience a broader range of emotions than they are accustomed to, or trans men beginning testosterone might be faced with adjusting to a higher libido

and feeling more emotionally reactive in stressful situations. These changes can be normalized as similar to the emotional adjustments that cisgender women and men experience during puberty. Some TGNC people will be able to adapt existing coping strategies, whereas others may need help developing additional skills (e.g., emotional regulation or assertiveness). Readers are encouraged to refer to the World Professional Association for Transgender Health Standards of Care for discussion of the possible effects of hormone therapy on a TGNC person's mood, affect, and behavior (Coleman et al., 2012).

Guideline 11. Psychologists recognize that TGNC people are more likely to experience positive life outcomes when they receive social support or trans-affirmative care.

Rationale. Research has primarily shown positive treatment outcomes when TGNC adults and adolescents receive TGNC-affirmative medical and psychological services (i.e., psychotherapy, hormones, surgery; Byne et al., 2012; R. Carroll, 1999; Cohen-Kettenis, Delemarre-van de Waal, & Gooren, 2008; Davis & Meier, 2014; De Cuypere et al., 2006; Gooren, Giltay, & Bunck, 2008; Kuhn et al., 2009), although sample sizes are frequently small with no population-based studies. In a meta-analysis of the hormone therapy treatment literature with TGNC adults and adolescents, researchers reported that 80% of participants receiving trans-affirmative care experienced an improved quality of life, decreased gender dysphoria, and a reduction in negative psychological symptoms (Murad et al., 2010).

In addition, TGNC people who receive social support about their gender identity and gender expression have improved outcomes and quality of life (Brill & Pepper, 2008; Pinto, Melendez, & Spector, 2008). Several studies indicate that family acceptance of TGNC adolescents and adults is associated with decreased rates of negative outcomes, such as depression, suicide, and HIV risk behaviors and infection (Bockting et al., 2013; Dhejne et al., 2011; Grant et al., 2011; Liu & Mustanski, 2012; Ryan, 2009). Family support is also a strong protective factor for TGNC adults and adolescents (Bockting et al., 2013; Moody & Smith, 2013; Ryan et al., 2010). TGNC people, however, frequently experience blatant or subtle antitrans prejudice, discrimination, and even violence within their families (Bradford et al., 2007). Such family rejection is associated with higher rates of HIV infection, suicide, incarceration, and homelessness for TGNC adults and adolescents (Grant et al., 2011; Liu & Mustanski, 2012). Family rejection and lower levels of social support are significantly correlated with depression (Clements-Nolle et al., 2006; Ryan, 2009). Many TGNC people seek support through peer relationships, chosen families, and communities in which they may be more likely to experience acceptance (Gonzalez & McNulty, 2010; Nuttbrock et al., 2009). Peer support from other TGNC people has been found to be a moderator between antitrans discrimination and mental health, with higher levels of peer support associated with better mental health (Bockting et al., 2013). For some TGNC people, support from religious and spiritual communities provides

an important source of resilience (Glaser, 2008; Kidd & Witten, 2008; Porter et al., 2013).

Application. Given the strong evidence for the positive influence of affirmative care, psychologists are encouraged to facilitate access to and provide trans-affirmative care to TGNC people. Whether through the provision of assessment and psychotherapy, or through assisting clients to access hormone therapy or surgery, psychologists may play a critical role in empowering and validating TGNC adults' and adolescents' experiences and increasing TGNC people's positive life outcomes (Bess & Stabb, 2009; Rachlin, 2002).

Psychologists are also encouraged to be aware of the importance of affirmative social support and assist TGNC adults and adolescents in building social support networks in which their gender identity is accepted and affirmed. Psychologists may assist TGNC people in negotiating family dynamics that may arise in the course of exploring and establishing gender identity. Depending on the context of psychological practice, these issues might be addressed in individual work with TGNC clients, conjoint sessions including members of their support system, family therapy, or group therapy. Psychologists may help TGNC people decide how and when to reveal their gender identity at work or school, in religious communities, and to friends and contacts in other settings. TGNC people who decide not to come out in all aspects of their lives can still benefit from TGNC-affirmative in-person or online peer support groups.

Clients may ask psychologists to assist family members in exploring feelings about their loved one's gender identity and gender expression. Published models of family adjustment (Emerson & Rosenfeld, 1996) may be useful to help normalize family members' reactions upon learning that they have a TGNC family member, and to reduce feelings of isolation. When working with family members or significant others, it may be helpful to normalize feelings of loss or fear of what may happen to current relationships as TGNC people disclose their gender identity and expression to others. Psychologists may help significant others adjust to changing relationships and consider how to talk to extended family, friends, and other community members about TGNC loved ones. Providing significant others with referrals to TGNC-affirmative providers, educational resources, and support groups can have a profound impact on their understanding of gender identity and their communication with TGNC loved ones. Psychologists working with couples and families may also help TGNC people identify ways to include significant others in their social or medical transition.

Psychologists working with TGNC people in rural settings may provide clients with resources to connect with other TGNC people online or provide information about in-person support groups in which they can explore the unique challenges of being TGNC in these geographic areas (Walinsky & Whitcomb, 2010). Psychologists serving TGNC military and veteran populations are encouraged to be sensitive to the barriers these individuals face, especially for people who are on active duty in the U.S. military

(OutServe-Servicemembers Legal Defense Network, n.d.). Psychologists may help TGNC military members and veterans establish specific systems of support that create a safe and affirming space to reduce isolation and to create a network of peers with a shared military experience. Psychologists who work with veterans are encouraged to educate themselves on recent changes to VA policy that support equal access to VA medical and mental health services (Department of Veterans Affairs, Veterans' Health Administration, 2013).

Guideline 12. Psychologists strive to understand the effects that changes in gender identity and gender expression have on the romantic and sexual relationships of TGNC people.

Rationale. Relationships involving TGNC people can be healthy and successful (Kins, Hoebeke, Heylens, Rubens, & De Cuyprere, 2008; Meier, Sharp, Michonski, Babcock, & Fitzgerald, 2013) as well as challenging (Brown, 2007; Iantaffi & Bockting, 2011). A study of successful relationships between TGNC men and cisgender women found that these couples attributed the success of their relationship to respect, honesty, trust, love, understanding, and open communication (Kins et al., 2008). Just as relationships between cisgender people can involve abuse, so can relationships between TGNC people and their partners (Brown, 2007), with some violent partners threatening to disclose a TGNC person's identity to exact control in the relationship (FORGE, n.d.).

In the early decades of medical and social transition for TGNC people, only those whose sexual orientations would be heterosexual posttransition (e.g., trans woman with a cisgender man) were deemed eligible for medical and social transition (Meyerowitz, 2002). This restriction prescribed only certain relationship partners (American Psychiatric Association, 1980; Benjamin, 1966; Chivers & Bailey, 2000), denied access to surgery for trans men identifying as gay or bisexual (Coleman & Bockting, 1988), or trans women identifying as lesbian or bisexual, and even required that TGNC people's existing legal marriages be dissolved before they could gain access to transition care (Lev, 2004).

Disclosure of a TGNC identity can have an important impact on the relationship between TGNC people and their partners. Disclosure of TGNC status earlier in the relationship tends to be associated with better relationship outcomes, whereas disclosure of TGNC status many years into an existing relationship may be perceived as a betrayal (Erhardt, 2007). When a TGNC person comes out in the context of an existing relationship, it can also be helpful if both partners are involved in decision making about the use of shared resources (i.e., how to balance the financial costs of transition with other family needs) and how to share this news with shared supports (i.e., friends and family). Sometimes relationship roles are renegotiated in the context of a TGNC person coming out to their partner (Samons, 2008). Assumptions about what it means to be a "husband" or a "wife" can shift if the gender identity of one's spouse shifts

(Erhardt, 2007). Depending on when gender issues are disclosed and how much of a change this creates in the relationship, partners may grieve the loss of aspects of their partner and the way the relationship used to be (Lev, 2004).

Although increasing alignment between gender identity and gender expression, whether it be through dress, behavior, or through medical interventions (i.e., hormones, surgery), does not necessarily affect to whom a TGNC person is attracted (Coleman et al., 1993), TGNC people may become more open to exploring their sexual orientation, may redefine sexual orientation as they move through transition, or both (Daskalos, 1998; H. Devor, 1993; Schleifer, 2006). Through increased comfort with their body and gender identity, TGNC people may explore aspects of their sexual orientation that were previously hidden or that felt discordant with their sex assigned at birth. Following a medical and/or social transition, a TGNC person's sexual orientation may remain constant or shift, either temporarily or permanently (e.g., renewed exploration of sexual orientation in the context of TGNC identity, shift in attraction or choice of sexual partners, widened spectrum of attraction, shift in sexual orientation identity; Meier, Sharp et al., 2013; Samons, 2008). For example, a trans man previously identified as a lesbian may later be attracted to men (Coleman et al., 1993; dickey, Burnes, & Singh, 2012), and a trans woman attracted to women pretransition may remain attracted to women posttransition (Lev, 2004).

Some TGNC people and their partners may fear the loss of mutual sexual attraction and other potential effects of shifting gender identities in the relationship. Lesbian-identified partners of trans men may struggle with the idea that being in a relationship with a man may cause others to perceive them as a heterosexual couple (Califa, 1997). Similarly, women in heterosexual relationships who later learn that their partners are trans women may be unfamiliar with navigating stigma associated with sexual minority status when viewed as a lesbian couple (Erhardt, 2007). Additionally, partners may find they are not attracted to a partner after transition. As an example, a lesbian whose partner transitions to a male identity may find that she is no longer attracted to this person because she is not sexually attracted to men. Partners of TGNC people may also experience grief and loss as their partners engage in social and/or medical transitions.

Application. Psychologists may help foster resilience in relationships by addressing issues specific to partners of TGNC people. Psychologists may provide support to partners of TGNC people who are having difficulty with their partner's evolving gender identity or transition, or are experiencing others having difficulty with the partner's transition. Partner peer support groups may be especially helpful in navigating internalized antitrans prejudice, shame, resentment, and relationship concerns related to a partner's gender transition. Meeting or knowing other TGNC people, other partners of TGNC people, and couples who have successfully navigated transition may also help TGNC people and their partners and serve as a protective factor (Brown, 2007). When TGNC status is disclosed during an existing relationship, psychologists may help

couples explore which relationship dynamics they want to preserve and which they might like to change.

In working with psychologists, TGNC people may explore a range of issues in their relationships and sexuality (dickey et al., 2012), including when and how to come out to current or potential romantic and sexual partners, communicating their sexual desires, renegotiating intimacy that may be lost during the TGNC partner's transition, adapting to bodily changes caused by hormone use or surgery, and exploring boundaries regarding touch, affection, and safer sex practices (Iantaffi & Bockting, 2011; Sevelius, 2009). TGNC people may experience increased sexual self-efficacy through transition. Although psychologists may aid partners in understanding a TGNC person's transition decisions, TGNC people may also benefit from help in cultivating awareness of the ways in which these decisions influence the lives of loved ones.

Guideline 13. Psychologists seek to understand how parenting and family formation among TGNC people take a variety of forms.

Rationale. Psychologists work with TGNC people across the life span to address parenting and family issues (Kenagy & Hsieh, 2005). There is evidence that many TGNC people have and want children (Wierckx et al., 2012). Some TGNC people conceive a child through sexual intercourse, whereas others may foster, adopt, pursue surrogacy, or employ assisted reproductive technologies, such as sperm or egg donation, to build or expand a family (De Sutter, Kira, Verschoor, & Hotimsky, 2002). Based on a small body of research to date, there is no indication that children of TGNC parents suffer long-term negative impacts directly related to parental gender change (R. Green, 1978, 1988; White & Ettner, 2004). TGNC people may find it both challenging to find medical providers who are willing to offer them reproductive treatment and to afford the cost (Coleman et al., 2012). Similarly, adoption can be quite costly, and some TGNC people may find it challenging to find foster care or adoption agencies that will work with them in a nondiscriminatory manner. Current or past use of hormone therapy may limit fertility and restrict a TGNC person's reproductive options (Darnery, 2008; Wierckx et al., 2012). Other TGNC people may have children or families before coming out as TGNC or beginning a gender transition.

TGNC people may present with a range of parenting and family-building concerns. Some will seek support to address issues within preexisting family systems, some will explore the creation or expansion of a family, and some will need to make decisions regarding potential fertility issues related to hormone therapy, pubertal suppression, or surgical transition. The medical and/or social transition of a TGNC parent may shift family dynamics, creating challenges and opportunities for partners, children, and other family members. One study of therapists' reflections on their experiences with TGNC clients suggested that family constellation and the parental relationship was more significant for children than the parent's social and/or medical

transition itself (White & Ettner, 2004). Although research has not documented that the transitions of TGNC people have an effect on their parenting abilities, preexisting partnerships or marriages may not survive the disclosure of a TGNC identity or a subsequent transition (dickey et al., 2012). This may result in divorce or separation, which may affect the children in the family. A positive relationship between parents, regardless of marital status, has been suggested to be an important protective factor for children (Amato, 2001; White & Ettner, 2007). This seems to be the case especially when children are reminded of the parent's love and assured of the parent's continued presence in their life (White & Ettner, 2007). Based on a small body of literature available, it is generally the case that younger children are best able to incorporate the transition of a parent, followed by adult children, with adolescents generally having the most difficulty (White & Ettner, 2007). If separated or divorced from their partners or spouses, TGNC parents may be at risk for loss of custody or visitation rights because some courts presume that there is a nexus between their gender identity or gender expression and parental fitness (Flynn, 2006). This type of prejudice is especially common for TGNC people of color (Grant et al., 2011).

Application. Psychologists are encouraged to attend to the parenting and family-building concerns of TGNC people. When working with TGNC people who have previous parenting experience, psychologists may help TGNC people identify how being a parent may influence decisions to come out as TGNC or to begin a transition (Freeman, Tasker, & Di Ceglie, 2002; Grant et al., 2011; Wierckx et al., 2012). Some TGNC people may choose to delay disclosure until their children have grown and left home (Bethua & McCollum, 2013). Clinical guidelines jointly developed by a Vancouver, British Columbia, TGNC community organization and a health care provider organization encourage psychologists and other mental health providers working with TGNC people to plan for disclosure to a partner, previous partner, or children, and to pay particular attention to resources that assist TGNC people to discuss their identity with children of various ages in developmentally appropriate ways (Bockting et al., 2006). Lev (2004) uses a developmental stage framework for the process that family members are likely to go through in coming to terms with a TGNC family member's identity that some psychologists may find helpful. Awareness of peer support networks for spouses and children of TGNC people can also be helpful (e.g., PFLAG, TransYouth Family Allies). Psychologists may provide family counseling to assist a family in managing disclosure, improve family functioning, and maintain family involvement of the TGNC person, as well as aiding the TGNC person in attending to the ways that their transition process has affected their family members (Samons, 2008). Helping parents to continue to work together to focus on the needs of their children and to maintain family bonds is likely to lead to the best results for the children (White & Ettner, 2007).

For TGNC people with existing families, psychologists may support TGNC people in seeking legal counsel regarding parental rights in adoption or custody. Depending on the situation, this may be desirable even if the TGNC parent is biologically related to the child (Minter & Wald, 2012). Although being TGNC is not a legal impediment to adoption in the United States, there is the potential for overt and covert discrimination and barriers, given the widespread prejudice against TGNC people. The question of whether to disclose TGNC status on an adoption application is a personal one, and a prospective TGNC parent would benefit from consulting a lawyer for legal advice, including what the laws in their jurisdiction say about disclosure. Given the extensive background investigation frequently conducted, it may be difficult to avoid disclosure. Many lawyers favor disclosure to avoid any potential legal challenges during the adoption process (Minter & Wald, 2012).

In discussing family-building options with TGNC people, psychologists are encouraged to remain aware that some of these options require medical intervention and are not available everywhere, in addition to being quite costly (Coleman et al., 2012). Psychologists may work with clients to manage feelings of loss, grief, anger, and resentment that may arise if TGNC people are unable to access or afford the services they need for building a family (Bockting et al., 2006; De Sutter et al., 2002).

When TGNC people consider beginning hormone therapy, psychologists may engage them in a conversation about the possibly permanent effects on fertility to better prepare TGNC people to make a fully informed decision. This may be of special importance with TGNC adolescents and young adults who often feel that family planning or loss of fertility is not a significant concern in their current daily lives, and therefore disregard the long-term reproductive implications of hormone therapy or surgery (Coleman et al., 2012). Psychologists are encouraged to discuss contraception and safer sex practices with TGNC people, given that they may still have the ability to conceive even when undergoing hormone therapy (Bockting, Robinson, & Rosser, 1998). Psychologists may play a critical role in educating TGNC adolescents and young adults and their parents about the long-term effects of medical interventions on fertility and assist them in offering informed consent prior to pursuing such interventions. Although hormone therapy may limit fertility (Coleman et al., 2012), psychologists may encourage TGNC people to refrain from relying on hormone therapy as the sole means of birth control, even when a person has amenorrhea (Gorton & Grubb, 2014). Education on safer sex practices may also be important, as some segments of the TGNC community (e.g., trans women and people of color) are especially vulnerable to sexually transmitted infections and have been shown to have high prevalence and incidence rates of HIV infection (Kellogg, Clements-Nolle, Dilley, Katz, & McFarland, 2001; Nemoto, Operario, Keatley, Han, & Soma, 2004).

Depending on the timing and type of options selected, psychologists may explore the physical, social, and emotional implications should TGNC people choose to delay or

stop hormone therapy, undergo fertility treatment, or become pregnant. Psychological effects of stopping hormone therapy may include depression, mood swings, and reactions to the loss of physical masculinization or feminization facilitated by hormone therapy (Coleman et al., 2012). TGNC people who choose to halt hormone therapy during attempts to conceive or during a pregnancy may need additional psychological support. For example, TGNC people and their families may need help in managing the additional antitrans prejudice and scrutiny that may result when a TGNC person with stereotypically masculine features becomes visibly pregnant. Psychologists may also assist TGNC people in addressing their loss when they cannot engage in reproductive activities that are consistent with their gender identity, or when they encounter barriers to conceiving, adopting, or fostering children not typically faced by other people (Vanderburgh, 2007). Psychologists are encouraged to assess the degree to which reproductive health services are TGNC-affirmative prior to referring TGNC people to them. Psychologists are also encouraged to provide TGNC-affirmative information to reproductive health service personnel when there is a lack of trans-affirmative knowledge.

Guideline 14. Psychologists recognize the potential benefits of an interdisciplinary approach when providing care to TGNC people and strive to work collaboratively with other providers.

Rationale. Collaboration across disciplines can be crucial when working with TGNC people because of the potential interplay of biological, psychological, and social factors in diagnosis and treatment (Hendricks & Testa, 2012). The challenges of living with a stigmatized identity and the need of many TGNC people to transition, socially and/or medically, may call for the involvement of health professionals from various disciplines, including psychologists, psychiatrists, social workers, primary health care providers, endocrinologists, nurses, pharmacists, surgeons, gynecologists, urologists, electrologists, speech therapists, physical therapists, pastoral counselors and chaplains, and career or educational counselors. Communication, cooperation, and collaboration will ensure optimal coordination and quality of care. Just as psychologists often refer TGNC people to medical providers for assessment and treatment of medical issues, medical providers may rely on psychologists to assess readiness and assist TGNC clients to prepare for the psychological and social aspects of transition before, during, and after medical interventions (Coleman et al., 2012; Hembree et al., 2009; Lev, 2009). Outcome research to date supports the value and effectiveness of an interdisciplinary, collaborative approach to TGNC-specific care (see Coleman et al., 2012 for a review).

Application. Psychologists' collaboration with colleagues in medical and associated health disciplines involved in TGNC clients' care (e.g., hormonal and surgical treatment, primary health care; Coleman et al., 2012; Lev, 2009) may take many forms and should occur in a timely manner that does not complicate access to needed

services (e.g., considerations of wait time). For example, a psychologist working with a trans man who has a diagnosis of bipolar disorder may need to coordinate with his primary care provider and psychiatrist to adjust his hormone levels and psychiatric medications, given that testosterone can have an activating effect, in addition to treating gender dysphoria. At a basic level, collaboration may entail the creation of required documentation that TGNC people present to surgeons or medical providers to access gender-affirming medical interventions (e.g., surgery, hormone therapy; Coleman et al., 2012). Psychologists may offer support, information, and education to interdisciplinary colleagues who are unfamiliar with issues of gender identity and gender expression to assist TGNC people in obtaining TGNC-affirmative care (Holman & Goldberg, 2006; Lev, 2009). For example, a psychologist who is assisting a trans woman with obtaining gender-affirming surgery may, with her consent, contact her new gynecologist in preparation for her first medical visit. This contact could include sharing general information about her gender history and discussing how both providers could most affirmatively support appropriate health checks to ensure her best physical health (Holman & Goldberg, 2006).

Psychologists in interdisciplinary settings could also collaborate with medical professionals prescribing hormone therapy by educating TGNC people and ensuring TGNC people are able to make fully informed decisions prior to starting hormone treatment (Coleman et al., 2012; Deutsch, 2012; Lev, 2009). Psychologists working with children and adolescents play a particularly important role on the interdisciplinary team due to considerations of cognitive and social development, family dynamics, and degree of parental support. This role is especially crucial when providing psychological evaluation to determine the appropriateness and timeliness of a medical intervention. When psychologists are not part of an interdisciplinary setting, especially in isolated or rural communities, they can identify interdisciplinary colleagues with whom they may collaborate and/or refer (Walinsky & Whitcomb, 2010). For example, a rural psychologist could identify a trans-affirmative pediatrician in a surrounding area and collaborate with the pediatrician to work with parents raising concerns about their TGNC and questioning children and adolescents.

In addition to working collaboratively with other providers, psychologists who obtain additional training to specialize in work with TGNC people may also serve as consultants in the field (e.g., providing additional support to providers working with TGNC people or assisting school and workplaces with diversity training). Psychologists who have expertise in working with TGNC people may play a consultative role with providers in inpatient settings seeking to provide affirmative care to TGNC clients. Psychologists may also collaborate with social service colleagues to provide TGNC people with affirmative referrals related to housing, financial support, vocational/educational counseling and training, TGNC-affirming religious or spiritual communities, peer support, and other community resources (Gehi & Arkles, 2007). This collaboration might also in-

clude assuring that TGNC people who are minors in the care of the state have access to culturally appropriate care.

Research, Education, and Training

Guideline 15. Psychologists respect the welfare and rights of TGNC participants in research and strive to represent results accurately and avoid misuse or misrepresentation of findings.

Rationale. Historically, in a set of demographic questions, psychological research has included one item on either sex or gender, with two response options—male and female. This approach wastes an opportunity to increase knowledge about TGNC people for whom neither option may fit their identity, and runs the risk of alienating TGNC research participants (IOM, 2011). For example, there is little knowledge about HIV prevalence, risks, and prevention needs of TGNC people because most of the research on HIV has not included demographic questions to identify TGNC participants within their samples. Instead, TGNC people have been historically subsumed within larger demographic categories (e.g., men who have sex with men, women of color), rendering the impact of the HIV epidemic on the TGNC population invisible (Herbst et al., 2008). Scholars have noted that this invisibility fails to draw attention to the needs of TGNC populations that experience the greatest health disparities, including TGNC people who are of color, immigrants, low income, homeless, veterans, incarcerated, live in rural areas, or have disabilities (Bauer et al., 2009; Hanssmann, Morrison, Russian, Shiu-Thornton, & Bowen, 2010; Shipherd et al., 2012; Walinsky & Whitcomb, 2010).

There is a great need for more research to inform practice, including affirmative treatment approaches with TGNC people. Although sufficient evidence exists to support current standards of care (Byne et al., 2012; Coleman et al., 2012), much is yet to be learned to optimize quality of care and outcome for TGNC clients, especially as it relates to the treatment of children (IOM, 2011; Mikalson et al., 2012). In addition, some research with TGNC populations has been misused and misinterpreted, negatively affecting TGNC people's access to health services to address issues of gender identity and gender expression (Namaste, 2000). This has resulted in justifiable skepticism and suspicion in the TGNC community when invited to participate in research initiatives. In accordance with the APA ethics code (APA, 2010), psychologists conduct research and distribute research findings with integrity and respect for their research participants. As TGNC research increases, some TGNC communities may experience being oversampled in particular geographic areas and/or TGNC people of color may not be well-represented in TGNC studies (Hwahng & Lin, 2009; Namaste, 2000).

Application. All psychologists conducting research, even when not specific to TGNC populations, are encouraged to provide a range of options for capturing demographic information about TGNC people so that TGNC people may be included and accurately represented

(Conron et al., 2008; Deutsch et al., 2013). One group of experts has recommended that population research, and especially government-sponsored surveillance research, use a two-step method, first asking for sex assigned at birth, and then following with a question about gender identity (GenIUSS, 2013). For research focused on TGNC people, including questions that assess both sex assigned at birth and current gender identity allows the disaggregation of subgroups within the TGNC population and has the potential to increase knowledge of differences within the population. In addition, findings about one subgroup of TGNC people may not apply to other subgroups. For example, results from a study of trans women of color with a history of sex work who live in urban areas (Nemoto, Operario, Keatley, & Villegas, 2004) may not generalize to all TGNC women of color or to the larger TGNC population (Bauer, Travers, Scanlon, & Coleman, 2012; Operario et al., 2008).

In conducting research with TGNC people, psychologists will confront the challenges associated with studying a relatively small, geographically dispersed, diverse, stigmatized, hidden, and hard-to-reach population (IOM, 2011). Because TGNC individuals are often hard to reach (IOM, 2011) and TGNC research is rapidly evolving, it is important to consider the strengths and limitations of the methods that have been or may be used to study the TGNC population, and to interpret and represent findings accordingly. Some researchers have strongly recommended collaborative research models (e.g., participatory action research) in which TGNC community members are integrally involved in these research activities (Clements-Nolle & Bachrach, 2003; Singh, Richmond, & Burnes, 2013). Psychologists who seek to educate the public by communicating research findings in the popular media will also confront challenges, because most journalists have limited knowledge about the scientific method and there is potential for the media to misinterpret, exploit, or sensationalize findings (Garber, 1992; Namaste, 2000).

Guideline 16. Psychologists Seek to Prepare Trainees in Psychology to Work Competently With TGNC People.

Rationale. The *Ethical Principles of Psychologists and Code of Conduct* (APA, 2010) include gender identity as one factor for which psychologists may need to obtain training, experience, consultation, or supervision in order to ensure their competence (APA, 2010). In addition, when APA-accredited programs are required to demonstrate a commitment to cultural and individual diversity, gender identity is specifically included (APA, 2015). Yet surveys of TGNC people suggest that many mental health care providers lack even basic knowledge and skills required to offer trans-affirmative care (Bradford et al., 2007; O'Hara, Dispenza, Brack, & Blood, 2013; Xavier et al., 2005). The APA Task Force on Gender Identity and Gender Variance (2009) projected that many, if not most, psychologists and graduate psychology students will at some point encounter TGNC people among their clients, colleagues, and trainees. Yet professional education and training in psychology includes little or no preparation for

working with TGNC people (Anton, 2009; APA TFGIGV, 2009), and continuing professional education available to practicing mental health clinicians is also scant (Lurie, 2005). Only 52% percent of psychologists and graduate students who responded to a survey conducted by an APA Task Force reported having had the opportunity to learn about TGNC issues in school; of those respondents, only 27% reported feeling adequately familiar with gender concerns ($n = 294$; APA TFGIGV, 2009).

Training on gender identity in professional psychology has frequently been subsumed under discussions of sexual orientation or in classes on human sexuality. Some scholars have suggested that psychologists and students may mistakenly believe that they have obtained adequate knowledge and awareness about TGNC people through training focused on LGB populations (Harper & Schneider, 2003). However, Israel and colleagues have found important differences between the therapeutic needs of TGNC people and those of LGB people in the perceptions of both clients and providers (Israel et al., 2008; Israel, Walther, Gorcheva, & Perry, 2011). Nadal and colleagues have suggested that the absence of distinct, accurate information about TGNC populations in psychology training not only perpetuates misunderstanding and marginalization of TGNC people by psychologists but also contributes to continued marginalization of TGNC people in society as a whole (Nadal et al., 2010, 2012).

Application. Psychologists strive to continue their education on issues of gender identity and gender expression with TGNC people as a foundational component of affirmative psychological practice. In addition to these guidelines, which educators may use as a resource in developing curricula and training experiences, ACA (2010) has also adopted a set of competencies that may be a helpful resource for educators. In addition to including TGNC people and their issues in foundational education in health service psychology (e.g., personality development, multiculturalism, research methods), some psychology programs may also provide coursework and training for students interested in developing more advanced expertise on issues of gender identity and gender expression.

Because of the high level of societal ignorance and stigma associated with TGNC people, ensuring that psychological education, training, and supervision is affirmative, and does not sensationalize (Namaste, 2000), exploit, or pathologize TGNC people (Lev, 2004), will require care on the part of educators. Students will benefit from support from their educators in developing a professional, nonjudgmental attitude toward people who may have a different experience of gender identity and gender expression from their own. A number of training resources have been published that may be helpful to psychologists in integrating information about TGNC people into the training they offer (e.g., Catalano, McCarthy, & Shlasko, 2007; Stryker, 2008; Wentling, Schilt, Windsor, & Lucal, 2008). Because most psychologists have had little or no training on TGNC populations and do not perceive themselves as having sufficient understanding of issues related to gender identity and gender expression (APA TFGIGV, 2009), psycholo-

gists with relevant expertise are encouraged to develop and distribute continuing education and training to help to address these gaps. Psychologists providing education can incorporate activities that increase awareness of cisgender privilege, antitrans prejudice and discrimination, host a panel of TGNC people to offer personal perspectives, or include narratives of TGNC people in course readings (ACA, 2010). When engaging these approaches, it is important to include a wide variety of TGNC experiences to reflect the inherent diversity within the TGNC community.

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Appendix A Definitions

Terminology within the health care field and transgender and gender nonconforming (TGNC) communities is constantly evolving (Coleman et al., 2012). The evolution of terminology has been especially rapid in the last decade, as the profession's awareness of gender diversity has increased, as more literature and research in this area has been published, and as voices of the TGNC community have strengthened. Some terms or definitions are not universally accepted, and there is some disagreement among professionals and communities as to the “correct” words or definitions, depending on theoretical orientation, geographic region, generation, or culture, with some terms seen as affirming and others as outdated or demeaning. American Psychological Association (APA) Task Force for *Guidelines for Psychological Practice with Transgender and Gender Nonconforming People* developed the definitions below by reviewing existing

definitions put forward by professional organizations (e.g., APA Task Force on Gender Identity and Gender Variance, 2009; the Institute of Medicine, 2011; and the World Professional Association for Transgender Health [Coleman et al., 2012]), health care agencies serving TGNC clients (e.g., Fenway Health Center), TGNC community resources (Gender Equity Resource Center, National Center for Transgender Equality), and professional literature. Psychologists are encouraged to refresh their knowledge and familiarity with evolving terminology on a regular basis as changes emerge in the community and/or the professional literature. The definitions below include terms frequently used within the *Guidelines*, by the TGNC community, and within professional literature.

Ally: a cisgender person who supports and advocates for TGNC people and/or communities.

(Appendices continue)

Antitrans prejudice (transprejudice, transnegativity, transphobia): prejudicial attitudes that may result in the devaluing, dislike, and hatred of people whose gender identity and/or gender expression do not conform to their sex assigned at birth. Antitrans prejudice may lead to discriminatory behaviors in such areas as employment and public accommodations, and may lead to harassment and violence. When TGNC people hold these negative attitudes about themselves and their gender identity, it is called *internalized transphobia* (a construct analogous to internalized homophobia). Transmisogyny describes a simultaneous experience of sexism and antitrans prejudice with particularly adverse effects on trans women.

Cisgender: an adjective used to describe a person whose gender identity and gender expression align with sex assigned at birth; a person who is not TGNC.

Cisgenderism: a systemic bias based on the ideology that gender expression and gender identities are determined by sex assigned at birth rather than self-identified gender identity. Cisgenderism may lead to prejudicial attitudes and discriminatory behaviors toward TGNC people or to forms of behavior or gender expression that lie outside of the traditional gender binary.

Coming out: a process by which individuals affirm and actualize a stigmatized identity. Coming out as TGNC can include disclosing a gender identity or gender history that does not align with sex assigned at birth or current gender expression. Coming out is an individual process and is partially influenced by one's age and other generational influences.

Cross dressing: wearing clothing, accessories, and/or make-up, and/or adopting a gender expression not associated with a person's assigned sex at birth according to cultural and environmental standards (Bullough & Bullough, 1993). Cross-dressing is not always reflective of gender identity or sexual orientation. People who cross-dress may or may not identify with the larger TGNC community.

Disorders of sex development (DSD, Intersex): term used to describe a variety of medical conditions associated with atypical development of an individual's physical sex characteristics (Hughes, Houk, Ahmed, & Lee, 2006). These conditions may involve differences of a person's internal and/or external reproductive organs, sex chromosomes, and/or sex-related hormones that may complicate sex assignment at birth. DSD conditions may be considered variations in biological diversity rather than disorders (M. Diamond, 2009); therefore some prefer the terms *intersex*, *intersexuality*, or *differences in sex development* rather than "disorders of sex development" (Coleman et al., 2012).

Drag: the act of adopting a gender expression, often as part of a performance. Drag may be enacted as a political

comment on gender, as parody, or as entertainment, and is not necessarily reflective of gender identity.

Female-to-male (FTM): individuals assigned a female sex at birth who have changed, are changing, or wish to change their body and/or gender identity to a more masculine body or gender identity. FTM persons are also often referred to as *transgender men*, *transmen*, or *trans men*.

Gatekeeping: the role of psychologists and other mental health professionals of evaluating a TGNC person's eligibility and readiness for hormone therapy or surgery according to the Standards of Care set forth by the World Professional Association for Transgender Health (Coleman et al., 2012). In the past, this role has been perceived as limiting a TGNC adult's autonomy and contributing to mistrust between psychologists and TGNC clients. Current approaches are sensitive to this history and are more affirming of a TGNC adult's autonomy in making decisions with regard to medical transition (American Counseling Association, 2010; Coleman et al., 2012; Singh & Burnes, 2010).

Gender-affirming surgery (sex reassignment surgery or gender reassignment surgery): surgery to change primary and/or secondary sex characteristics to better align a person's physical appearance with their gender identity. Gender-affirming surgery can be an important part of medically necessary treatment to alleviate gender dysphoria and may include mastectomy, hysterectomy, metoidioplasty, phalloplasty, breast augmentation, orchiectomy, vaginoplasty, facial feminization surgery, and/or other surgical procedures.

Gender binary: the classification of gender into two discrete categories of boy/man and girl/woman.

Gender dysphoria: discomfort or distress related to incongruence between a person's gender identity, sex assigned at birth, gender identity, and/or primary and secondary sex characteristics (Knudson, De Cuypere, & Bockting, 2010). In 2013, the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*; American Psychiatric Association, 2013) adopted the term *gender dysphoria* as a diagnosis characterized by "a marked incongruence between" a person's gender assigned at birth and gender identity (American Psychiatric Association, 2013, p. 453). Gender dysphoria replaced the diagnosis of gender identity disorder (GID) in the previous version of the *DSM* (American Psychiatric Association, 2000).

Gender expression: the presentation of an individual, including physical appearance, clothing choice and accessories, and behaviors that express aspects of gender identity or role. Gender expression may or may not conform to a person's gender identity.

(Appendices continue)

Gender identity: a person's deeply felt, inherent sense of being a boy, a man, or male; a girl, a woman, or female; or an alternative gender (e.g., genderqueer, gender nonconforming, gender neutral) that may or may not correspond to a person's sex assigned at birth or to a person's primary or secondary sex characteristics. Because gender identity is internal, a person's gender identity is not necessarily visible to others. "Affirmed gender identity" refers to a person's gender identity after coming out as TGNC or undergoing a social and/or medical transition process.

Gender marker: an indicator (M, F) of a person's sex or gender found on identification (e.g., driver's license, passport) and other legal documents (e.g., birth certificate, academic transcripts).

Gender nonconforming (GNC): an adjective used as an umbrella term to describe people whose gender expression or gender identity differs from gender norms associated with their assigned birth sex. Subpopulations of the TGNC community can develop specialized language to represent their experience and culture, such as the term "masculine of center" (MOC; Cole & Han, 2011) that is used in communities of color to describe one's GNC identity.

Gender questioning: an adjective to describe people who may be questioning or exploring their gender identity and whose gender identity may not align with their sex assigned at birth.

Genderqueer: a term to describe a person whose gender identity does not align with a binary understanding of gender (i.e., a person who does not identify fully as either a man or a woman). People who identify as genderqueer may redefine gender or decline to define themselves as gendered altogether. For example, people who identify as genderqueer may think of themselves as both man and woman (bigender, pangender, androgyne); neither man nor woman (genderless, gender neutral, neutrois, agender); moving between genders (genderfluid); or embodying a third gender.

Gender role: refers to a pattern of appearance, personality, and behavior that, in a given culture, is associated with being a boy/man/male or being a girl/woman/female. The appearance, personality, and behavior characteristics may or may not conform to what is expected based on a person's sex assigned at birth according to cultural and environmental standards. Gender role may also refer to the social role in which one is living (e.g., as a woman, a man, or another gender), with some role characteristics conforming and others not conforming to what is associated with girls/women or boys/men in a given culture and time.

Hormone therapy (gender-affirming hormone therapy, hormone replacement therapy): the use of hormones to masculinize or feminize a person's body to better

align that person's physical characteristics with their gender identity. People wishing to feminize their body receive antiandrogens and/or estrogens; people wishing to masculinize their body receive testosterone. Hormone therapy may be an important part of medically necessary treatment to alleviate gender dysphoria.

Male-to-female (MTF): individuals whose assigned sex at birth was male and who have changed, are changing, or wish to change their body and/or gender role to a more feminized body or gender role. MTF persons are also often referred to as *transgender women*, *transwomen*, or *trans women*.

Passing: the ability to blend in with cisgender people without being recognized as transgender based on appearance or gender role and expression; being perceived as cisgender. Passing may or may not be a goal for all TGNC people.

Puberty suppression (puberty blocking, puberty delaying therapy): a treatment that can be used to temporarily suppress the development of secondary sex characteristics that occur during puberty in youth, typically using gonadotropin-releasing hormone (GnRH) analogues. Puberty suppression may be an important part of medically necessary treatment to alleviate gender dysphoria. Puberty suppression can provide adolescents time to determine whether they desire less reversible medical intervention and can serve as a diagnostic tool to determine if further medical intervention is warranted.

Sex (sex assigned at birth): sex is typically assigned at birth (or before during ultrasound) based on the appearance of external genitalia. When the external genitalia are ambiguous, other indicators (e.g., internal genitalia, chromosomal and hormonal sex) are considered to assign a sex, with the aim of assigning a sex that is most likely to be congruent with the child's gender identity (MacLaughlin & Donahoe, 2004). For most people, gender identity is congruent with sex assigned at birth (see *cisgender*); for TGNC individuals, gender identity differs in varying degrees from sex assigned at birth.

Sexual orientation: a component of identity that includes a person's sexual and emotional attraction to another person and the behavior and/or social affiliation that may result from this attraction. A person may be attracted to men, women, both, neither, or to people who are genderqueer, androgynous, or have other gender identities. Individuals may identify as lesbian, gay, heterosexual, bisexual, queer, pansexual, or asexual, among others.

Stealth (going stealth): a phrase used by some TGNC people across the life span (e.g., children, adolescents) who choose to make a transition in a new environment (e.g., school) in their affirmed gender without openly sharing their identity as a TGNC person.

(Appendices continue)

TGNC: an abbreviation used to refer to people who are transgender or gender nonconforming.

Trans: common short-hand for the terms transgender, transsexual, and/or gender nonconforming. Although the term “trans” is commonly accepted, not all transsexual or gender nonconforming people identify as trans.

Trans-affirmative: being respectful, aware and supportive of the needs of TGNC people.

Transgender: an adjective that is an umbrella term used to describe the full range of people whose gender identity and/or gender role do not conform to what is typically associated with their sex assigned at birth. Although the term “transgender” is commonly accepted, not all TGNC people self-identify as transgender.

Transgender man, trans man, or transman: a person whose sex assigned at birth was female, but who identifies as a man (see FTM).

Transgender woman, trans woman, or transwoman: a person whose sex assigned at birth was male, but who identifies as a woman (see MTF).

Transition: a process some TGNC people progress through when they shift toward a gender role that differs from the one associated with their sex assigned at birth. The length, scope, and process of transition are unique to

each person’s life situation. For many people, this involves developing a gender role and expression that is more aligned with their gender identity. A transition typically occurs over a period of time; TGNC people may proceed through a social transition (e.g., changes in gender expression, gender role, name, pronoun, and gender marker) and/or a medical transition (e.g., hormone therapy, surgery, and/or other interventions).

Transsexual: term to describe TGNC people who have changed or are changing their bodies through medical interventions (e.g., hormones, surgery) to better align their bodies with a gender identity that is different than their sex assigned at birth. Not all people who identify as transsexual consider themselves to be TGNC. For example, some transsexual individuals identify as female or male, without identifying as TGNC. Transsexualism is used as a medical diagnosis in the [World Health Organization’s \(2015\) International Classification of Diseases version 10](#).

Two-spirit: term used by some Native American cultures to describe people who identify with both male and female gender roles; this can include both gender identity and sexual orientation. Two-spirit people are often respected and carry unique spiritual roles for their community.

Appendix B

Guidelines for Psychological Practice With Transgender and Gender Nonconforming People

Foundational Knowledge and Awareness

Guideline 1. Psychologists understand that gender is a nonbinary construct that allows for a range of gender identities and that a person’s gender identity may not align with sex assigned at birth.

Guideline 2. Psychologists understand that gender identity and sexual orientation are distinct but interrelated constructs.

Guideline 3. Psychologists seek to understand how gender identity intersects with the other cultural identities of TGNC people.

Guideline 4. Psychologists are aware of how their attitudes about and knowledge of gender identity and gen-

der expression may affect the quality of care they provide to TGNC people and their families.

Stigma, Discrimination, and Barriers to Care

Guideline 5. Psychologists recognize how stigma, prejudice, discrimination, and violence affect the health and well-being of TGNC people.

Guideline 6. Psychologists strive to recognize the influence of institutional barriers on the lives of TGNC people and to assist in developing TGNC-affirmative environments.

Guideline 7. Psychologists understand the need to promote social change that reduces the negative effects of stigma on the health and well-being of TGNC people.

(Appendices continue)

Life Span Development

Guideline 8. Psychologists working with gender-questioning and TGNC youth understand the different developmental needs of children and adolescents and that not all youth will persist in a TGNC identity into adulthood.

Guideline 9. Psychologists strive to understand both the particular challenges that TGNC elders experience and the resilience they can develop.

Assessment, Therapy, and Intervention

Guideline 10. Psychologists strive to understand how mental health concerns may or may not be related to a TGNC person's gender identity and the psychological effects of minority stress.

Guideline 11. Psychologists recognize that TGNC people are more likely to experience positive life outcomes when they receive social support or trans-affirmative care.

Guideline 12. Psychologists strive to understand the effects that changes in gender identity and gender expression have on the romantic and sexual relationships of TGNC people.

Guideline 13. Psychologists seek to understand how parenting and family formation among TGNC people take a variety of forms.

Guideline 14. Psychologists recognize the potential benefits of an interdisciplinary approach when providing care to TGNC people and strive to work collaboratively with other providers.

Research, Education, and Training

Guideline 15. Psychologists respect the welfare and rights of TGNC participants in research and strive to represent results accurately and avoid misuse or misrepresentation of findings.

Guideline 16. Psychologists Seek to Prepare Trainees in Psychology to Work Competently With TGNC People.

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POLICY STATEMENT Organizational Principles to Guide and Define the Child Health Care System
and/or Improve the Health of all Children

American Academy
of Pediatrics



DEDICATED TO THE HEALTH OF ALL CHILDREN™

Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents

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As a traditionally underserved population that faces numerous health disparities, youth who identify as transgender and gender diverse (TGD) and their families are increasingly presenting to pediatric providers for education, care, and referrals. The need for more formal training, standardized treatment, and research on safety and medical outcomes often leaves providers feeling ill equipped to support and care for patients that identify as TGD and families. In this policy statement, we review relevant concepts and challenges and provide suggestions for pediatric providers that are focused on promoting the health and positive development of youth that identify as TGD while eliminating discrimination and stigma.

INTRODUCTION

In its dedication to the health of all children, the American Academy of Pediatrics (AAP) strives to improve health care access and eliminate disparities for children and teenagers who identify as lesbian, gay, bisexual, transgender, or questioning (LGBTQ) of their sexual or gender identity.^{1,2} Despite some advances in public awareness and legal protections, youth who identify as LGBTQ continue to face disparities that stem from multiple sources, including inequitable laws and policies, societal discrimination, and a lack of access to quality health care, including mental health care. Such challenges are often more intense for youth who do not conform to social expectations and norms regarding gender. Pediatric providers are increasingly encountering such youth and their families, who seek medical advice and interventions, yet they may lack the formal training to care for youth that identify as transgender and gender diverse (TGD) and their families.³

This policy statement is focused specifically on children and youth that identify as TGD rather than the larger LGBTQ population, providing brief, relevant background on the basis of current available research

abstract



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Dr Rafferty conceptualized the statement, drafted the initial manuscript, reviewed and revised the manuscript, approved the final manuscript as submitted, and agrees to be accountable for all aspects of the work.

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TABLE 1 Relevant Terms and Definitions Related to Gender Care

Term	Definition
Sex	An assignment that is made at birth, usually male or female, typically on the basis of external genital anatomy but sometimes on the basis of internal gonads, chromosomes, or hormone levels
Gender identity	A person's deep internal sense of being female, male, a combination of both, somewhere in between, or neither; resulting from a multifaceted interaction of biological traits, environmental factors, self-understanding, and cultural expectations
Gender expression	The external way a person expresses their gender; such as with clothing, hair, mannerisms, activities, or social roles
Gender perception	The way others interpret a person's gender expression
Gender diverse	A term that is used to describe people with gender behaviors, appearances, or identities that are incongruent with those culturally assigned to their birth sex; gender-diverse individuals may refer to themselves with many different terms, such as transgender, nonbinary, genderqueer; ⁷ gender fluid, gender creative, gender independent, or noncisgender. "Gender diverse" is used to acknowledge and include the vast diversity of gender identities that exists. It replaces the former term, "gender nonconforming," which has a negative and exclusionary connotation.
Transgender	A subset of gender-diverse youth whose gender identity does not match their assigned sex and generally remains persistent, consistent, and insistent over time; the term "transgender" also encompasses many other labels individuals may use to refer to themselves.
Cisgender	A term that is used to describe a person who identifies and expresses a gender that is consistent with the culturally defined norms of the sex they were assigned at birth
Agender	A term that is used to describe a person who does not identify as having a particular gender
Affirmed gender	When a person's true gender identity, or concern about their gender identity, is communicated to and validated from others as authentic
MTF; affirmed female; trans female	Terms that are used to describe individuals who were assigned male sex at birth but who have a gender identity and/or expression that is asserted to be more feminine
FTM; affirmed male; trans male	Terms that are used to describe individuals who were assigned female sex at birth but who have a gender identity and/or expression that is asserted to be more masculine
Gender dysphoria	A clinical symptom that is characterized by a sense of alienation to some or all of the physical characteristics or social roles of one's assigned gender; also, gender dysphoria is the psychiatric diagnosis in the <i>DSM-5</i> , which has focus on the distress that stems from the incongruence between one's expressed or experienced (affirmed) gender and the gender assigned at birth.
Gender identity disorder	A psychiatric diagnosis defined previously in the <i>DSM-IV</i> (changed to "gender dysphoria" in the <i>DSM-5</i>); the primary criteria include a strong, persistent cross-sex identification and significant distress and social impairment. This diagnosis is no longer appropriate for use and may lead to stigma, but the term may be found in older research.
Sexual orientation	A person's sexual identity in relation to the gender(s) to which they are attracted; sexual orientation and gender identity develop separately.

This list is not intended to be all inclusive. The pronouns "they" and "their" are used intentionally to be inclusive rather than the binary pronouns "he" and "she" and "his" and "her." Adapted from Bonifacio HJ, Rosenthal SM. Gender variance and dysphoria in children and adolescents. *Pediatr Clin North Am*. 2015;62(4):1001–1016. Adapted from Vance SR Jr, Ehrensaft D, Rosenthal SM. Psychological and medical care of gender nonconforming youth. *Pediatrics*. 2014;134(6):1184–1192. *DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; *DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; FTM, female to male; MTF, male to female.

and expert opinion from clinical and research leaders, which will serve as the basis for recommendations. It is not a comprehensive review of clinical approaches and nuances to pediatric care for children and youth that identify as TGD. Professional understanding of youth that identify as TGD is a rapidly evolving clinical field in which research on appropriate clinical management is limited by insufficient funding.^{3,4}

DEFINITIONS

To clarify recommendations and discussions in this policy statement, some definitions are provided. However, brief descriptions of human behavior or identities may not capture nuance in this evolving field.

"Sex," or "natal gender," is a label, generally "male" or "female," that is typically assigned at birth on the basis of genetic and anatomic characteristics, such as genital anatomy, chromosomes, and sex hormone levels. Meanwhile, "gender identity" is one's internal sense of who one is, which results from a multifaceted interaction of biological traits, developmental influences, and environmental conditions. It may be male, female, somewhere in between, a combination of both, or neither (ie, not conforming to a binary conceptualization of gender). Self-recognition of gender identity develops over time, much the same way as a child's physical body does. For some people, gender identity can be fluid, shifting in different contexts. "Gender expression"

refers to the wide array of ways people display their gender through clothing, hair styles, mannerisms, or social roles. Exploring different ways of expressing gender is common for children and may challenge social expectations. The way others interpret this expression is referred to as "gender perception" (Table 1).^{5,6}

These labels may or may not be congruent. The term "cisgender" is used if someone identifies and expresses a gender that is consistent with the culturally defined norms of the sex that was assigned at birth. "Gender diverse" is an umbrella term to describe an ever-evolving array of labels that people may apply when their gender identity, expression, or even perception does not conform

to the norms and stereotypes others expect of their assigned sex. “Transgender” is usually reserved for a subset of such youth whose gender identity does not match their assigned sex and generally remains persistent, consistent, and insistent over time. These terms are not diagnoses; rather, they are personal and often dynamic ways of describing one’s own gender experience.

Gender identity is not synonymous with “sexual orientation,” which refers to a person’s identity in relation to the gender(s) to which they are sexually and romantically attracted. Gender identity and sexual orientation are distinct but interrelated constructs.⁸ Therefore, being transgender does not imply a sexual orientation, and people who identify as transgender still identify as straight, gay, bisexual, etc, on the basis of their attractions. (For more information, *The Gender Book*, found at www.thegenderbook.com, is a resource with illustrations that are used to highlight these core terms and concepts.)

EPIDEMIOLOGY

In population-based surveys, questions related to gender identity are rarely asked, which makes it difficult to assess the size and characteristics of the population that is TGD. In the 2014 Behavioral Risk Factor Surveillance System of the Centers for Disease Control and Prevention, only 19 states elected to include optional questions on gender identity. Extrapolation from these data suggests that the US prevalence of adults who identify as transgender or “gender nonconforming” is 0.6% (1.4 million), ranging from 0.3% in North Dakota to 0.8% in Hawaii.⁹ On the basis of these data, it has been estimated that 0.7% of youth ages 13 to 17 years (~150 000) identify as transgender.¹⁰ This number is much higher than previous estimates, which were

extrapolated from individual states or specialty clinics, and is likely an underestimate given the stigma regarding those who openly identify as transgender and the difficulty in defining “transgender” in a way that is inclusive of all gender-diverse identities.¹¹

There have been no large-scale prevalence studies among children and adolescents, and there is no evidence that adult statistics reflect young children or adolescents. In the 2014 Behavioral Risk Factor Surveillance System, those 18 to 24 years of age were more likely than older age groups to identify as transgender (0.7%).⁹ Children report being aware of gender incongruence at young ages. Children who later identify as TGD report first having recognized their gender as “different” at an average age of 8.5 years; however, they did not disclose such feelings until an average of 10 years later.¹²

MENTAL HEALTH IMPLICATIONS

Adolescents and adults who identify as transgender have high rates of depression, anxiety, eating disorders, self-harm, and suicide.^{13–20} Evidence suggests that an identity of TGD has an increased prevalence among individuals with autism spectrum disorder, but this association is not yet well understood.^{21,22} In 1 retrospective cohort study, 56% of youth who identified as transgender reported previous suicidal ideation, and 31% reported a previous suicide attempt, compared with 20% and 11% among matched youth who identified as cisgender, respectively.¹³ Some youth who identify as TGD also experience gender dysphoria, which is a specific diagnosis given to those who experience impairment in peer and/or family relationships, school performance, or other aspects of their life as a consequence of the

incongruence between their assigned sex and their gender identity.²³

There is no evidence that risk for mental illness is inherently attributable to one’s identity of TGD. Rather, it is believed to be multifactorial, stemming from an internal conflict between one’s appearance and identity, limited availability of mental health services, low access to health care providers with expertise in caring for youth who identify as TGD, discrimination, stigma, and social rejection.²⁴ This was affirmed by the American Psychological Association in 2008²⁵ (with practice guidelines released in 2015⁸) and the American Psychiatric Association, which made the following statement in 2012:

Being transgender or gender variant implies no impairment in judgment, stability, reliability, or general social or vocational capabilities; however, these individuals often experience discrimination due to a lack of civil rights protections for their gender identity or expression.... [Such] discrimination and lack of equal civil rights is damaging to the mental health of transgender and gender variant individuals.²⁶

Youth who identify as TGD often confront stigma and discrimination, which contribute to feelings of rejection and isolation that can adversely affect physical and emotional well-being. For example, many youth believe that they must hide their gender identity and expression to avoid bullying, harassment, or victimization. Youth who identify as TGD experience disproportionately high rates of homelessness, physical violence (at home and in the community), substance abuse, and high-risk sexual behaviors.^{5,6,12,27–31} Among the 3 million HIV testing events that were reported in 2015, the highest percentages of new infections were among women who identified as transgender³² and were also at particular risk for not knowing their HIV status.³⁰

GENDER-AFFIRMATIVE CARE

In a gender-affirmative care model (GACM), pediatric providers offer developmentally appropriate care that is oriented toward understanding and appreciating the youth's gender experience. A strong, nonjudgmental partnership with youth and their families can facilitate exploration of complicated emotions and gender-diverse expressions while allowing questions and concerns to be raised in a supportive environment.⁵ In a GACM, the following messages are conveyed:

- transgender identities and diverse gender expressions do not constitute a mental disorder;
- variations in gender identity and expression are normal aspects of human diversity, and binary definitions of gender do not always reflect emerging gender identities;
- gender identity evolves as an interplay of biology, development, socialization, and culture; and
- if a mental health issue exists, it most often stems from stigma and negative experiences rather than being intrinsic to the child.^{27,33}

The GACM is best facilitated through the integration of medical, mental health, and social services, including specific resources and supports for parents and families.²⁴ Providers work together to destigmatize gender variance, promote the child's self-worth, facilitate access to care, educate families, and advocate for safer community spaces where children are free to develop and explore their gender.⁵ A specialized gender-affirmative therapist, when available, may be an asset in helping children and their families build skills for dealing with gender-based stigma, address symptoms of anxiety or depression, and reinforce the child's overall resiliency.^{34,35} There is a limited but growing body

of evidence that suggests that using an integrated affirmative model results in young people having fewer mental health concerns whether they ultimately identify as transgender.^{24,36,37}

In contrast, "conversion" or "reparative" treatment models are used to prevent children and adolescents from identifying as transgender or to dissuade them from exhibiting gender-diverse expressions. The Substance Abuse and Mental Health Services Administration has concluded that any therapeutic intervention with the goal of changing a youth's gender expression or identity is inappropriate.³³ Reparative approaches have been proven to be not only unsuccessful³⁸ but also deleterious and are considered outside the mainstream of traditional medical practice.^{29,39–42} The AAP described reparative approaches as "unfair and deceptive."⁴³ At the time of this writing,^{*} conversion therapy was banned by executive regulation in New York and by legislative statutes in 9 other states as well as the District of Columbia.⁴⁴

Pediatric providers have an essential role in assessing gender concerns and providing evidence-based information to assist youth and families in medical decision-making. Not doing so can prolong or exacerbate gender dysphoria and contribute to abuse and stigmatization.³⁵ If a pediatric provider does not feel prepared to address gender concerns when they occur, then referral to a pediatric or mental health provider with more expertise is appropriate. There is little research on communication and efficacy with transfers in care for youth who identify as TGD,

particularly from pediatric to adult providers.

DEVELOPMENTAL CONSIDERATIONS

Acknowledging that the capacity for emerging abstract thinking in childhood is important to conceptualize and reflect on identity, gender-affirmation guidelines are being focused on individually tailored interventions on the basis of the physical and cognitive development of youth who identify as TGD.⁴⁵ Accordingly, research substantiates that children who are prepubertal and assert an identity of TGD know their gender as clearly and as consistently as their developmentally equivalent peers who identify as cisgender and benefit from the same level of social acceptance.⁴⁶ This developmental approach to gender affirmation is in contrast to the outdated approach in which a child's gender-diverse assertions are held as "possibly true" until an arbitrary age (often after pubertal onset) when they can be considered valid, an approach that authors of the literature have termed "watchful waiting." This outdated approach does not serve the child because critical support is withheld. Watchful waiting is based on binary notions of gender in which gender diversity and fluidity is pathologized; in watchful waiting, it is also assumed that notions of gender identity become fixed at a certain age. The approach is also influenced by a group of early studies with validity concerns, methodologic flaws, and limited follow-up on children who identified as TGD and, by adolescence, did not seek further treatment ("desisters").^{45,47} More robust and current research suggests that, rather than focusing on who a child will become, valuing them for who they are, even at a young age, fosters secure attachment and resilience, not only for the child but also for the whole family.^{5,45,48,49}

* For more information regarding state-specific laws, please contact the AAP Division of State Government Affairs at stgov@aap.org.

MEDICAL MANAGEMENT

Pediatric primary care providers are in a unique position to routinely inquire about gender development in children and adolescents as part of recommended well-child visits⁵⁰ and to be a reliable source of validation, support, and reassurance. They are often the first provider to be aware that a child may not identify as cisgender or that there may be distress related to a gender-diverse identity. The best way to approach gender with patients is to inquire directly and nonjudgmentally about their experience and feelings before applying any labels.^{27,51}

Many medical interventions can be offered to youth who identify as TGD and their families. The decision of whether and when to initiate gender-affirmative treatment is personal and involves careful consideration of risks, benefits, and other factors unique to each patient and family. Many protocols suggest that clinical assessment of youth who identify as TGD is ideally conducted on an ongoing basis in the setting of a collaborative, multidisciplinary approach, which, in addition to the patient and family, may include the pediatric provider, a mental health provider (preferably with expertise in caring for youth who identify as TGD), social and legal supports, and a pediatric endocrinologist or adolescent-medicine gender specialist, if available.^{6,28} There is no prescribed path, sequence, or end point. Providers can make every effort to be aware of the influence of their own biases. The medical options also vary depending on pubertal and developmental progression.

Clinical Setting

In the past year, 1 in 4 adults who identified as transgender avoided a necessary doctor's visit because of fear of being mistreated.³¹ All clinical office staff have a role in affirming a patient's gender identity. Making flyers available or displaying posters

related to LGBTQ health issues, including information for children who identify as TGD and families, reveals inclusivity and awareness. Generally, patients who identify as TGD feel most comfortable when they have access to a gender-neutral restroom. Diversity training that encompasses sensitivity when caring for youth who identify as TGD and their families can be helpful in educating clinical and administrative staff. A patient-asserted name and pronouns are used by staff and are ideally reflected in the electronic medical record without creating duplicate charts.^{52,53} The US Centers for Medicare and Medicaid Services and the National Coordinator for Health Information Technology require all electronic health record systems certified under the Meaningful Use incentive program to have the capacity to confidentially collect information on gender identity.^{54,55} Explaining and maintaining confidentiality procedures promotes openness and trust, particularly with youth who identify as LGBTQ.¹ Maintaining a safe clinical space can provide at least 1 consistent, protective refuge for patients and families, allowing authentic gender expression and exploration that builds resiliency.

Pubertal Suppression

Gonadotrophin-releasing hormones have been used to delay puberty since the 1980s for central precocious puberty.⁵⁶ These reversible treatments can also be used in adolescents who experience gender dysphoria to prevent development of secondary sex characteristics and provide time up until 16 years of age for the individual and the family to explore gender identity, access psychosocial supports, develop coping skills, and further define appropriate treatment goals. If pubertal suppression treatment is

suspended, then endogenous puberty will resume.^{20,57,58}

Often, pubertal suppression creates an opportunity to reduce distress that may occur with the development of secondary sexual characteristics and allow for gender-affirming care, including mental health support for the adolescent and the family. It reduces the need for later surgery because physical changes that are otherwise irreversible (protrusion of the Adam's apple, male pattern baldness, voice change, breast growth, etc) are prevented. The available data reveal that pubertal suppression in children who identify as TGD generally leads to improved psychological functioning in adolescence and young adulthood.^{20,57–59}

Pubertal suppression is not without risks. Delaying puberty beyond one's peers can also be stressful and can lead to lower self-esteem and increased risk taking.⁶⁰ Some experts believe that genital underdevelopment may limit some potential reconstructive options.⁶¹ Research on long-term risks, particularly in terms of bone metabolism⁶² and fertility,⁶³ is currently limited and provides varied results.^{57,64,65} Families often look to pediatric providers for help in considering whether pubertal suppression is indicated in the context of their child's overall well-being as gender diverse.

Gender Affirmation

As youth who identify as TGD reflect on and evaluate their gender identity, various interventions may be considered to better align their gender expression with their underlying identity. This process of reflection, acceptance, and, for some, intervention is known as "gender affirmation." It was formerly referred to as "transitioning," but many view the process as an affirmation and acceptance of who they have always been rather than a transition

TABLE 2 The Process of Gender Affirmation May Include ≥ 1 of the Following Components

Component	Definition	General Age Range ^a	Reversibility ^a
Social affirmation	Adopting gender-affirming hairstyles, clothing, name, gender pronouns, and restrooms and other facilities	Any	Reversible
Puberty blockers	Gonadotropin-releasing hormone analogues, such as leuprolide and histrelin	During puberty (Tanner stage 2–5) ^b	Reversible ^c
Cross-sex hormone therapy	Testosterone (for those who were assigned female at birth and are masculinizing); estrogen plus androgen inhibitor (for those who were assigned male at birth and are feminizing)	Early adolescence onward	Partially reversible (skin texture, muscle mass, and fat deposition); irreversible once developed (testosterone: Adam's apple protrusion, voice changes, and male pattern baldness; estrogen: breast development); unknown reversibility (effect on fertility)
Gender-affirming surgeries	“Top” surgery (to create a male-typical chest shape or enhance breasts); “bottom” surgery (surgery on genitals or reproductive organs); facial feminization and other procedures	Typically adults (adolescents on case-by-case basis ^d)	Not reversible
Legal affirmation	Changing gender and name recorded on birth certificate, school records, and other documents	Any	Reversible

^a Note that the provided age range and reversibility is based on the little data that are currently available.

^b There is limited benefit to starting gonadotropin-releasing hormone after Tanner stage 5 for pubertal suppression. However, when cross-sex hormones are initiated with a gradually increasing schedule, the initial levels are often not high enough to suppress endogenous sex hormone secretion. Therefore, gonadotropin-releasing hormone may be continued in accordance with the Endocrine Society Guidelines.⁶⁸

^c The effect of sustained puberty suppression on fertility is unknown. Pubertal suppression can be, and often is indicated to be, followed by cross-sex hormone treatment. However, when cross-sex hormones are initiated without endogenous hormones, then fertility may be decreased.⁶⁸

^d Eligibility criteria for gender-affirmative surgical interventions among adolescents are not clearly defined between established protocols and practice. When applicable, eligibility is usually determined on a case-by-case basis with the adolescent and the family along with input from medical, mental health, and surgical providers.^{68–71}

from 1 gender identity to another. Accordingly, some people who have gone through the process prefer to call themselves “affirmed females, males, etc” (or just “females, males, etc”), rather than using the prefix “trans-.” Gender affirmation is also used to acknowledge that some individuals who identify as TGD may feel affirmed in their gender without pursuing medical or surgical interventions.^{7,66}

Supportive involvement of parents and family is associated with better mental and physical health outcomes.⁶⁷ Gender affirmation among adolescents with gender dysphoria often reduces the emphasis on gender in their lives, allowing them to attend to other developmental tasks, such as academic success, relationship building, and future-oriented planning.⁶⁴ Most protocols for gender-affirming interventions incorporate World Professional Association of Transgender

Health³⁵ and Endocrine Society⁶⁸ recommendations and include ≥ 1 of the following elements (Table 2):

1. Social Affirmation: This is a reversible intervention in which children and adolescents express partially or completely in their asserted gender identity by adapting hairstyle, clothing, pronouns, name, etc. Children who identify as transgender and socially affirm and are supported in their asserted gender show no increase in depression and only minimal (clinically insignificant) increases in anxiety compared with age-matched averages.⁴⁸ Social affirmation can be complicated given the wide range of social interactions children have (eg, extended families, peers, school, community, etc). There is little guidance on the best approach (eg, all at once, gradual, creating new social networks, or affirming within existing networks, etc). Pediatric providers

can best support families by anticipating and discussing such complexity proactively, either in their own practice or through enlisting a qualified mental health provider.

2. Legal Affirmation: Elements of a social affirmation, such as a name and gender marker, become official on legal documents, such as birth certificates, passports, identification cards, school documents, etc. The processes for making these changes depend on state laws and may require specific documentation from pediatric providers.
3. Medical Affirmation: This is the process of using cross-sex hormones to allow adolescents who have initiated puberty to develop secondary sex characteristics of the opposite biological sex. Some changes are partially reversible if hormones are stopped, but others become

irreversible once they are fully developed (Table 2).

4. **Surgical Affirmation:** Surgical approaches may be used to feminize or masculinize features, such as hair distribution, chest, or genitalia, and may include removal of internal organs, such as ovaries or the uterus (affecting fertility). These changes are irreversible. Although current protocols typically reserve surgical interventions for adults,^{35,68} they are occasionally pursued during adolescence on a case-by-case basis, considering the necessity and benefit to the adolescent's overall health and often including multidisciplinary input from medical, mental health, and surgical providers as well as from the adolescent and family.^{69–71}

For some youth who identify as TGD whose natal gender is female, menstruation, breakthrough bleeding, and dysmenorrhea can lead to significant distress before or during gender affirmation. The American College of Obstetrics and Gynecology suggests that, although limited data are available to outline management, menstruation can be managed without exogenous estrogens by using a progesterone-only pill, a medroxyprogesterone acetate shot, or a progesterone-containing intrauterine or implantable device.⁷² If estrogen can be tolerated, oral contraceptives that contain both progesterone and estrogen are more effective at suppressing menses.⁷³ The Endocrine Society guidelines also suggest that gonadotrophin-releasing hormones can be used for menstrual suppression before the anticipated initiation of testosterone or in combination with testosterone for breakthrough bleeding (enables phenotypic masculinization at a lower dose than if testosterone is used alone).⁶⁸ Masculinizing hormones in natal female patients may lead to a cessation of menses,

but unplanned pregnancies have been reported, which emphasizes the need for ongoing contraceptive counseling with youth who identify as TGD.⁷²

HEALTH DISPARITIES

In addition to societal challenges, youth who identify as TGD face several barriers within the health care system, especially regarding access to care. In 2015, a focus group of youth who identified as transgender in Seattle, Washington, revealed 4 problematic areas related to health care:

1. safety issues, including the lack of safe clinical environments and fear of discrimination by providers;
2. poor access to physical health services, including testing for sexually transmitted infections;
3. inadequate resources to address mental health concerns; and
4. lack of continuity with providers.⁷⁴

This study reveals the obstacles many youth who identify as TGD face in accessing essential services, including the limited supply of appropriately trained medical and psychological providers, fertility options, and insurance coverage denials for gender-related treatments.⁷⁴

Insurance denials for services related to the care of patients who identify as TGD are a significant barrier. Although the Office for Civil Rights of the US Department of Health and Human Services explicitly stated in 2012 that the nondiscrimination provision in the Patient Protection and Affordable Care Act includes people who identify as gender diverse,^{75,76} insurance claims for gender affirmation, particularly among youth who identify as TGD, are frequently denied.^{54,77} In 1 study, it was found that approximately 25% of individuals

who identified as transgender were denied insurance coverage because of being transgender.³¹ The burden of covering medical expenses that are not covered by insurance can be financially devastating, and even when expenses are covered, families describe high levels of stress in navigating and submitting claims appropriately.⁷⁸ In 2012, a large gender center in Boston, Massachusetts, reported that most young patients who identified as transgender and were deemed appropriate candidates for recommended gender care were unable to obtain it because of such denials, which were based on the premise that gender dysphoria was a mental disorder, not a physical one, and that treatment was not medically or surgically necessary.²⁴ This practice not only contributes to stigma, prolonged gender dysphoria, and poor mental health outcomes,⁷⁷ but it may also lead patients to seek nonmedically supervised treatments that are potentially dangerous.²⁴ Furthermore, insurance denials can reinforce a socioeconomic divide between those who can finance the high costs of uncovered care and those who cannot.^{24,77}

The transgender youth group in Seattle likely reflected the larger TGD population when they described how obstacles adversely affect self-esteem and contribute to the perception that they are undervalued by society and the health care system.^{74,77} Professional medical associations, including the AAP, are increasingly calling for equity in health care provisions regardless of gender identity or expression.^{1,8,23,72} There is a critical need for investments in research on the prevalence, disparities, biological underpinnings, and standards of care relating to gender-diverse populations. Pediatric providers who work with state government and insurance officials can play an essential role in advocating for

stronger nondiscrimination policies and improved coverage.

There is a lack of quality research on the experience of youth of color who identify as transgender. One theory suggests that the intersection of racism, transphobia, and sexism may result in the extreme marginalization that is experienced among many women of color who identify as transgender,⁷⁹ including rejection from their family and dropping out of school at younger ages (often in the setting of rigid religious beliefs regarding gender),⁸⁰ increased levels of violence and body objectification,⁸¹ 3 times the risk of poverty compared with the general population,³¹ and the highest prevalence of HIV compared with other risk groups (estimated as high as 56.3% in 1 meta-analysis).³⁰ One model suggests that pervasive stigma and oppression can be associated with psychological distress (anxiety, depression, and suicide) and adoption of risk behaviors by such youth to obtain a sense of validation toward their complex identities.⁷⁹

FAMILY ACCEPTANCE

Research increasingly suggests that familial acceptance or rejection ultimately has little influence on the gender identity of youth; however, it may profoundly affect young people's ability to openly discuss or disclose concerns about their identity. Suppressing such concerns can affect mental health.⁸² Families often find it hard to understand and accept their child's gender-diverse traits because of personal beliefs, social pressure, and stigma.^{49,83} Legitimate fears may exist for their child's welfare, safety, and acceptance that pediatric providers need to appreciate and address. Families can be encouraged to communicate their concerns and questions. Unacknowledged concerns can contribute to shame and hesitation in regard to offering support and understanding.⁸⁴

which is essential for the child's self-esteem, social involvement, and overall health as TGD.^{48,85–87} Some caution has been expressed that unquestioning acceptance per se may not best serve questioning youth or their families. Instead, psychological evidence suggests that the most benefit comes when family members and youth are supported and encouraged to engage in reflective perspective taking and validate their own and the other's thoughts and feelings despite divergent views.^{49,82}

In this regard, suicide attempt rates among 433 adolescents in Ontario who identified as “trans” were 4% among those with strongly supportive parents and as high as 60% among those whose parents were not supportive.⁸⁵ Adolescents who identify as transgender and endorse at least 1 supportive person in their life report significantly less distress than those who only experience rejection. In communities with high levels of support, it was found that nonsupportive families tended to increase their support over time, leading to dramatic improvement in mental health outcomes among their children who identified as transgender.⁸⁸

Pediatric providers can create a safe environment for parents and families to better understand and listen to the needs of their children while receiving reassurance and education.⁸³ It is often appropriate to assist the child in understanding the parents' concerns as well. Despite expectations by some youth with transgender identity for immediate acceptance after “coming out,” family members often proceed through a process of becoming more comfortable and understanding of the youth's gender identity, thoughts, and feelings. One model suggests that the process resembles grieving, wherein the family separates from their expectations for their child to embrace a new reality. This process may proceed through stages of shock,

denial, anger, feelings of betrayal, fear, self-discovery, and pride.⁸⁹ The amount of time spent in any of these stages and the overall pace varies widely. Many family members also struggle as they are pushed to reflect on their own gender experience and assumptions throughout this process. In some situations, youth who identify as TGD may be at risk for internalizing the difficult emotions that family members may be experiencing. In these cases, individual and group therapy for the family members may be helpful.^{49,78}

Family dynamics can be complex, involving disagreement among legal guardians or between guardians and their children, which may affect the ability to obtain consent for any medical management or interventions. Even in states where minors may access care without parental consent for mental health services, contraception, and sexually transmitted infections, parental or guardian consent is required for hormonal and surgical care of patients who identify as TGD.^{72,90} Some families may take issue with providers who address gender concerns or offer gender-affirming care. In rare cases, a family may deny access to care that raises concerns about the youth's welfare and safety; in those cases, additional legal or ethical support may be useful to consider. In such rare situations, pediatric providers may want to familiarize themselves with relevant local consent laws and maintain their primary responsibility for the welfare of the child.

SAFE SCHOOLS AND COMMUNITIES

Youth who identify as TGD are becoming more visible because gender-diverse expression is increasingly admissible in the media, on social media, and in schools and communities. Regardless of whether a youth with a gender-diverse

identity ultimately identifies as transgender, challenges exist in nearly every social context, from lack of understanding to outright rejection, isolation, discrimination, and victimization. In the US Transgender Survey of nearly 28 000 respondents, it was found that among those who were out as or perceived to be TGD between kindergarten and eighth grade, 54% were verbally harassed, 24% were physically assaulted, and 13% were sexually assaulted; 17% left school because of maltreatment.³¹ Education and advocacy from the medical community on the importance of safe schools for youth who identify as TGD can have a significant effect.

At the time of this writing,* only 18 states and the District of Columbia had laws that prohibited discrimination based on gender expression when it comes to employment, housing, public accommodations, and insurance benefits. Over 200 US cities have such legislation. In addition to basic protections, many youth who identify as TGD also have to navigate legal obstacles when it comes to legally changing their name and/or gender marker.⁵⁴ In addition to advocating and working with policy makers to promote equal protections for youth who identify as TGD, pediatric providers can play an important role by developing a familiarity with local laws and organizations that provide social work and legal assistance to youth who identify as TGD and their families.

School environments play a significant role in the social and emotional development of children. Every child has a right to feel safe

and respected at school, but for youth who identify as TGD, this can be challenging. Nearly every aspect of school life may present safety concerns and require negotiations regarding their gender expression, including name/pronoun use, use of bathrooms and locker rooms, sports teams, dances and activities, overnight activities, and even peer groups. Conflicts in any of these areas can quickly escalate beyond the school's control to larger debates among the community and even on a national stage.

The formerly known Gay, Lesbian, and Straight Education Network (GLSEN), an advocacy organization for youth who identify as LGBTQ, conducts an annual national survey to measure LGBTQ well-being in US schools. In 2015, students who identified as LGBTQ reported high rates of being discouraged from participation in extracurricular activities. One in 5 students who identified as LGBTQ reported being hindered from forming or participating in a club to support lesbian, gay, bisexual, or transgender students (eg, a gay straight alliance, now often referred to as a genders and sexualities alliance) despite such clubs at schools being associated with decreased reports of negative remarks about sexual orientation or gender expression, increased feelings of safety and connectedness at school, and lower levels of victimization. In addition, >20% of students who identified as LGBTQ reported being blocked from writing about LGBTQ issues in school yearbooks or school newspapers or being prevented or discouraged by coaches and school staff from participating in sports because of their sexual orientation or gender expression.⁹¹

One strategy to prevent conflict is to proactively support policies and protections that promote inclusion and safety of all students. However, such policies are far from

consistent across districts. In 2015, GLSEN found that 43% of children who identified as LGBTQ reported feeling unsafe at school because of their gender expression, but only 6% reported that their school had official policies to support youth who identified as TGD, and only 11% reported that their school's antibullying policies had specific protections for gender expression.⁹¹ Consequently, more than half of the students who identified as transgender in the study were prevented from using the bathroom, names, or pronouns that aligned with their asserted gender at school. A lack of explicit policies that protected youth who identified as TGD was associated with increased reported victimization, with more than half of students who identified as LGBTQ reporting verbal harassment because of their gender expression. Educators and school administrators play an essential role in advocating for and enforcing such policies. GLSEN found that when students recognized actions to reduce gender-based harassment, both students who identified as transgender and cisgender reported a greater connection to staff and feelings of safety.⁹¹ In another study, schools were open to education regarding gender diversity and were willing to implement policies when they were supported by external agencies, such as medical professionals.⁹²

Academic content plays an important role in building a safe school environment as well. The 2015 GLSEN survey revealed that when positive representations of people who identified as LGBTQ were included in the curriculum, students who identified as LGBTQ reported less hostile school environments, less victimization and greater feelings of safety, fewer school absences because of feeling unsafe, greater feelings of connectedness to their school

* For more information regarding state-specific laws, please contact the AAP Division of State Government Affairs at stgov@aap.org.

community, and an increased interest in high school graduation and postsecondary education.⁹¹ At the time of this writing,* 8 states had laws that explicitly forbade teachers from even discussing LGBTQ issues.⁵⁴

MEDICAL EDUCATION

One of the most important ways to promote high-quality health care for youth who identify as TGD and their families is increasing the knowledge base and clinical experience of pediatric providers in providing culturally competent care to such populations, as recommended by the recently released guidelines by the Association of American Medical Colleges.⁹³ This begins with the medical school curriculum in areas such as human development, sexual health, endocrinology, pediatrics, and psychiatry. In a 2009–2010 survey of US medical schools, it was found that the median number of hours dedicated to LGBTQ health was 5, with one-third of US medical schools reporting no LGBTQ curriculum during the clinical years.⁹⁴

During residency training, there is potential for gender diversity to be emphasized in core rotations, especially in pediatrics, psychiatry, family medicine, and obstetrics and gynecology. Awareness could be promoted through the inclusion of topics relevant to caring for children who identify as TGD in the list of core competencies published by the American Board of Pediatrics, certifying examinations, and relevant study materials. Continuing education and maintenance of certification activities can include topics relevant to TGD populations as well.

RECOMMENDATIONS

The AAP works toward all children and adolescents, regardless of gender identity or expression, receiving care to promote optimal physical, mental, and social well-being. Any discrimination based on gender identity or expression, real or perceived, is damaging to the socioemotional health of children, families, and society. In particular, the AAP recommends the following:

1. that youth who identify as TGD have access to comprehensive, gender-affirming, and developmentally appropriate health care that is provided in a safe and inclusive clinical space;
2. that family-based therapy and support be available to recognize and respond to the emotional and mental health needs of parents, caregivers, and siblings of youth who identify as TGD;
3. that electronic health records, billing systems, patient-centered notification systems, and clinical research be designed to respect the asserted gender identity of each patient while maintaining confidentiality and avoiding duplicate charts;
4. that insurance plans offer coverage for health care that is specific to the needs of youth who identify as TGD, including coverage for medical, psychological, and, when indicated, surgical gender-affirming interventions;
5. that provider education, including medical school, residency, and continuing education, integrate core competencies on the emotional and physical health needs and best practices for the care of youth who identify as TGD and their families;
6. that pediatricians have a role in advocating for, educating, and developing liaison relationships

with school districts and other community organizations to promote acceptance and inclusion of all children without fear of harassment, exclusion, or bullying because of gender expression;

7. that pediatricians have a role in advocating for policies and laws that protect youth who identify as TGD from discrimination and violence;
8. that the health care workforce protects diversity by offering equal employment opportunities and workplace protections, regardless of gender identity or expression; and
9. that the medical field and federal government prioritize research that is dedicated to improving the quality of evidence-based care for youth who identify as TGD.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
GACM: gender-affirmative care model
GLSEN: Gay, Lesbian, and Straight Education Network
LGBTQ: lesbian, gay, bisexual, transgender, or questioning
TGD: transgender and gender diverse

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FIFTH EDITION

DSM-5™



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Gender Dysphoria

In this chapter, there is one overarching diagnosis of gender dysphoria, with separate developmentally appropriate criteria sets for children and for adolescents and adults. The area of sex and gender is highly controversial and has led to a proliferation of terms whose meanings vary over time and within and between disciplines. An additional source of confusion is that in English "sex" connotes both male/female and sexuality. This chapter employs constructs and terms as they are widely used by clinicians from various disciplines with specialization in this area. In this chapter, *sex* and *sexual* refer to the biological indicators of male and female (understood in the context of reproductive capacity), such as in sex chromosomes, gonads, sex hormones, and nonambiguous internal and external genitalia. Disorders of sex development denote conditions of inborn somatic deviations of the reproductive tract from the norm and/or discrepancies among the biological indicators of male and female. *Cross-sex* hormone treatment denotes the use of feminizing hormones in an individual assigned male at birth based on traditional biological indicators or the use of masculinizing hormones in an individual assigned female at birth.

The need to introduce the term *gender* arose with the realization that for individuals with conflicting or ambiguous biological indicators of sex (i.e., "intersex"), the lived role in society and/or the identification as male or female could not be uniformly associated with or predicted from the biological indicators and, later, that some individuals develop an identity as female or male at variance with their uniform set of classical biological indicators. Thus, *gender* is used to denote the public (and usually legally recognized) lived role as boy or girl, man or woman, but, in contrast to certain social constructionist theories, biological factors are seen as contributing, in interaction with social and psychological factors, to gender development. *Gender assignment* refers to the initial assignment as male or female. This occurs usually at birth and, thereby, yields the "natal gender." *Gender-atypical* refers to somatic features or behaviors that are not typical (in a statistical sense) of individuals with the same assigned gender in a given society and historical era; for behavior, *gender-nonconforming* is an alternative descriptive term. *Gender reassignment* denotes an official (and usually legal) change of gender. *Gender identity* is a category of social identity and refers to an individual's identification as male, female, or, occasionally, some category other than male or female. *Gender dysphoria* as a general descriptive term refers to an individual's affective/cognitive discontent with the assigned gender but is more specifically defined when used as a diagnostic category. *Transgender* refers to the broad spectrum of individuals who transiently or persistently identify with a gender different from their natal gender. *Transsexual* denotes an individual who seeks, or has undergone, a social transition from male to female or female to male, which in many, but not all, cases also involves a somatic transition by cross-sex hormone treatment and genital surgery (*sex reassignment surgery*).

Gender dysphoria refers to the distress that may accompany the incongruence between one's experienced or expressed gender and one's assigned gender. Although not all individuals will experience distress as a result of such incongruence, many are distressed if the desired physical interventions by means of hormones and/or surgery are not available. The current term is more descriptive than the previous DSM-IV term *gender identity disorder* and focuses on dysphoria as the clinical problem, not identity per se.

Gender Dysphoria

Diagnostic Criteria

Gender Dysphoria in Children

302.6 (F64.2)

- A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least six of the following (one of which must be Criterion A1):
1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender).
 2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire; or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing.
 3. A strong preference for cross-gender roles in make-believe play or fantasy play.
 4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender.
 5. A strong preference for playmates of the other gender.
 6. In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities.
 7. A strong dislike of one's sexual anatomy.
 8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender.
- B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning.

Specify if:

With a disorder of sex development (e.g., a congenital adrenogenital disorder such as 255.2 [E25.0] congenital adrenal hyperplasia or 259.50 [E34.50] androgen insensitivity syndrome).

Coding note: Code the disorder of sex development as well as gender dysphoria.

Gender Dysphoria in Adolescents and Adults

302.85 (F64.1)

- A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least two of the following:
1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics).
 2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).
 3. A strong desire for the primary and/or secondary sex characteristics of the other gender.
 4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender).
 5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender).
 6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).

- B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

With a disorder of sex development (e.g., a congenital adrenogenital disorder such as 255.2 [E25.0] congenital adrenal hyperplasia or 259.50 [E34.50] androgen insensitivity syndrome).

Coding note: Code the disorder of sex development as well as gender dysphoria.

Specify if:

Posttransition: The individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one cross-sex medical procedure or treatment regimen—namely, regular cross-sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in a natal male; mastectomy or phalloplasty in a natal female).

Specifiers

The posttransition specifier may be used in the context of continuing treatment procedures that serve to support the new gender assignment.

Diagnostic Features

Individuals with gender dysphoria have a marked incongruence between the gender they have been assigned to (usually at birth, referred to as *natal gender*) and their experienced/expressed gender. This discrepancy is the core component of the diagnosis. There must also be evidence of distress about this incongruence. Experienced gender may include alternative gender identities beyond binary stereotypes. Consequently, the distress is not limited to a desire to simply be of the other gender, but may include a desire to be of an alternative gender, provided that it differs from the individual's assigned gender.

Gender dysphoria manifests itself differently in different age groups. Prepubertal natal girls with gender dysphoria may express the wish to be a boy, assert they are a boy, or assert they will grow up to be a man. They prefer boys' clothing and hairstyles, are often perceived by strangers as boys, and may ask to be called by a boy's name. Usually, they display intense negative reactions to parental attempts to have them wear dresses or other feminine attire. Some may refuse to attend school or social events where such clothes are required. These girls may demonstrate marked cross-gender identification in role-playing, dreams, and fantasies. Contact sports, rough-and-tumble play, traditional boyhood games, and boys as playmates are most often preferred. They show little interest in stereotypically feminine toys (e.g., dolls) or activities (e.g., feminine dress-up or role-play). Occasionally, they refuse to urinate in a sitting position. Some natal girls may express a desire to have a penis or claim to have a penis or that they will grow one when older. They may also state that they do not want to develop breasts or menstruate.

Prepubertal natal boys with gender dysphoria may express the wish to be a girl or assert they are a girl or that they will grow up to be a woman. They have a preference for dressing in girls' or women's clothes or may improvise clothing from available materials (e.g., using towels, aprons, and scarves for long hair or skirts). These children may role-play female figures (e.g., playing "mother") and often are intensely interested in female fantasy figures. Traditional feminine activities, stereotypical games, and pastimes (e.g., "playing house"; drawing feminine pictures; watching television or videos of favorite female characters) are most often preferred. Stereotypical female-type dolls (e.g., Barbie) are often favorite toys, and girls are their preferred playmates. They avoid rough-and-tumble play and competitive sports and have little interest in stereotypically masculine toys (e.g., cars, trucks). Some may pretend not to have a penis and insist on sitting to urinate. More

rarely, they may state that they find their penis or testes disgusting, that they wish them removed, or that they have, or wish to have, a vagina.

In young adolescents with gender dysphoria, clinical features may resemble those of children or adults with the condition, depending on developmental level. As secondary sex characteristics of young adolescents are not yet fully developed, these individuals may not state dislike of them, but they are concerned about imminent physical changes.

In adults with gender dysphoria, the discrepancy between experienced gender and physical sex characteristics is often, but not always, accompanied by a desire to be rid of primary and/or secondary sex characteristics and/or a strong desire to acquire some primary and/or secondary sex characteristics of the other gender. To varying degrees, adults with gender dysphoria may adopt the behavior, clothing, and mannerisms of the experienced gender. They feel uncomfortable being regarded by others, or functioning in society, as members of their assigned gender. Some adults may have a strong desire to be of a different gender and treated as such, and they may have an inner certainty to feel and respond as the experienced gender without seeking medical treatment to alter body characteristics. They may find other ways to resolve the incongruence between experienced/expressed and assigned gender by partially living in the desired role or by adopting a gender role neither conventionally male nor conventionally female.

Associated Features Supporting Diagnosis

When visible signs of puberty develop, natal boys may shave their legs at the first signs of hair growth. They sometimes bind their genitals to make erections less visible. Girls may bind their breasts, walk with a stoop, or use loose sweaters to make breasts less visible. Increasingly, adolescents request, or may obtain without medical prescription and supervision, hormonal suppressors ("blockers") of gonadal steroids (e.g., gonadotropin-releasing hormone [GnRH] analog, spironolactone). Clinically referred adolescents often want hormone treatment and many also wish for gender reassignment surgery. Adolescents living in an accepting environment may openly express the desire to be and be treated as the experienced gender and dress partly or completely as the experienced gender, have a hairstyle typical of the experienced gender, preferentially seek friendships with peers of the other gender, and/or adopt a new first name consistent with the experienced gender. Older adolescents, when sexually active, usually do not show or allow partners to touch their sexual organs. For adults with an aversion toward their genitals, sexual activity is constrained by the preference that their genitals not be seen or touched by their partners. Some adults may seek hormone treatment (sometimes without medical prescription and supervision) and gender reassignment surgery. Others are satisfied with either hormone treatment or surgery alone.

Adolescents and adults with gender dysphoria before gender reassignment are at increased risk for suicidal ideation, suicide attempts, and suicides. After gender reassignment, adjustment may vary, and suicide risk may persist.

Prevalence

For natal adult males, prevalence ranges from 0.005% to 0.014%, and for natal females, from 0.002% to 0.003%. Since not all adults seeking hormone treatment and surgical reassignment attend specialty clinics, these rates are likely modest underestimates. Sex differences in rate of referrals to specialty clinics vary by age group. In children, sex ratios of natal boys to girls range from 2:1 to 4.5:1. In adolescents, the sex ratio is close to parity; in adults, the sex ratio favors natal males, with ratios ranging from 1:1 to 6.1:1. In two countries, the sex ratio appears to favor natal females (Japan: 2.2:1; Poland: 3.4:1).

Development and Course

Because expression of gender dysphoria varies with age, there are separate criteria sets for children versus adolescents and adults. Criteria for children are defined in a more con-

crete, behavioral manner than those for adolescents and adults. Many of the core criteria draw on well-documented behavioral gender differences between typically developing boys and girls. Young children are less likely than older children, adolescents, and adults to express extreme and persistent anatomic dysphoria. In adolescents and adults, incongruence between experienced gender and somatic sex is a central feature of the diagnosis. Factors related to distress and impairment also vary with age. A very young child may show signs of distress (e.g., intense crying) only when parents tell the child that he or she is "really" not a member of the other gender but only "desires" to be. Distress may not be manifest in social environments supportive of the child's desire to live in the role of the other gender and may emerge only if the desire is interfered with. In adolescents and adults, distress may manifest because of strong incongruence between experienced gender and somatic sex. Such distress may, however, be mitigated by supportive environments and knowledge that biomedical treatments exist to reduce incongruence. Impairment (e.g., school refusal, development of depression, anxiety, and substance abuse) may be a consequence of gender dysphoria.

Gender dysphoria without a disorder of sex development. For clinic-referred children, onset of cross-gender behaviors is usually between ages 2 and 4 years. This corresponds to the developmental time period in which most typically developing children begin expressing gendered behaviors and interests. For some preschool-age children, both pervasive cross-gender behaviors and the expressed desire to be the other gender may be present, or, more rarely, labeling oneself as a member of the other gender may occur. In some cases, the expressed desire to be the other gender appears later, usually at entry into elementary school. A small minority of children express discomfort with their sexual anatomy or will state the desire to have a sexual anatomy corresponding to the experienced gender ("anatomic dysphoria"). Expressions of anatomic dysphoria become more common as children with gender dysphoria approach and anticipate puberty.

Rates of persistence of gender dysphoria from childhood into adolescence or adulthood vary. In natal males, persistence has ranged from 2.2% to 30%. In natal females, persistence has ranged from 12% to 50%. Persistence of gender dysphoria is modestly correlated with dimensional measures of severity ascertained at the time of a childhood baseline assessment. In one sample of natal males, lower socioeconomic background was also modestly correlated with persistence. It is unclear if particular therapeutic approaches to gender dysphoria in children are related to rates of long-term persistence. Extant follow-up samples consisted of children receiving no formal therapeutic intervention or receiving therapeutic interventions of various types, ranging from active efforts to reduce gender dysphoria to a more neutral, "watchful waiting" approach. It is unclear if children "encouraged" or supported to live socially in the desired gender will show higher rates of persistence, since such children have not yet been followed longitudinally in a systematic manner. For both natal male and female children showing persistence, almost all are sexually attracted to individuals of their natal sex. For natal male children whose gender dysphoria does not persist, the majority are *androphilic* (sexually attracted to males) and often self-identify as gay or homosexual (ranging from 63% to 100%). In natal female children whose gender dysphoria does not persist, the percentage who are *gynephilic* (sexually attracted to females) and self-identify as lesbian is lower (ranging from 32% to 50%).

In both adolescent and adult natal males, there are two broad trajectories for development of gender dysphoria: early onset and late onset. *Early-onset gender dysphoria* starts in childhood and continues into adolescence and adulthood; or, there is an intermittent period in which the gender dysphoria desists and these individuals self-identify as gay or homosexual, followed by recurrence of gender dysphoria. *Late-onset gender dysphoria* occurs around puberty or much later in life. Some of these individuals report having had a desire to be of the other gender in childhood that was not expressed verbally to others. Others do not recall any signs of childhood gender dysphoria. For adolescent males with late-onset gender dysphoria, parents often report surprise because they did not see signs of gender

dysphoria during childhood. Expressions of anatomic dysphoria are more common and salient in adolescents and adults once secondary sex characteristics have developed.

Adolescent and adult natal males with early-onset gender dysphoria are almost always sexually attracted to men (androphilic). Adolescents and adults with late-onset gender dysphoria frequently engage in transvestic behavior with sexual excitement. The majority of these individuals are gynephilic or sexually attracted to other posttransition natal males with late-onset gender dysphoria. A substantial percentage of adult males with late-onset gender dysphoria cohabit with or are married to natal females. After gender transition, many self-identify as lesbian. Among adult natal males with gender dysphoria, the early-onset group seeks out clinical care for hormone treatment and reassignment surgery at an earlier age than does the late-onset group. The late-onset group may have more fluctuations in the degree of gender dysphoria and be more ambivalent about and less likely satisfied after gender reassignment surgery.

In both adolescent and adult natal females, the most common course is the early-onset form of gender dysphoria. The late-onset form is much less common in natal females compared with natal males. As in natal males with gender dysphoria, there may have been a period in which the gender dysphoria desisted and these individuals self-identified as lesbian; however, with recurrence of gender dysphoria, clinical consultation is sought, often with the desire for hormone treatment and reassignment surgery. Parents of natal adolescent females with the late-onset form also report surprise, as no signs of childhood gender dysphoria were evident. Expressions of anatomic dysphoria are much more common and salient in adolescents and adults than in children.

Adolescent and adult natal females with early-onset gender dysphoria are almost always gynephilic. Adolescents and adults with the late-onset form of gender dysphoria are usually androphilic and after gender transition self-identify as gay men. Natal females with the late-onset form do not have co-occurring transvestic behavior with sexual excitement.

Gender dysphoria in association with a disorder of sex development. Most individuals with a disorder of sex development who develop gender dysphoria have already come to medical attention at an early age. For many, starting at birth, issues of gender assignment were raised by physicians and parents. Moreover, as infertility is quite common for this group, physicians are more willing to perform cross-sex hormone treatments and genital surgery before adulthood.

Disorders of sex development in general are frequently associated with gender-atypical behavior starting in early childhood. However, in the majority of cases, this does not lead to gender dysphoria. As individuals with a disorder of sex development become aware of their medical history and condition, many experience uncertainty about their gender, as opposed to developing a firm conviction that they are another gender. However, most do not progress to gender transition. Gender dysphoria and gender transition may vary considerably as a function of a disorder of sex development, its severity, and assigned gender.

Risk and Prognostic Factors

Temperamental. For individuals with gender dysphoria without a disorder of sex development, atypical gender behavior among individuals with early-onset gender dysphoria develops in early preschool age, and it is possible that a high degree of atypicality makes the development of gender dysphoria and its persistence into adolescence and adulthood more likely.

Environmental. Among individuals with gender dysphoria without a disorder of sex development, males with gender dysphoria (in both childhood and adolescence) more commonly have older brothers than do males without the condition. Additional predisposing

factors under consideration, especially in individuals with late-onset gender dysphoria (adolescence, adulthood), include habitual fetishistic transvestism developing into autogynephilia (i.e., sexual arousal associated with the thought or image of oneself as a woman) and other forms of more general social, psychological, or developmental problems.

Genetic and physiological. For individuals with gender dysphoria without a disorder of sex development, some genetic contribution is suggested by evidence for (weak) familiarity of transsexualism among nontwin siblings, increased concordance for transsexualism in monozygotic compared with dizygotic same-sex twins, and some degree of heritability of gender dysphoria. As to endocrine findings, no endogenous systemic abnormalities in sex-hormone levels have been found in 46,XY individuals, whereas there appear to be increased androgen levels (in the range found in hirsute women but far below normal male levels) in 46,XX individuals. Overall, current evidence is insufficient to label gender dysphoria without a disorder of sex development as a form of intersexuality limited to the central nervous system.

In gender dysphoria associated with a disorder of sex development, the likelihood of later gender dysphoria is increased if prenatal production and utilization (via receptor sensitivity) of androgens are grossly atypical relative to what is usually seen in individuals with the same assigned gender. Examples include 46,XY individuals with a history of normal male prenatal hormone milieu but inborn nonhormonal genital defects (as in cloacal bladder exstrophy or penile agenesis) and who have been assigned to the female gender. The likelihood of gender dysphoria is further enhanced by additional, prolonged, highly gender-atypical postnatal androgen exposure with somatic virilization as may occur in female-raised and noncastrated 46,XY individuals with 5-alpha reductase-2 deficiency or 17-beta-hydroxysteroid dehydrogenase-3 deficiency or in female-raised 46,XX individuals with classical congenital adrenal hyperplasia with prolonged periods of non-adherence to glucocorticoid replacement therapy. However, the prenatal androgen milieu is more closely related to gendered behavior than to gender identity. Many individuals with disorders of sex development and markedly gender-atypical behavior do not develop gender dysphoria. Thus, gender-atypical behavior by itself should not be interpreted as an indicator of current or future gender dysphoria. There appears to be a higher rate of gender dysphoria and patient-initiated gender change from assigned female to male than from assigned male to female in 46,XY individuals with a disorder of sex development.

Culture-Related Diagnostic Issues

Individuals with gender dysphoria have been reported across many countries and cultures. The equivalent of gender dysphoria has also been reported in individuals living in cultures with institutionalized gender categories other than male or female. It is unclear whether with these individuals the diagnostic criteria for gender dysphoria would be met.

Diagnostic Markers

Individuals with a somatic disorder of sex development show some correlation of final gender identity outcome with the degree of prenatal androgen production and utilization. However, the correlation is not robust enough for the biological factor, where ascertainable, to replace a detailed and comprehensive diagnostic interview evaluation for gender dysphoria.

Functional Consequences of Gender Dysphoria

Preoccupation with cross-gender wishes may develop at all ages after the first 2-3 years of childhood and often interfere with daily activities. In older children, failure to develop age-typical same-sex peer relationships and skills may lead to isolation from peer groups and to distress. Some children may refuse to attend school because of teasing and harass-

ment or pressure to dress in attire associated with their assigned sex. Also in adolescents and adults, preoccupation with cross-gender wishes often interferes with daily activities. Relationship difficulties, including sexual relationship problems, are common, and functioning at school or at work may be impaired. Gender dysphoria, along with atypical gender expression, is associated with high levels of stigmatization, discrimination, and victimization, leading to negative self-concept, increased rates of mental disorder comorbidity, school dropout, and economic marginalization, including unemployment, with attendant social and mental health risks, especially in individuals from resource-poor family backgrounds. In addition, these individuals' access to health services and mental health services may be impeded by structural barriers, such as institutional discomfort or inexperience in working with this patient population.

Differential Diagnosis

Nonconformity to gender roles. Gender dysphoria should be distinguished from simple nonconformity to stereotypical gender role behavior by the strong desire to be of another gender than the assigned one and by the extent and pervasiveness of gender-variant activities and interests. The diagnosis is not meant to merely describe nonconformity to stereotypical gender role behavior (e.g., "tomboyism" in girls, "girly-boy" behavior in boys, occasional cross-dressing in adult men). Given the increased openness of atypical gender expressions by individuals across the entire range of the transgender spectrum, it is important that the clinical diagnosis be limited to those individuals whose distress and impairment meet the specified criteria.

Transvestic disorder. Transvestic disorder occurs in heterosexual (or bisexual) adolescent and adult males (rarely in females) for whom cross-dressing behavior generates sexual excitement and causes distress and/or impairment without drawing their primary gender into question. It is occasionally accompanied by gender dysphoria. An individual with transvestic disorder who also has clinically significant gender dysphoria can be given both diagnoses. In many cases of late-onset gender dysphoria in gynephilic natal males, transvestic behavior with sexual excitement is a precursor.

Body dysmorphic disorder. An individual with body dysmorphic disorder focuses on the alteration or removal of a specific body part because it is perceived as abnormally formed, not because it represents a repudiated assigned gender. When an individual's presentation meets criteria for both gender dysphoria and body dysmorphic disorder, both diagnoses can be given. Individuals wishing to have a healthy limb amputated (termed by some *body integrity identity disorder*) because it makes them feel more "complete" usually do not wish to change gender, but rather desire to live as an amputee or a disabled person.

Schizophrenia and other psychotic disorders. In schizophrenia, there may rarely be delusions of belonging to some other gender. In the absence of psychotic symptoms, insistence by an individual with gender dysphoria that he or she is of some other gender is not considered a delusion. Schizophrenia (or other psychotic disorders) and gender dysphoria may co-occur.

Other clinical presentations. Some individuals with an emasculation desire who develop an alternative, nonmale/nonfemale gender identity do have a presentation that meets criteria for gender dysphoria. However, some males seek castration and/or penectomy for aesthetic reasons or to remove psychological effects of androgens without changing male identity; in these cases, the criteria for gender dysphoria are not met.

Comorbidity

Clinically referred children with gender dysphoria show elevated levels of emotional and behavioral problems—most commonly, anxiety, disruptive and impulse-control, and de-

pressive disorders. In prepubertal children, increasing age is associated with having more behavioral or emotional problems; this is related to the increasing non-acceptance of gender-variant behavior by others. In older children, gender-variant behavior often leads to peer ostracism, which may lead to more behavioral problems. The prevalence of mental health problems differs among cultures; these differences may also be related to differences in attitudes toward gender variance in children. However, also in some non-Western cultures, anxiety has been found to be relatively common in individuals with gender dysphoria, even in cultures with accepting attitudes toward gender-variant behavior. Autism spectrum disorder is more prevalent in clinically referred children with gender dysphoria than in the general population. Clinically referred adolescents with gender dysphoria appear to have comorbid mental disorders, with anxiety and depressive disorders being the most common. As in children, autism spectrum disorder is more prevalent in clinically referred adolescents with gender dysphoria than in the general population. Clinically referred adults with gender dysphoria may have coexisting mental health problems, most commonly anxiety and depressive disorders.

Other Specified Gender Dysphoria

302.6 (F64.8)

This category applies to presentations in which symptoms characteristic of gender dysphoria that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for gender dysphoria. The other specified gender dysphoria category is used in situations in which the clinician chooses to communicate the specific reason that the presentation does not meet the criteria for gender dysphoria. This is done by recording "other specified gender dysphoria" followed by the specific reason (e.g., "brief gender dysphoria").

An example of a presentation that can be specified using the "other specified" designation is the following:

The current disturbance meets symptom criteria for gender dysphoria, but the duration is less than 6 months.

Unspecified Gender Dysphoria

302.6 (F64.9)

This category applies to presentations in which symptoms characteristic of gender dysphoria that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for gender dysphoria. The unspecified gender dysphoria category is used in situations in which the clinician chooses *not* to specify the reason that the criteria are not met for gender dysphoria, and includes presentations in which there is insufficient information to make a more specific diagnosis.

**IN THE UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF ARKANSAS
CENTRAL DIVISION**

DYLAN BRANDT, et al.,

PLAINTIFFS,

v.

No. 4:21-CV-00450-JM

LESLIE RUTLEDGE, et al.,

DEFENDANTS.

EXPERT DECLARATION OF ROGER HIATT, JR., M.D.

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

1. My name is Roger Hiatt, Jr., M.D., and I have personal knowledge of the statements contained in this declaration. A copy of my curriculum vitae is attached as Exhibit A.

2. I am a Child and Adolescent Psychiatrist licensed and practicing in Arkansas for twenty-five years. I received my M.D. from the University of Tennessee, Memphis, in 1992, and completed psychiatric residency at the University of Arkansas for Medical Sciences in 1997. My residency included two years of specialized Child and Adolescent Psychiatry training centered at Arkansas Children's Hospital.

3. From 1997 until 2015, I practiced psychiatry at Centers for Youth and Families in Little Rock. While there, I worked with thousands of Arkansas children and teenagers, including some identifying as transgender, in residential care, day treatment, therapeutic foster care, and outpatient services.

4. I became Medical Director at the Springville campus of Provo Canyon School, a large residential psychiatric treatment center in Utah, from 2015 until 2019. During my time at Provo Canyon, I worked with hundreds of children and adolescents from a majority of the fifty United States, including dozens diagnosed with Gender Dysphoria, some of whom had been administered hormonal interventions by other physicians.



5. Since 2019, I have served as Medical Director for two Child and Adolescent Residential Treatment Centers, one in Arkansas and one in Tennessee. I continue to treat a number of youth presenting with gender-related issues.

6. I base the following statements on my own knowledge, research, and experience. The materials I have relied on in forming these impressions are the standard materials used by other experts in my field. I am receiving no financial compensation for the many hours I have worked on behalf of the defense in this case.

7. I, along with other Arkansas physicians, testified before the Arkansas General Assembly in support of the SAFE Act.

8. When the House Public Health and Welfare Committee hearing on the SAFE Act was held on March 9, 2021, two board-certified physicians testified in favor of the Act: Dr. James Grady Crosland of Little Rock, a pediatric anesthesiologist, and Dr. Kendall Wagner of Fort Smith, a pediatrician.

9. I personally testified in support of the Act before the Arkansas Senate Public Health, Welfare and Labor Committee on March 22, 2021, along with Dr. Charles Lewis, who also has treated several patients with Gender Dysphoria.

10. On April 2, 2021, Dr. Melanie Conway, a Diplomate of the American Board of Psychiatry and Neurology with extensive experience treating adolescents with Gender Dysphoria, participated in a conference call urging the Act's approval. She also addressed members of the Arkansas Legislature in person for the same purpose.

11. Additional Arkansas physicians joined Dr. Lewis, Dr. Conway, and me in submitting a letter on April 6, 2021, urging the General Assembly to approve the Act. Those additional

physicians included pediatricians Dr. Anton Duke and Dr. Kristi Hawkins, as well as Dr. Michael Beheshti, an interventional radiologist, Dr. Gareth Tobler, a thoracic surgeon, Dr. David Rhodes, an orthopedic surgeon, and Dr. David Warner, an ophthalmologist.

12. I have personally been involved in the treatment of dozens of patients with Gender Dysphoria throughout my career, beginning in residency in the mid-1990's. I first treated a child with this condition shortly after residency, around 1998. The patients I treated early in my career were all natal males presenting as female.

13. During my eighteen years of work at Centers for Youth and Families in Arkansas, from 1997 to 2015, I worked directly with a number of young patients struggling with gender-related issues. These were also primarily natal males.

14. At the time of my arrival at the Provo Canyon School in 2015, none of the initial 200 residents I encountered presented with gender incongruence. But over the course of the next four years, from 2015 to 2019, I observed a noteworthy trend as the portion of patients under my care exhibiting gender incongruence ballooned from zero to more than ten percent.

15. Significantly, the overwhelming majority of transgender patients at Provo Canyon were natal females identifying as male. This is despite the fact that the Provo Canyon School serves approximately the same number of natal males as natal females.

16. Upon my return to Arkansas, I have continued working with several gender-dysphoric youth, who are also predominantly natal females.

17. These trends are consistent with a widely recognized departure from the demographics published in the most recent edition of the Diagnostic and Statistical Manual of Mental Disorders, which identifies natal males presenting with gender incongruence far more

frequently than females: “For natal adult males, prevalence ranges from 0.005% to 0.014%, and for natal females, from 0.002% to 0.003%.”¹

18. The demographics of gender dysphoria have changed drastically over the past decade. In 2013, the above prevalence ratios indicated that from 2-to-4.5 times as many natal males experienced gender dysphoria as did natal females. By the time the 2018 LGBTQ Youth Report was completed, however, that ratio had flipped, with natal girls outnumbering natal boys among those self-identified as transgender by a ratio of over 8.5:1.²

19. Throughout my career, I have noted that certain diagnoses become “trendy” or “vogue” over time. While the 1990’s were replete with Attention-Deficit/Hyperactivity Disorder (ADHD or ADD), the turn of the century saw an explosion in Bipolar diagnoses, followed by the Autism boom. Eating disorders and self-harm by cutting have more recently become markedly more prevalent.

20. Gender Dysphoria is the vogue diagnosis of our time. It holds in common with previous diagnostic trends the appeal of being unique or belonging to an exclusive group. Positive reinforcement and accolades are readily accessible through social media and public notoriety. Unlike other diagnostic trends, however, it is a diagnosis based solely on self-report and cannot be confirmed objectively. Also unlike other diagnoses, the treatment regimens advocated serve to medicalize patients and permanently alter the natural course of their biology.

¹ The Am. Psychiatric Ass’n, *Diagnostic and Statistical Manual of Mental Disorders* 454 (5th ed. 2013) (DSM-5).

² Human Rights Campaign, *2018 LGBTQ Youth Report* 24, <https://hrc-prod-requests.s3-us-west-2.amazonaws.com/files/assets/resources/2018-YouthReport-NoVid.pdf?mtime=20200713131634&focal=none>.

21. My young patients with gender incongruence, representative of such youth generally, are very heterogeneous, with a wide variety of backgrounds, presentations, and attitudes toward identifying as transgender. Not all meet the criteria for a diagnosis of Gender Dysphoria, which requires accompanying “clinically significant distress.” Further, those who identify as transgender do not routinely desire to receive puberty blockers, cross-sex hormones, or surgery.

22. A few examples of adolescent patients whom I have treated over the years:

- a. A 15 y.o. natal female who self-identified as “gender fluid” and is now in distance;
- b. A 16 y.o. natal female who presented as male and whose preferred name was the name of a deceased twin brother;
- c. A 12 y.o. natal female who presented as male and self-identified as transgender, but stated, “I’ll be a girl when I go home”;
- d. A 15 y.o. natal female who self-identified as transgender, but explained, “I identify as female, I’m just not comfortable with my birth name”;
- e. A 16 y.o. natal female with a puberty-blocking implant in arm who told me, “I came out as transgender, but you can just say female, non-binary”;
- f. A 17 y.o. natal female with whom I had worked for two years without mention of any gender identity issues, who precipitously declared, “I’m a boy!”

23. Almost without exception, patients presenting with gender incongruence also experience concomitant mental illness and trauma. Frequently they have suffered sexual abuse, often at a very early age. Physical abuse and neglect are also common. Anxiety is nearly universal, as is mood disturbance. Invariably, the diagnosis of Gender Dysphoria is concurrent with several other significant psychiatric diagnoses.

24. Based on my clinical experience with troubled youth, gender incongruence in most cases ought not be the primary focus of therapeutic attention. On the contrary, a hyperfocus on gender incongruence distracts from addressing underlying trauma and mental illness. Indeed, patients often embrace such distractions to avoid the hard work of therapy.

25. My clinical practice is to treat minors with gender incongruence with a combination of psychiatric care addressing underlying mental health issues and watchful waiting. None have demonstrated evidence of harm or increased suicidality as a result. Many have spontaneously desisted from identifying as transgender and embraced their biological sex.

26. My clinical experience contradicts claims made by others that social transitioning and affirmation of a transgender identity is the only way to relieve the distress that accompanies Gender Dysphoria. On the contrary, the most favorable long-term prognosis is attained through a combination of psychiatric care addressing underlying mental health issues and watchful waiting. It runs contrary to well-established principles of medical ethics to subject children who self-identify as transgender to immediate social transition followed by puberty blockers, hormones, and surgery when the vast majority will desist by adulthood if simply allowed to develop unimpeded by activist and unproven experimentation.

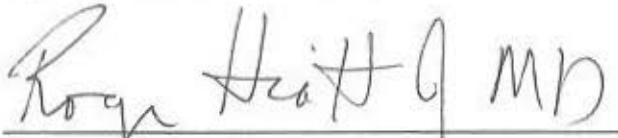
27. In conclusion, my clinical experience is consistent with the scientific evidence that the vast majority of minors who identify as transgender will desist in time. Furthermore, it is indisputable that no amount of social transitioning, hormonal manipulation, or surgical intervention can achieve the desired result: a complete change from one sex to the other, which is a biological impossibility. On the contrary, once children begin cross-sex hormones, they face a lifetime of infertility, frequent doses of exogenous hormones, and social and medical complications. From that point forward, they must live with the medicalization of what could have been a relatively healthy, intervention-free existence, because the biological, genotypic reality continually resists alteration. Indeed, the inability to alter genotypic sex likely underlies the fact that

those who undergo gender transition efforts continue to suffer a suicide rate 19 times greater than that of the general population.³

28. Therefore, I unequivocally affirm that watchful waiting, including appropriate mental health treatment to address concomitant mental illness and trauma, is the most compassionate and scientifically based course of treatment with the greatest potential for a positive long-term outcome in gender dysphoric children and adolescents.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on July 6, 2021.



Roger Hjatt, Jr., M.D.

³ See Dhejne C, Lichtenstein P, Boman M, Johansson ALV, Långström N, Landén M (2011) *Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden*. PLoS ONE 6(2): e16885. doi:10.1371/journal.pone.0016885.

CURRICULUM VITAE**ROGER LEW HIATT, JR., M.D.****IDENTIFICATION**ARKANSASS BUSINESS ADDRESS

Perimeter Behavioral Health
 600H 7th Street
 West Memphis, AR 72301

BUSINESS PHONE NUMBER

[REDACTED]

TENNESSEE BUSINESS ADDRESS

Perimeter Behavioral Health
 49 Old Hickory Blvd
 Jackson, TN 38305

BUSINESS PHONE NUMBER

[REDACTED]

BIRTHDATE

[REDACTED]

BIRTHPLACE

[REDACTED]

MARITAL STATUS

Married, with six children

CITIZENSHIP

United States of America

EDUCATIONINSTITUTION AND LOCATIONPROGRAMYEARS

University of Arkansas for Medical Sciences
 Division of Pediatric Psychiatry
 800 Marshall Slot #500
 Little Rock, Arkansas 72202

Child
 Psychiatry
 Residency

1995-1997

University of Arkansas for Medical Sciences
 Department of Psychiatry
 4301 West Markham Slot #589
 Little Rock, Arkansas 72205

General
 Psychiatry
 Residency

1993-1995

University of Arkansas for Medical Sciences
 Department of Psychiatry
 4301 West Markham Slot #589
 Little Rock, Arkansas 72205

General
 Psychiatry
 Internship

1992-1993

University of Tennessee, Memphis
 62 South Dunlap
 Memphis, Tennessee 38163

M.D.

1988-1992

Brigham Young University
 B-150 Abraham Smoot Building
 Provo, Utah 84602

B.A.

1980-1985

EXHIBIT
A

<u>BOARD EXAMINATION AND LICENSURE</u>	<u>YEAR</u>
Medical License [REDACTED] Tennessee State Medical Board	2018
Medical License [REDACTED], Utah State Medical Board	2015
Medical License [REDACTED] Arkansas State Medical Board	1993
Board Eligible, American Board of Psychiatry and Neurology Certification in Child and Adolescent Psychiatry	1997
Board Eligible, American Board of Psychiatry and Neurology Certification in General Psychiatry	1996
Board Certified, National Board of Medical Examiners (Parts I, II, & III)	1993

PROFESSIONAL ACTIVITY

<u>APPOINTMENTS</u>	<u>YEARS</u>
Medical Director Perimeter of West Memphis, Arkansas residential 600N 7th Street West Memphis, Arkansas 72301	2019 - present
Medical Director Perimeter of Jackson, Tennessee residential 49 Old hickory Blvd E Jackson, Tennessee 38305	2019 - present
Medical Director Family Service Agency 628 West Broadway, Suite #300 North Little Rock, Arkansas 72114	2021 - present
Medical Director Provo Canyon School, Springville Campus 763 N 1650 W Springville, Utah 84663	2015 - 2020
Staff Psychiatrist Centers for Youth and Families 6501 West 12th Street Little Rock, Arkansas 72225	1997 - 2015

Consulting Medical Staff	2013 - 2014
Riverview Behavioral Health	
701 Arkansas Boulevard	
Texarkana, Arkansas 71854	

Consulting Medical Staff	2013
Rivendell Psychiatric Center	1994 - 1999
100 Rivendell Drive	
Benton, Arkansas 72015	

HONORS AND AWARDSYEARS

Volunteer Faculty	2013 - 2014
University of Tennessee, College of Nursing	
Advanced Practice Nursing Program	

Chief Resident	1996 - 1997
University of Arkansas for Medical Sciences	
Division of Pediatric Psychiatry	

Missionary	1982 - 1983
The Church of Jesus Christ of Latter-day Saints	
(developed fluency in the Spanish language)	

Eagle Scout	1980
Boy Scouts of America	

PROFESSIONAL ORGANIZATIONSYEARS

American Academy of Child and Adolescent Psychiatry	1995 - 2015

Collegium Aesculapium	1985 - present

American Psychiatric Association	1992 - 1997

American Medical Association	1988 - 1997

**IN THE UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF ARKANSAS
CENTRAL DIVISION**

DYLAN BRANDT, et al.,

PLAINTIFFS,

v.

No. 4:21-CV-00450-JM

LESLIE RUTLEDGE, et al.,

DEFENDANTS.

DECLARATION OF CHRISTINE CRYER

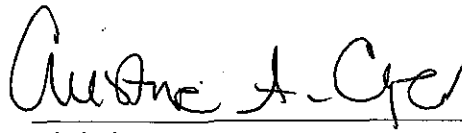
Pursuant to 28 U.S.C. 1746, I declare:

1. My name is Christine Cryer, and I am the Chief Legal Counsel for the Arkansas Department of Corrections (ADC). I have personal knowledge of the facts in this declaration.
2. Attached as Exhibit A to this declaration is a true and correct copy of Administrative Directive Number 14-19, effective April 11, 2014 (AD 14-19).
3. One of my responsibilities as Chief Legal Counsel is to oversee those who maintain custody of documents like AD 14-19.
4. AD 14-19 is a record created by ADC that sets out its activities in providing certain procedures for inmates. Under Arkansas Administrative Code section 004.00.2-001, ADC is under a legal duty to report the information contained in AD 14-19.
5. Additionally, AD 14-19 was made at or near the time of the act it records—namely, amending ADC's policies regarding certain procedures for inmates—by, or from information transmitted by, someone with knowledge of the act it records. It was the regular practice of ADC staff to make AD 14-19, and AD 14-19 was kept in the course of ADC's regular conducted activities of administering Arkansas's correctional facilities.

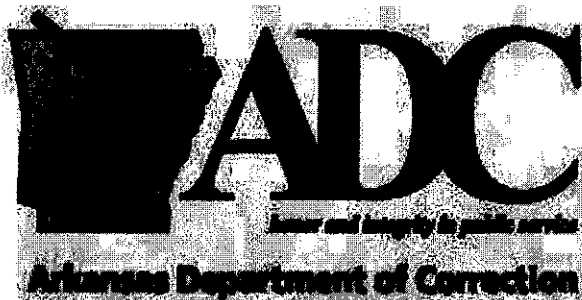


I declare under penalty of perjury that the foregoing is true and correct.

Executed on June 29th, 2021.

A handwritten signature in black ink, appearing to read "Christine A. Cryer", written over a horizontal line.

Christine Cryer
Chief Legal Counsel
Arkansas Department of Corrections



PO Box 8707
Pine Bluff, AR 71611-8707
Phone: 870-267-6200
Fax: 870-267-6244
www.state.ar.us/doc

ADMINISTRATIVE DIRECTIVE

SUBJECT: Gender Dysphoria and Intersex Inmates

NUMBER: 14-19

SUPERSEDES: 12-06

APPLICABILITY: All ADC staff

REFERENCE: AR 833

PAGE 1 of 3

APPROVED: Original signed by Ray Hobbs

EFFECTIVE DATE: 04/11/2014

I. POLICY:

It is the policy of the Department to provide the appropriate treatment to inmates meeting the criteria for the current Diagnostic Statistical Manual (DSM) diagnosis of Gender Dysphoria.

II. EXPLANATION:

This policy establishes the responsibilities, policies, and procedures to ensure a standard of care for the treatment of Gender Dysphoria.

III. DEFINITIONS:

- A. Gender Dysphoria (GD) - A mental disorder where individuals have a marked difference between the individual's expressed/experienced gender and the gender they have been assigned (at birth), and it must continue for at least six (6) months. There must also be evidence of distress about this difference.
- B. Hormonal Replacement Treatment – A medical procedure in which male or female hormones are prescribed as a result of the patient's inability to produce an adequate amount of these hormones naturally.

EXHIBIT

A

- C. Sexual Reassignment Therapy – A treatment for gender dysphoria in which hormone medications or surgical procedures is utilized to alter a person's physical appearance, in an attempt to adopt the physical characteristics of the opposite gender.
- D. Sex Offender – A male or female convicted of a criminal sex offense.
- E. Intersex – A condition in which a person is born with external genitalia, internal reproductive organs, chromosome patterns, and/or an endocrine system that does not fit typical definitions of male or female.

IV. **GD RESPONSIBILITIES:**

The Gender Dysphoria Management and Treatment (GDMT) Committee is responsible for determining the appropriate treatment referrals for identified GD and Intersex inmates.

V. **HOUSING:**

- A. Housing placement of diagnosed GD or Intersex inmates will be made on a case-by-case basis taking into consideration the inmate's health and safety and whether the placement would present management or security problems, giving serious consideration to the inmate's own views regarding his or her own safety. Both GD and Intersex inmates shall be given the opportunity to shower separately from other inmates.
- B. GD and Intersex inmates shall not be housed in dedicated facilities, units or wings of any Unit within ADC on the basis of such identification or status. The Department shall insure that these inmates have the same access to programming, recreation, and other activities as other inmates.

VI. **TREATMENT:**

- A. The initiation of sexual reassignment is impractical in a correctional setting. Self-inflicted genital mutilation or other forms of self-mutilation are contraindications for sexual reassignment treatment. No surgical procedures for the purpose of sexual reassignment will be provided to any inmate without approval of the GDMT committee following a finding of medical necessity by the medical director.
- B. Inmates entering the Department with prior surgical alteration of genitals and/or prescribed hormonal therapy procedures will continue to receive maintenance hormone replacements until their individual case is reviewed and assessed. Treatment with hormonal medications for the purpose of

sexual reassignment treatment may be initiated while incarcerated in the Department as determined to be medically necessary.

- C. An inmate receiving hormonal medications as part of an established sexual reassignment treatment regimen under the supervision of a medical doctor at the time of incarceration will be allowed to continue hormonal medications unless medical and mental health staff determines the continuance is contrary to appropriate medical care.

VII. PROCEDURES:

The intake staff will refer any inmate presenting with symptoms of GD to the GDMT Committee.

1. The committee is comprised of a designee from each of the following: the Medical Director, the Mental Health Administrator, the Medical Administrator, the Deputy Director for Health & Correctional Programs and the Classification Administrator.
2. A specialist in the treatment of gender dysphoria may be consulted on specific cases.
3. The diagnosis of GD will be based on the current DSM criteria and will be assigned and/or approved by a licensed psychiatrist or psychologist. The GDMT committee will:
 - a. Review evaluation records of each identified inmate.
 - b. Review an individualized treatment plan for each identified inmate consistent with Mental Health Policy No. 1134.00.
 - c. Have input in a treatment plans to address medical, mental health, and personal adjustment needs.

**IN THE UNITED STATES DISTRICT COURT
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LESLIE RUTLEDGE, et al.,

DEFENDANTS.

DECLARATION OF CLIFTON FRANCIS BURLEIGH, JR.

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

1. My name is Clifton Francis Burleigh, Jr., although most people know me as “Billy.” I have personal knowledge of the statements contained in this declaration.

2. When I was a young man, I transitioned from presenting as a male to presenting as a female. I began the process medically, through cross-sex hormone therapy, and progressed to surgery. I experienced no mental health benefits from my gender transition procedures. After presenting myself as a woman for seven years, I detransitioned and resumed presenting myself as a man.

3. As a young boy in the first grade I began having the recurring thought that “God made a mistake. I am a girl.” I would pray before going to bed, “God, please make me a girl before I wake up.” I tried to push the thought that I was a girl out of my mind, but the thought was consistent and persistent throughout childhood and into my college years.

4. Around the time I finished my undergraduate studies, I sought help from a gender therapist for the disconnect between my mind telling me I was a woman and my body telling me I was a man. I received therapy nearly every week from her for an hour at a time. I also researched transgenderism, reading books and journal articles on what it was and what caused it.

Although I wanted to remain a man and be free of the thought that I was a woman, the message I



received was that the only way to overcome the disconnect was to change my body to conform to what my mind was telling me.

5. After five to six years of gender therapy, depression began to set in. I was not suicidal, but suicide was coming to seem like more of an option for me. I was willing to try anything, so I told my therapist that I wanted to transition. She told me that she was glad that I had finally made that decision, and she gave me a note to take to a doctor to start hormone therapy.

6. I began taking a testosterone blocker and estrogen. My emotions were up and down, and my body was changing. But it made me feel happy that I was supposedly on a new road to happiness.

7. The next step was surgery, but I needed two letters to begin male-to-female surgeries, so I began seeing a second therapist. About three years after beginning hormone therapy, I had my first surgery—a penile inversion, an Adam’s apple shave, and a brow shave. Afterwards, the doctor and nurses had difficulty stopping the bleeding from my new “vagina.” They packed my artificial vagina with gauze and put a sandbag on my lower abdomen in an effort to stop the bleeding. But it would not stop, and I had to be administered a blood transfusion and plasma. My mother told me later that going into my hospital room was awful. The odor in the room was like that of an overly saturated tampon. I was discharged only after spending three weeks in the hospital. But changing my penis to an artificial vagina required two surgeries. So only four months after my first surgery I went back for the second one.

8. I had more feminization surgeries in addition to these first two. I jumped through all the hoops and did everything I was supposed to do to change my presentation from male to female. But no matter how many surgeries I had, every time I looked in the mirror I saw a man staring back at me. They were never enough to make my mind and body connect.

9. Seven years after transitioning to presenting as female, I had more problems than before I had begun. Changing my body did not resolve my internal conflict and it did not make me happy. But it had left me with a scarred body, and it drained my financial resources. Depression began to set back in and suicide was again coming to seem like more of an option.

10. By about 38 years old, I had endured many surgeries and tried many lifestyle changes, but they had not helped me. I began the process of detransitioning, which took about 2 to 3 years. I changed my name and all my documents and returned to being, identifying, and presenting as male.

11. I am now 54 years old. My thoughts are clear and I am free of the mental turmoil I had as a kid and growing up. I am happily married. I have two beautiful stepdaughters. I have peace of mind.

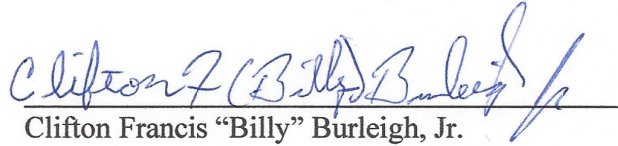
12. With the benefit of age and experience, I recognize that the healthcare I received failed me in several areas. First, no mental health professional counseled me that everyone has a continuing need for acceptance, significance, and security. As a child I thought that, by being a girl, my psychological needs would be fulfilled. But that was wrong. Second, the mental health professionals simply assumed that the only way I could be mentally healthy was to pursue the thought that I should have been, and therefore was, a girl and woman. But that was also wrong. The many medical and surgical procedures they provided for me left me worse off than when I began. Third, I had a number of childhood issues that the mental health professionals failed to uncover and adequately address. Had those issues, including a speech impediment, a learning disability, and childhood sexual abuse, been properly dealt with, I might not have had to go down the expensive and painful road I've traveled.

13. I have great compassion for children and teenagers who struggle with gender dysphoria today. They look to their parents and health care professionals to help them. Even as an adult, I relied on the mental health counseling I received in deciding to pursue gender transition. My decision to begin hormone therapy and surgery was prompted by it. But in my experience, the mental health profession is so quick to “affirm” what is perceived to be a transgender identity that a gender transition is presented as the only real solution for those struggling with gender dysphoria. The doctors and surgeons then simply provide the requested hormones and surgeries.

14. My mental health professionals led me to make a horrible mistake. They were wrong about the right course of action for me as a mature, responsible adult with years of therapy. My experience has led me to question whether mental health professionals can confidently make the right recommendations for still-developing children and teenagers with gender dysphoria.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on June 21, 2021.


Clifton Francis “Billy” Burleigh, Jr.

**IN THE UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF ARKANSAS
CENTRAL DIVISION**

DYLAN BRANDT, et al.,

PLAINTIFFS,

v.

No. 4:21-CV-00450-JM

LESLIE RUTLEDGE, et al.,

DEFENDANTS.

DECLARATION OF WALT HEYER

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

1. My name is Walt Heyer, and I have personal knowledge of the statements contained in this declaration.
2. My grandmother dressed me as a girl when I was 4, 5, and 6 years old. I was far too young to comprehend the long-term consequences of being encouraged to cross-dress at such a young age, much less fight back. In my child's mind, it felt good to be the center of her attention. The desire to not only cross-dress but to actually become a female took root and grew stronger every day.
3. Although this desire never went away, in high school I did typical boy activities. I was on the football team and in the car club. I dated girls. Throughout this time, however, I continued cross-dressing in secret.
4. Eventually I got engaged and told my future wife about my cross-dressing and my early childhood. She was undaunted by the idea, and we got married. We would go on to have two children.
5. By the time I was in my thirties in the 1970s I started to hear about individuals who were changing genders. They said they had a strong desire, just like I did, and there was a



name for it: gender identity disorder (what is now called gender dysphoria). At the cross-dressing bars in San Francisco that I frequented, people were talking about a doctor who would administer cross-gender hormones.

6. I still wanted to become a girl, so decided that I needed to find out if I had gender identity disorder. I scheduled an appointment with a leading expert, Dr. Paul Walker, PhD, the distinguished chairperson and one of the original authors of the Harry Benjamin International Standards of Care, the same standards published today in revised version by the successor organization, World Professional Association for Transgender Health (WPATH). Dr. Walker diagnosed me with Gender Identity Disorder and provided an approval letter that said I was someone who would benefit from hormone therapy and gender-reassignment surgery. I started hormone therapy at the direction of Dr. Walker. I waited more than two years then returned to see Dr. Walker again to see if he had changed his diagnosis of me. Dr. Walker was steadfast in his diagnosis and the need for me to be treated with hormones and gender-reassignment surgery. He prepared an updated letter, again approving me for male-to-female surgery.

7. I looked forward to finally having resolution to my life-long desire to be female and I scheduled the surgery. I went ahead with the gender-reassignment surgery in the hands of the world-renowned Dr. Stanley Biber, who over his lifetime performed over 4,000 gender-reassignment surgeries. Reassignment surgery for male to female consists of removing the testicles while retaining the penis, but surgically inverting the penis into a pouch. Legally I became Laura Jensen, female. As a result of my transition, my wife filed for divorce.

8. I lived nearly 8 years as a female in San Francisco. There were happy times at first, but as the years passed my gender dysphoria re-emerged. I became concerned and depressed because the male-to-female reassignment surgery was a huge life change and my gender

dysphoria symptoms had returned. I was switching between Laura and Walt every few days. I was even more confused than I had been before my change to Laura. I consulted a psychologist who told me to “give it time.” Eight years seemed like enough time to me. But the counselor, a specialist in gender dysphoria, told me adapting to Laura would take time, even years.

9. During this time, I began studying psychology at the University of Santa Cruz. I wanted to better understand addictive behaviors and wanted to learn how I could help other people who were struggling from difficult childhoods. A new awareness came while I was employed in a psychiatric unit. A staff psychiatrist pulled me aside to ask me questions about my childhood. After a few days of talking with me, he suggested I might have a previously undiagnosed and untreated disorder. At his suggestion I spent time with a psychologist who could assess whether or not I had a co-existing disorder, and if so, what it was.

10. I was diagnosed with a dissociative disorder. With the knowledge I had been suffering all my life from a co-existing disorder in addition to gender dysphoria, I went headlong into psychotherapy. There I learned that engaging in cross-dressing at a young age for a two-year period most likely was a contributing factor of my dissociative disorder. According to the additional diagnosis of dissociative disorder, I needed to reintegrate my fragmented identities, including my identity as Laura, into the surgically mutilated male body of Walt. The stunning moment for me came when a psychologist told me that the treatment I had undergone for gender dysphoria—hormone therapy and gender-reassignment surgery—would make re-integration of the identities extremely difficult because I had a body that was fashioned to look like Laura.

11. Because Dr. Walker only focused his attention and diagnosis on gender dysphoria (a correct diagnosis), he failed to take the next step—exploring the existence of co-existing disorders that might also be causing my gender distress. It was clear my co-existing psychological disorder should have been treated prior to any hormones or gender surgery.

12. Hope of living a happy life was fading away. I attempted suicide because I was so distressed. My gender-transition surgery did not resolve the problems that started in my early childhood.

13. It took a long time and restoration was extremely difficult. I was in counseling for years, sometimes meeting every day, but I was finally able to put my gender dysphoria to rest through psychotherapy to effectively treat the co-existing dissociative disorder. When the dissociative disorder and the childhood pain that had led to it were treated, the feelings of wanting to be a girl went away. It was only after treating the dissociative disorder that I achieved the serenity and happiness I had always wanted.

14. The feelings of discomfort with my male gender went away, but I am left with a body permanently mutilated and functionally altered. For example, because the surgery removed body parts that manufacture testosterone, my hormone levels have been difficult to regulate so that my body functions well. Also, the feminizing cosmetic surgeries on my face cause people to mistake me for a woman.

15. Detransitioning was a process—continuing with therapy to cope with the emotions, getting my legal identity documents (such as birth certificate, driver's license, passport, social security card) changed back to male, and adopting a masculine-appearing hair style and wardrobe.

16. I have come into contact with other people who like me detransitioned after going through gender-transition procedures. This includes people who began to undergo these procedures in their teens and chose to detransition in their twenties. Despite this, they had already made irreversible changes to their bodies, including losing their ability to have children.

17. Thankfully, the gender-transition procedures I underwent did not define my entire life. By the age of 55, I finally felt whole again living as a man. I've been married now for 24 years. I'm at peace with my body and my biological sex and I enjoy helping other people find the same serenity and wholeness that I have found beyond the transgender life.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on July 5, 2021.


Walt Heyer

**IN THE UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF ARKANSAS
CENTRAL DIVISION**

**DYLAN BRANDT, by and through his mother,
Joanna Brandt, *et al.*,**

PLAINTIFFS,

v.

No. 4:21-CV-00450-JM

**LESLIE RUTLEDGE, in her official capacity as
the Arkansas Attorney General, *et al.*,**

DEFENDANTS.

DECLARATION OF LAURA PERRY

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

1. My name is Laura Perry, and I have personal knowledge of the statements contained in this declaration.

2. I was raised in a home that was very religious by a mother who exhausted herself trying to be the perfect Christian. I was hyperactive and obnoxious, and my mom was often agitated, irritable, and seemed to not want me around. I came to believe that she loved boys more than girls because she treated my brother differently than she treated me. Then one day I learned that my mother had miscarried two boys before I was born. I excitedly said, “Hey, if my brothers had lived, we would have five kids.” My mother responded, “No, we only wanted to have three kids. You likely wouldn’t be here if either of them had lived.” Although she didn’t mean it this way, I took her as saying that my brothers had to die for me to be born. I believed she had wished one of them would have lived instead of me. I was devastated with feelings of guilt.

3. At eight years old, I was sexually abused. This added to my confusion. As a teenager, men began to objectify and use me sexually. So I grew to associate being female with being disgusting, filthy, and worthless. I felt that I had no value as a female and began to hate myself. In college, I began fantasizing through pornography and virtual sex games about the



idea of having been a man instead of a woman. Over the next few years, the desire to become a man intensified until at the age of 25, I decided that I was supposed to have been a man and had just been born in the wrong body. I thought something had happened in the womb like a birth defect or a genetic anomaly. I saw no connection to childhood trauma. I was completely convinced by that point in my life that I had been born that way.

4. In 2007, at 25 years old, I began living as “Jake,” and I was on what I thought was the road to freedom. I did not know the hell I was in for.

5. Before beginning hormone treatment, I was required to attend at least three one-hour counseling sessions from a licensed therapist. At the time, I was completely convinced that I was a man trapped in a woman’s body. I was unable to entertain any other possibility, so I had no interest in counseling. I went to the therapist only because getting hormone treatments required getting a letter stating that I was diagnosed with Gender Identity Disorder. During the course of the third session, the therapist set down her notebook, looked me right in the eyes, and said, “Wow, you really have issues with your mom.” I was stunned. How did we get from talking about how I was really a man to talking about my mother? I blew up at her and spat back, “I am not here to talk about my mom!” She looked at me sadly and said softly, “So you just want me to give you the letter?” I said, “Yes, that’s all I’m here for. I don’t need counseling.”

6. The therapist gave me the letter, even though it was the opposite of what I needed. Not until years later did I realize what the therapist had discerned—that my unresolved, deep, and bitter resentment toward my mother led me to reject femininity. What I needed was psychological counseling to help me forgive my mother and the many others whom (I thought) had rejected me as a woman. Things could have very gone differently if the therapist had

required me to work through my other issues before issuing me the letter I wanted so desperately. Had I done that, I don't think I would have ever gone down the transgender road.

7. After I took the letter stating I had been diagnosed with Gender Identity Disorder to my family doctor, he asked, "Are you sure this is what you want to do?" I said, "Yes," and he said, "Okay," and wrote me a prescription for Testosterone Cypionate and the syringes I would need to self-administer the injections. The nurse administered my first dose, but I learned to inject it on my own so I would not have to pay to have it administered.

8. I began taking testosterone by injecting it at home into my quadriceps muscle. The testosterone gave me more energy. I had an increased sex drive, and I was less emotional. My voice began to deepen, and my body and face began to look more masculine.

9. In spring 2009 I changed my legal name to Jacobe Nathan Perry and changed my birth certificate and other legal documents. I also had a double mastectomy. By 2012 I was fully passing as male. I had a job where I was known only as male, and no one knew my past. I had everything I had dreamed of. But I realized that the legal changes and surgery had not actually made me a man, so depression began to set in.

10. I had thought hormones and surgery would transform me into a man, and I would be able to leave all of the pain behind. Then I had thought just another year or two of hormones would make the dysphoria go away. But it never did. I decided to pursue more surgery because I did not want to have a trace of anything female. I did not want a single reminder of the truth I was trying to erase from existence.

11. In fall 2012 I had all of my female organs removed by undergoing a full hysterectomy and oophorectomy. I was devastated to realize that, even after having everything female about my body removed, I was still not a man. I had been using a prosthetic male

genitalia that allowed me to use urinals and looked and felt somewhat natural. But I longed for it to be completely real. So I began looking into the final stage: genital reassignment surgery.

12. I was shocked to realize the reality of what genital reassignment involved. Phalloplasty would have required multiple invasive surgeries—a minimum of three. I learned that there was a very real possibility that surgery could cause a loss of sexual sensation and that many patients, in fact, did lose it. Many who had genital reassignment suffered urinary complications and other problems. Some needed additional, corrective surgeries. There was no way to be sure of what all I would ultimately have to suffer through or what the end result would be. What was sure was that the surgery would not give me real male genitalia. The surgeon would have to cut donor muscle from my arm. Genital reassignment would involve placement of an artificial implant, which would have to be inflated for sexual purposes. The implant would have been unusually long in its flaccid state, making it very uncomfortable most of the time. And it would not give me a man's ability to father a child.

13. I was desperate and willing to roll the dice. But genital reassignment would have cost me over \$100,000.00. I could not afford that, and my insurance did not cover it. I knew there was no way I was ever going to have that kind of money. So I fell into deep depression. In horror, I realized there was nothing that was ever going to make my male identity real. I felt hopeless. I knew I was not really a man, but it was far too painful to return to being female.

14. The hormone treatments began causing medical problems, including a dangerously high hematocrit level that eventually required therapeutic blood withdraw to thin my blood. The doctor warned that I was in serious danger of a stroke. I had chronic dizzy spells and would often get light-headed when standing. By 2014, at age 32, I began having heart problems. Sometimes I would simply walk across my apartment and my heart would start pounding. In

addition, I began having cognitive problems including memory loss, reduced reading comprehension, and inability to focus. I had begun seeing a new doctor who specialized in treating transgender patients, but I was afraid to keep telling her about the health issues I was having because I feared she would stop the testosterone.

15. After nine years of taking testosterone and all of the surgeries, I was left empty and broken. I was devastated to realize that none of the changes had actually made me a man. All I had done was change the outside. Although I truly believed that I was not a woman, I knew I could never be a man, no matter how badly I wanted it. So then I felt trapped in a world between male and female. I lived in a world of lies, suspended in limbo between reality and fantasy. I wanted to erase the existence of “Laura” so badly that even after realizing I could not be a man I decided to hide and pretend and be the “best man I could be,” rather than embracing myself as a woman. I realized that my transgender identity had become a mask hiding the truth.

16. What had promised to be freedom had in fact become my prison cell. I had become enslaved to wearing clothes that never fit right, injecting myself over and over with testosterone, and wearing prosthetics that were a constant reminder of how fake it all was. The hormones had caused puffiness and swelling in my face and extraordinary weight gain. This is a side effect that is not widely known that happens to many female-to-male transgender people, especially in certain body types.

17. My relationship with my parents had been almost nonexistent for years aside from an occasional phone call or dinner meeting. My mom stubbornly refused to call me by my chosen name, “Jake,” instead insisting on calling me “Laura.” Although I hated that, it was a tether to reality that eventually became a lifeline to me. It constantly reminded me of the truth that I was still Laura no matter how much I had changed my appearance.

18. Unknown to me, my mother had herself undergone a dramatic change. The angry, stressed-out mother I grew up with had been completely transformed. Her exhausting legalistic religion had been exchanged for a genuinely life-giving faith in Jesus. Once I came to realize the extent of the change in my mother, I knew I wanted the same thing. I wanted desperately to be a man of God. I tried to convince myself that God had intended me to be a man and that maybe I just had a birth defect. But, over the following months I consistently listened to a radio broadcast that explained, “We are not just made up of our feelings, instincts, and inclinations. We are made in the image of God, and we can choose our behavior despite how we feel.” I didn’t want to admit this was true, but I knew it was.

19. At this time, at almost 34 years old, I was living in complete stealth mode, as I called it. No one except family and my partner knew I was transgender. I knew God wanted me to leave the transgender lifestyle, but it was too painful to face being a woman. But one night I felt that He asked me, “If you stood before me tonight, what name would I call?” I was devastated. I had hoped so desperately God saw me as Jake now. He said, “You cannot claim to love me and yet reject my creation.” I thought I was doomed and condemned. I thought, if God doesn’t accept me as Jake, then there’s no hope for me. But in the most loving voice I have ever heard in all my life, He whispered to me and He said, “Let me tell you who you are.” And that is what began to free me. I realized then that no matter what I did to myself, God still saw me as Laura, just like my parents. And I knew He wasn’t finished with me despite how much damage I had done to my life.

20. But I still did not know how to fix it. Having grown up in such a legalistic religion, I kept thinking I had to fix my brokenness so God would be pleased and accept me. I did not yet understand His offer to let Him tell me who I was. After exhausting every option and

not knowing how to fix it all, I prayed to God with all my heart, asking him to take my life. I felt like I had fallen into a deep, dark pit from which I could not escape. It was then that I experienced a vision of Jesus reaching into my pit with an outstretched arm, asking me to leave everything and follow him. I trusted him, and I walked away from everything I had known: my job, my partner of almost eight years, my financial security, and my entire transgender identity. I lived with my parents over the next few months as I detransitioned back to living as a woman. I was embraced by the women at my mother's Bible study and I was overwhelmed with their affirmation of me as a woman. As a result, my belief that I was meant to be a man vanished.

21. It has been five years since I began to detransition. Over that time, I have come to know a wholeness that I never knew was possible. As I have healed, I have come to understand the causes of my struggles. As I became more involved in church, I attended Bible studies that helped me learn more about God and how much He loved me. He began to peel the layers of the onion away little by little, and I began to understand all of the lies I had believed and all of the wounds I had suffered. As the women in my mom's Bible study and church loved on me and accepted me as one of the women, and as I forgave my mom and reconciled with my parents, the transgender feelings melted away. They have never returned. I am 100% free today, and I have not only embraced my female identity but also absolutely love being feminine.

22. I wish that my therapist had never given me the letter to pursue hormone therapy, which put me on the road to medically transitioning to live as a transgender person. At the time, I was so convinced that was what I needed. But I was so wrong. Although I wanted so badly to believe that the hormones and surgery would resolve my dysphoria, that just wasn't the case. I spent so much money and so many years of my life pursuing step after step of medical procedures in vain striving to obtain peace and happiness. But those things didn't help me.

Instead, they left me with a great deal of debt, physical and emotional scars, and lifelong medical issues. The only intervention that has ever helped me without hurting me far worse is psychological counseling. It is only by finding peace with God and working through the childhood issues that gave rise to my dysphoria with a counselor that I have finally been able to heal.

23. I fully support laws that save children from making the same horrible mistakes that I did. I have met many former transgender people, and, like me, they all say the same things: the physical transition was never real, it never resolved the gender dysphoria, and what they actually needed was psychological counseling, not hormones and surgery.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on June 21, 2021.



Laura Perry