EXHIBIT 10

Endocrine Treatment of Gender-Dysphoric/ Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline

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Objective: To update the "Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline," published by the Endocrine Society in 2009.

Participants: The participants include an Endocrine Society–appointed task force of nine experts, a methodologist, and a medical writer.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation approach to describe the strength of recommendations and the quality of evidence. The task force commissioned two systematic reviews and used the best available evidence from other published systematic reviews and individual studies.

Consensus Process: Group meetings, conference calls, and e-mail communications enabled consensus. Endocrine Society committees, members and cosponsoring organizations reviewed and commented on preliminary drafts of the guidelines.

Conclusion: Gender affirmation is multidisciplinary treatment in which endocrinologists play an important role. Gender-dysphoric/gender-incongruent persons seek and/or are referred to endocrinologists to develop the physical characteristics of the affirmed gender. They require a safe and effective hormone regimen that will (1) suppress endogenous sex hormone secretion determined by the person's genetic/gonadal sex and (2) maintain sex hormone levels within the normal range for the person's affirmed gender. Hormone treatment is not recommended for prepubertal gender-dysphoric/gender-incongruent persons. Those clinicians who recommend gender-affirming endocrine treatments—appropriately trained diagnosing clinicians (required), a mental health provider for adolescents (required) and mental health

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 24 July 2017. Accepted 24 August 2017.
First Published Online 13 September 2017

Abbreviations: BMD, bone mineral density; DSD, disorder/difference of sex development; DSM, Diagnostic and Statistical Manual of Mental Disorders; GD, gender dysphoria; GnRH, gonadotropin-releasing hormone; ICD, International Statistical Classification of Diseases and Related Health Problems; MHP, mental health professional; VTE, venous thromboembolism.

professional for adults (recommended)—should be knowledgeable about the diagnostic criteria and criteria for gender-affirming treatment, have sufficient training and experience in assessing psychopathology, and be willing to participate in the ongoing care throughout the endocrine transition. We recommend treating gender-dysphoric/gender-incongruent adolescents who have entered puberty at Tanner Stage G2/B2 by suppression with gonadotropin-releasing hormone agonists. Clinicians may add gender-affirming hormones after a multidisciplinary team has confirmed the persistence of gender dysphoria/gender incongruence and sufficient mental capacity to give informed consent to this partially irreversible treatment. Most adolescents have this capacity by age 16 years old. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to age 16 years, although there is minimal published experience treating prior to 13.5 to 14 years of age. For the care of peripubertal youths and older adolescents, we recommend that an expert multidisciplinary team comprised of medical professionals and mental health professionals manage this treatment. The treating physician must confirm the criteria for treatment used by the referring mental health practitioner and collaborate with them in decisions about gender-affirming surgery in older adolescents. For adult gender-dysphoric/gender-incongruent persons, the treating clinicians (collectively) should have expertise in transgender-specific diagnostic criteria, mental health, primary care, hormone treatment, and surgery, as needed by the patient. We suggest maintaining physiologic levels of gender-appropriate hormones and monitoring for known risks and complications. When high doses of sex steroids are required to suppress endogenous sex steroids and/or in advanced age, clinicians may consider surgically removing natal gonads along with reducing sex steroid treatment. Clinicians should monitor both transgender males (female to male) and transgender females (male to female) for reproductive organ cancer risk when surgical removal is incomplete. Additionally, clinicians should persistently monitor adverse effects of sex steroids. For gender-affirming surgeries in adults, the treating physician must collaborate with and confirm the criteria for treatment used by the referring physician. Clinicians should avoid harming individuals (via hormone treatment) who have conditions other than gender dysphoria/gender incongruence and who may not benefit from the physical changes associated with this treatment. (***J Clin Endocrinol Metab* 102: 3869–3903, 2017**)

Summary of Recommendations

1.0 Evaluation of youth and adults

1.1. We advise that only trained mental health professionals (MHPs) who meet the following criteria should diagnose gender dysphoria (GD)/gender incongruence in adults: (1) competence in using the Diagnostic and Statistical Manual of Mental Disorders (DSM) and/or the International Statistical Classification of Diseases and Related Health Problems (ICD) for diagnostic purposes, (2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings. (Ungraded Good Practice Statement)

1.2. We advise that only MHPs who meet the following criteria should diagnose GD/gender incongruence in children and adolescents: (1) training in child and adolescent developmental psychology and psychopathology, (2) competence in using the DSM and/or the ICD for diagnostic purposes, (3) the ability to make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (4) training in diagnosing psychiatric conditions, (5) the ability to undertake or refer for appropriate treatment, (6) the ability to psychosocially assess the person's understanding and social conditions that can impact gender-affirming hormone therapy, (7) a practice of regularly attending relevant professional meetings, and (8) knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents. (Ungraded Good Practice Statement)

1.3. We advise that decisions regarding the social transition of prepubertal youths with GD/gender incongruence are made with the assistance of an MHP or another experienced professional. (Ungraded Good Practice Statement).

doi: 10.1210/jc.2017-01658

1.4. We recommend against puberty blocking and gender-affirming hormone treatment in prepubertal children with GD/gender incongruence. (1 |⊕⊕◯◯)

1.5. We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults. (1 |⊕⊕⊕◯)

2.0 Treatment of adolescents

2.1. We suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment, and are requesting treatment should initially undergo treatment to suppress pubertal development. (2 |⊕⊕◯◯)

2.2. We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty. (2 |⊕⊕◯◯)

2.3. We recommend that, where indicated, GnRH analogues are used to suppress pubertal hormones. (1 |⊕⊕◯◯)

2.4. In adolescents who request sex hormone treatment (given this is a partly irreversible treatment), we recommend initiating treatment using a gradually increasing dose schedule after a multidisciplinary team of medical and MHPs has confirmed the persistence of GD/gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years. (1 |⊕⊕◯◯).

2.5. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to the age of 16 years in some adolescents with GD/gender incongruence, even though there are minimal published studies of gender-affirming hormone treatments administered before age 13.5 to 14 years. As with the care of adolescents ≥16 years of age, we recommend that an expert multidisciplinary team of medical and MHPs manage this treatment. (1 |⊕◯◯◯)

2.6. We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment. (2 |⊕⊕◯◯)

3.0 Hormonal therapy for transgender adults

3.1. We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and the criteria for the endocrine phase of gender transition before beginning treatment. (1 |⊕⊕⊕◯)

3.2. We recommend that clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment. (1 |⊕⊕⊕◯)

3.3. We suggest that clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender. (2 |⊕⊕◯◯)

3.4. We suggest that endocrinologists provide education to transgender individuals undergoing treatment about the onset and time course of physical changes induced by sex hormone treatment. (2 |⊕◯◯◯)

4.0 Adverse outcome prevention and long-term care

4.1. We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every 3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly. (2 |⊕⊕◯◯)

4.2. We suggest periodically monitoring prolactin levels in transgender females treated with estrogens. (2 |⊕⊕◯◯)

4.3. We suggest that clinicians evaluate transgender persons treated with hormones for cardiovascular risk factors using fasting lipid profiles, diabetes screening, and/or other diagnostic tools. (2 |⊕⊕◯◯)

4.4. We recommend that clinicians obtain bone mineral density (BMD) measurements when risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. (1 |⊕⊕◯◯)

4.5. We suggest that transgender females with no known increased risk of breast cancer follow breast-screening guidelines recommended for non-transgender females. (2 |⊕⊕◯◯)

4.6. We suggest that transgender females treated with estrogens follow individualized screening according to personal risk for prostatic disease and prostate cancer. (2 |⊕◯◯◯)

4.7. We advise that clinicians determine the medical necessity of including a total hysterectomy and oophorectomy as part of gender-affirming surgery. (Ungraded Good Practice Statement)

5.0 Surgery for sex reassignment and gender confirmation

5.1. We recommend that a patient pursue genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically necessary and would benefit the patient's overall health and/or well-being. (1 ⊕⊕◯◯)

5.2. We advise that clinicians approve genital gender-affirming surgery only after completion of at least 1 year of consistent and compliant hormone treatment, unless hormone therapy is not desired or medically contraindicated. (Ungraded Good Practice Statement)

5.3. We advise that the clinician responsible for endocrine treatment and the primary care provider ensure appropriate medical clearance of transgender individuals for genital gender-affirming surgery and collaborate with the surgeon regarding hormone use during and after surgery. (Ungraded Good Practice Statement)

5.4. We recommend that clinicians refer hormone-treated transgender individuals for genital surgery when: (1) the individual has had a satisfactory social role change, (2) the individual is satisfied about the hormonal effects, and (3) the individual desires definitive surgical changes. (1 ⊕◯◯◯)

5.5. We suggest that clinicians delay gender-affirming genital surgery involving gonadectomy and/or hysterectomy until the patient is at least 18 years old or legal age of majority in his or her country. (2 ⊕⊕◯◯).

5.6. We suggest that clinicians determine the timing of breast surgery for transgender males based upon the physical and mental health status of the individual. There is insufficient evidence to recommend a specific age requirement. (2 ⊕◯◯◯)

Changes Since the Previous Guideline

Both the current guideline and the one published in 2009 contain similar sections. Listed here are the sections contained in the current guideline and the corresponding number of recommendations: Introduction, Evaluation of Youth and Adults (5), Treatment of Adolescents (6), Hormonal Therapy for Transgender Adults (4), Adverse Outcomes Prevention and Long-term Care (7), and Surgery for Sex Reassignment and Gender Confirmation (6). The current introduction updates the diagnostic classification of "gender dysphoria/gender incongruence." It also reviews the development of "gender identity" and summarizes its natural development. The section on clinical evaluation of both youth and adults, defines in detail the professional qualifications required of those who diagnose and treat both adolescents and adults. We advise that decisions regarding the social transition of prepubertal youth are made with the assistance of a mental health professional or similarly experienced professional. We recommend against puberty blocking followed by gender-affirming hormone treatment of prepubertal children. Clinicians should inform pubertal children, adolescents, and adults seeking gender-confirming treatment of their options for fertility preservation. Prior to treatment, clinicians should evaluate the presence of medical conditions that may be worsened by hormone depletion and/or treatment. A multidisciplinary team, preferably composed of medical and mental health professionals, should monitor treatments. Clinicians evaluating transgender adults for endocrine treatment should confirm the diagnosis of persistent gender dysphoria/gender incongruence. Physicians should educate transgender persons regarding the time course of steroid-induced physical changes. Treatment should include periodic monitoring of hormone levels and metabolic parameters, as well as assessments of bone density and the impact upon prostate, gonads, and uterus. We also make recommendations for transgender persons who plan genital gender-affirming surgery.

Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee (CGS) of the Endocrine Society deemed the diagnosis and treatment of individuals with GD/gender incongruence a priority area for revision and appointed a task force to formulate evidence-based recommendations. The task force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation group, an international group with expertise in the development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The task force used the best available research evidence to develop the recommendations. The task force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase "we recommend" and the number 1, and weak recommendations use the phrase "we suggest" and the number 2. Cross-filled circles indicate the quality of the evidence, such that ⊕◯◯◯ denotes very low–quality evidence; ⊕⊕◯◯, low quality; ⊕⊕⊕◯, moderate quality; and ⊕⊕⊕⊕, high quality. The task force has confidence that persons who receive care according to the strong recommendations will derive, on average, more benefit than harm. Weak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence and the

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

Biological sex, biological male or female: These terms refer to physical aspects of maleness and femaleness. As these may not be in line with each other (*e.g.*, a person with XY chromosomes may have female-appearing genitalia), the terms biological sex and biological male or female are imprecise and should be avoided.
Cisgender: This means not transgender. An alternative way to describe individuals who are not transgender is "non-transgender people."
Gender-affirming (hormone) treatment: See "gender reassignment"
Gender dysphoria: This is the distress and unease experienced if gender identity and designated gender are not completely congruent (see Table 2). In 2013, the American Psychiatric Association released the fifth edition of the DSM-5, which replaced "gender identity disorder" with "gender dysphoria" and changed the criteria for diagnosis.
Gender expression: This refers to external manifestations of gender, expressed through one's name, pronouns, clothing, haircut, behavior, voice, or body characteristics. Typically, transgender people seek to make their gender expression align with their gender identity, rather than their designated gender.
Gender identity/experienced gender: This refers to one's internal, deeply held sense of gender. For transgender people, their gender identity does not match their sex designated at birth. Most people have a gender identity of man or woman (or boy or girl). For some people, their gender identity does not fit neatly into one of those two choices. Unlike gender expression (see below), gender identity is not visible to others.
Gender identity disorder: This is the term used for GD/gender incongruence in previous versions of DSM (see "gender dysphoria"). The ICD-10 still uses the term for diagnosing child diagnoses, but the upcoming ICD-11 has proposed using "gender incongruence of childhood."
Gender incongruence: This is an umbrella term used when the gender identity and/or gender expression differs from what is typically associated with the designated gender. Gender incongruence is also the proposed name of the gender identity–related diagnoses in ICD-11. Not all individuals with gender incongruence have gender dysphoria or seek treatment.
Gender variance: See "gender incongruence"
Gender reassignment: This refers to the treatment procedure for those who want to adapt their bodies to the experienced gender by means of hormones and/or surgery. This is also called gender-confirming or gender-affirming treatment.
Gender-reassignment surgery (gender-confirming/gender-affirming surgery): These terms refer only to the surgical part of gender-confirming/gender-affirming treatment.
Gender role: This refers to behaviors, attitudes, and personality traits that a society (in a given culture and historical period) designates as masculine or feminine and/or that society associates with or considers typical of the social role of men or women.
Sex designated at birth: This refers to sex assigned at birth, usually based on genital anatomy.
Sex: This refers to attributes that characterize biological maleness or femaleness. The best known attributes include the sex-determining genes, the sex chromosomes, the H-Y antigen, the gonads, sex hormones, internal and external genitalia, and secondary sex characteristics.
Sexual orientation: This term describes an individual's enduring physical and emotional attraction to another person. Gender identity and sexual orientation are not the same. Irrespective of their gender identity, transgender people may be attracted to women (gynephilic), attracted to men (androphilic), bisexual, asexual, or queer.
Transgender: This is an umbrella term for people whose gender identity and/or gender expression differs from what is typically associated with their sex designated at birth. Not all transgender individuals seek treatment.
Transgender male (also: trans man, female-to-male, transgender male): This refers to individuals assigned female at birth but who identify and live as men.
Transgender woman (also: trans woman, male-to female, transgender female): This refers to individuals assigned male at birth but who identify and live as women.
Transition: This refers to the process during which transgender persons change their physical, social, and/or legal characteristics consistent with the affirmed gender identity. Prepubertal children may choose to transition socially.
Transsexual: This is an older term that originated in the medical and psychological communities to refer to individuals who have permanently transitioned through medical interventions or desired to do so.

exstrophy and penile agenesis, the occurrence of transgender male changes was significantly more prevalent than in the general population (30, 31). However, the fact that a high percentage of individuals with the same conditions did not change gender suggests that cultural factors may play a role as well.

With respect to genetics and gender identity, several studies have suggested heritability of GD/gender incongruence (32, 33). In particular, a study by Heylens *et al.* (33) demonstrated a 39.1% concordance rate for gender identity disorder (based on the DSM-IV criteria) in 23 monozygotic twin pairs but no concordance in 21 same-sex dizygotic or seven opposite-sex twin pairs. Although numerous investigators have sought to identify specific genes associated with GD/gender incongruence, such studies have been inconsistent and without strong statistical significance (34–38).

Studies focusing on brain structure suggest that the brain phenotypes of people with GD/gender incongruence differ in various ways from control males and females, but that there is not a complete sex reversal in brain structures (39).

In summary, although there is much that is still unknown with respect to gender identity and its expression, compelling studies support the concept that biologic factors, in addition to environmental factors, contribute to this fundamental aspect of human development.

Natural History of Children With GD/Gender Incongruence

With current knowledge, we cannot predict the psychosexual outcome for any specific child. Prospective follow-up studies show that childhood GD/gender incongruence does not invariably persist into adolescence and adulthood (so-called "desisters"). Combining all outcome studies to date, the GD/gender incongruence of a minority of prepubertal children appears to persist in adolescence (20, 40). In adolescence, a significant number of these desisters identify as homosexual or bisexual. It may be that children who only showed some gender nonconforming characteristics have been included in the follow-up studies, because the DSM-IV text revision criteria for a diagnosis were rather broad. However, the persistence of GD/gender incongruence into adolescence is more likely if it had been extreme in childhood (41, 42). With the newer, stricter criteria of the DSM-5 (Table 2), persistence rates may well be different in future studies.

1.0 Evaluation of Youth and Adults

Gender-affirming treatment is a multidisciplinary effort. After evaluation, education, and diagnosis, treatment may include mental health care, hormone therapy, and/or surgical therapy. Together with an MHP, hormone-prescribing clinicians should examine the psychosocial impact of the potential changes on people's lives, including mental health, friends, family, jobs, and their role in society. Transgender individuals should be encouraged to experience living in the new gender role and assess whether this improves their quality of life. Although the focus of this guideline is gender-affirming hormone therapy, collaboration with appropriate professionals responsible for each aspect of treatment maximizes a successful outcome.

Diagnostic assessment and mental health care

GD/gender incongruence may be accompanied with psychological or psychiatric problems (43–51). It is therefore necessary that clinicians who prescribe hormones and are involved in diagnosis and psychosocial assessment meet the following criteria: (1) are competent in using the DSM and/or the ICD for diagnostic purposes, (2) are able to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) are trained in diagnosing psychiatric conditions, (4) undertake or refer for appropriate treatment, (5) are able to do a psychosocial assessment of the patient's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) regularly attend relevant professional meetings.

Because of the psychological vulnerability of many individuals with GD/gender incongruence, it is important that mental health care is available before, during, and sometimes also after transitioning. For children and adolescents, an MHP who has training/experience in child and adolescent gender development (as well as child and adolescent psychopathology) should make the diagnosis, because assessing GD/gender incongruence in children and adolescents is often extremely complex.

During assessment, the clinician obtains information from the individual seeking gender-affirming treatment. In the case

Table 2. DSM-5 Criteria for Gender Dysphoria in Adolescents and Adults

A. A marked incongruence between one's experienced/expressed gender and natal gender of at least 6 mo in duration, as manifested by at least two of the following:
   1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)
   2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)
   3. A strong desire for the primary and/or secondary sex characteristics of the other gender
   4. A strong desire to be of the other gender (or some alternative gender different from one's designated gender)
   5. A strong desire to be treated as the other gender (or some alternative gender different from one's designated gender)
   6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's designated gender)

B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:
   1. The condition exists with a disorder of sex development.
   2. The condition is posttransitional, in that the individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one sex-related medical procedure or treatment regimen—namely, regular sex hormone treatment or gender reassignment surgery confirming the desired gender (*e.g.*, penectomy, vaginoplasty in natal males; mastectomy or phalloplasty in natal females).

Reference: American Psychiatric Association (14).

of adolescents, the clinician also obtains information from the parents or guardians regarding various aspects of the child's general and psychosexual development and current functioning. On the basis of this information, the clinician:

- decides whether the individual fulfills criteria for treatment (see Tables 2 and 3) for GD/gender incongruence (DSM-5) or transsexualism (DSM-5 and/or ICD-10);
- informs the individual about the possibilities and limitations of various kinds of treatment (hormonal/surgical and nonhormonal), and if medical treatment is desired, provides correct information to prevent unrealistically high expectations;
- assesses whether medical interventions may result in unfavorable psychological and social outcomes.

In cases in which severe psychopathology, circumstances, or both seriously interfere with the diagnostic work or make satisfactory treatment unlikely, clinicians should assist the adolescent in managing these other issues. Literature on postoperative regret suggests that besides poor quality of surgery, severe psychiatric comorbidity and lack of support may interfere with positive outcomes (52–56).

For adolescents, the diagnostic procedure usually includes a complete psychodiagnostic assessment (57) and an assessment of the decision-making capability of the youth. An evaluation to assess the family's ability to endure stress, give support, and deal with the complexities of the adolescent's situation should be part of the diagnostic phase (58).

Social transitioning

A change in gender expression and role (which may involve living part time or full time in another gender role that is consistent with one's gender identity) may test the person's resolve, the capacity to function in the affirmed gender, and the adequacy of social, economic, and psychological supports. It assists both the individual and the clinician in their judgments about how to proceed (16). During social transitioning, the person's feelings about the social transformation (including coping with the responses of others) is a major focus of the counseling. The optimal timing for social transitioning may differ between individuals. Sometimes people wait until they start gender-affirming hormone treatment to make social transitioning easier, but individuals increasingly start social transitioning long before they receive medically supervised, gender-affirming hormone treatment.

Criteria

Adolescents and adults seeking gender-affirming hormone treatment and surgery should satisfy certain criteria before proceeding (16). Criteria for gender-affirming hormone therapy for adults are in Table 4, and criteria for gender-affirming hormone therapy for adolescents are in Table 5. Follow-up studies in adults meeting these criteria indicate a high satisfaction rate with treatment (59). However, the quality of evidence is usually low. A few follow-up studies on adolescents who fulfilled these criteria also indicated good treatment results (60–63).

Recommendations for Those Involved in the Gender-Affirming Hormone Treatment of Individuals With GD/Gender Incongruence

1.1. We advise that only trained MHPs who meet the following criteria should diagnose GD/gender incongruence in adults: (1) competence in using the DSM and/or the ICD for diagnostic purposes, (2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings. (Ungraded Good Practice Statement)

1.2. We advise that only MHPs who meet the following criteria should diagnose GD/gender incongruence in children and adolescents: (1) training in child and adolescent developmental psychology and psychopathology, (2) competence in using the DSM and/or ICD for diagnostic

Table 3. ICD-10 Criteria for Transsexualism

Transsexualism (F64.0) has three criteria:
1. The desire to live and be accepted as a member of the opposite sex, usually accompanied by the wish to make his or her body as congruent as possible with the preferred sex through surgery and hormone treatments.
2. The transsexual identity has been present persistently for at least 2 y.
3. The disorder is not a symptom of another mental disorder or a genetic, DSD, or chromosomal abnormality.

Table 4. Criteria for Gender-Affirming Hormone Therapy for Adults

1. Persistent, well-documented gender dysphoria/gender incongruence
2. The capacity to make a fully informed decision and to consent for treatment
3. The age of majority in a given country (if younger, follow the criteria for adolescents)
4. Mental health concerns, if present, must be reasonably well controlled

Reproduced from World Professional Association for Transgender Health (16).

purposes, (3) the ability to make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (4) training in diagnosing psychiatric conditions, (5) the ability to undertake or refer for appropriate treatment, (6) the ability to psychosocially assess the person's understanding and social conditions that can impact gender-affirming hormone therapy, (7) a practice of regularly attending relevant professional meetings, and (8) knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents. (Ungraded Good Practice Statement)

Evidence

Individuals with gender identity issues may have psychological or psychiatric problems (43–48, 50, 51, 64, 65). It is therefore necessary that clinicians making the diagnosis are able to make a distinction between GD/gender incongruence and conditions that have similar features. Examples of conditions with similar features are body dysmorphic disorder, body identity integrity disorder (a condition in which individuals have a sense that their anatomical configuration as an able-bodied person is somehow wrong or inappropriate) (66), or certain forms of eunuchism (in which a person is preoccupied with or engages in castration and/or penectomy for

Table 5. Criteria for Gender-Affirming Hormone Therapy for Adolescents

Adolescents are eligible for GnRH agonist treatment if:

1. A qualified MHP has confirmed that:
   - the adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed),
   - gender dysphoria worsened with the onset of puberty,
   - any coexisting psychological, medical, or social problems that could interfere with treatment (*e.g.*, that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment,
   - the adolescent has sufficient mental capacity to give informed consent to this (reversible) treatment,
2. And the adolescent:
   - has been informed of the effects and side effects of treatment (including potential loss of fertility if the individual subsequently continues with sex hormone treatment) and options to preserve fertility,
   - has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,
3. And a pediatric endocrinologist or other clinician experienced in pubertal assessment
   - agrees with the indication for GnRH agonist treatment,
   - has confirmed that puberty has started in the adolescent (Tanner stage ≥G2/B2),
   - has confirmed that there are no medical contraindications to GnRH agonist treatment.

Adolescents are eligible for subsequent sex hormone treatment if:

1. A qualified MHP has confirmed:
   - the persistence of gender dysphoria,
   - any coexisting psychological, medical, or social problems that could interfere with treatment (*e.g.*, that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start sex hormone treatment,
   - the adolescent has sufficient mental capacity (which most adolescents have by age 16 years) to estimate the consequences of this (partly) irreversible treatment, weigh the benefits and risks, and give informed consent to this (partly) irreversible treatment,
2. And the adolescent:
   - has been informed of the (irreversible) effects and side effects of treatment (including potential loss of fertility and options to preserve fertility),
   - has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,
3. And a pediatric endocrinologist or other clinician experienced in pubertal induction:
   - agrees with the indication for sex hormone treatment,
   - has confirmed that there are no medical contraindications to sex hormone treatment.

Reproduced from World Professional Association for Transgender Health (16).

doi: 10.1210/jc.2017-01658

reasons that are not gender identity related) (11). Clinicians should also be able to diagnose psychiatric conditions accurately and ensure that these conditions are treated appropriately, particularly when the conditions may complicate treatment, affect the outcome of gender-affirming treatment, or be affected by hormone use.

Values and preferences

The task force placed a very high value on avoiding harm from hormone treatment in individuals who have conditions other than GD/gender incongruence and who may not benefit from the physical changes associated with this treatment and placed a low value on any potential benefit these persons believe they may derive from hormone treatment. This justifies the good practice statement.

1.3. We advise that decisions regarding the social transition of prepubertal youths with GD/gender incongruence are made with the assistance of an MHP or another experienced professional. (Ungraded Good Practice Statement).

1.4. We recommend against puberty blocking and gender-affirming hormone treatment in prepubertal children with GD/gender incongruence. (1 |⊕⊕◯◯)

Evidence

In most children diagnosed with GD/gender incongruence, it did not persist into adolescence. The percentages differed among studies, probably dependent on which version of the DSM clinicians used, the patient's age, the recruitment criteria, and perhaps cultural factors. However, the large majority (about 85%) of prepubertal children with a childhood diagnosis did not remain GD/gender incongruent in adolescence (20). If children have completely socially transitioned, they may have great difficulty in returning to the original gender role upon entering puberty (40). Social transition is associated with the persistence of GD/gender incongruence as a child progresses into adolescence. It may be that the presence of GD/gender incongruence in prepubertal children is the earliest sign that a child is destined to be transgender as an adolescent/adult (20). However, social transition (in addition to GD/gender incongruence) has been found to contribute to the likelihood of persistence.

This recommendation, however, does not imply that children should be discouraged from showing gender-variant behaviors or should be punished for exhibiting such behaviors. In individual cases, an early complete social transition may result in a more favorable outcome, but there are currently no criteria to identify the GD/gender-incongruent children to whom this applies. At the present time, clinical experience suggests that persistence of GD/gender incongruence can only be reliably assessed after the first signs of puberty.

Values and preferences

The task force placed a high value on avoiding harm with gender-affirming hormone therapy in prepubertal children with GD/gender incongruence. This justifies the strong recommendation in the face of low-quality evidence.

1.5. We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults. (1 |⊕⊕⊕◯)

Remarks

Persons considering hormone use for gender affirmation need adequate information about this treatment in general and about fertility effects of hormone treatment in particular to make an informed and balanced decision (67, 68). Because young adolescents may not feel qualified to make decisions about fertility and may not fully understand the potential effects of hormonal interventions, consent and protocol education should include parents, the referring MHP(s), and other members of the adolescent's support group. To our knowledge, there are no formally evaluated decision aids available to assist in the discussion and decision regarding the future fertility of adolescents or adults beginning gender-affirming treatment.

Treating early pubertal youth with GnRH analogs will temporarily impair spermatogenesis and oocyte maturation. Given that an increasing number of transgender youth want to preserve fertility potential, delaying or temporarily discontinuing GnRH analogs to promote gamete maturation is an option. This option is often not preferred, because mature sperm production is associated with later stages of puberty and with the significant development of secondary sex characteristics.

For those designated male at birth with GD/gender incongruence and who are in early puberty, sperm production and the development of the reproductive tract are insufficient for the cryopreservation of sperm. However, prolonged pubertal suppression using GnRH analogs is reversible and clinicians should inform these individuals that sperm production can be initiated following prolonged gonadotropin suppression. This can be accomplished by spontaneous gonadotropin recovery after

cessation of GnRH analogs or by gonadotropin treatment and will probably be associated with physical manifestations of testosterone production, as stated above. Note that there are no data in this population concerning the time required for sufficient spermatogenesis to collect enough sperm for later fertility. In males treated for precocious puberty, spermarche was reported 0.7 to 3 years after cessation of GnRH analogs (69). In adult men with gonadotropin deficiency, sperm are noted in seminal fluid by 6 to 12 months of gonadotropin treatment. However, sperm numbers when partners of these patients conceive are far below the "normal range" (70, 71).

In girls, no studies have reported long-term, adverse effects of pubertal suppression on ovarian function after treatment cessation (72, 73). Clinicians should inform adolescents that no data are available regarding either time to spontaneous ovulation after cessation of GnRH analogs or the response to ovulation induction following prolonged gonadotropin suppression.

In males with GD/gender incongruence, when medical treatment is started in a later phase of puberty or in adulthood, spermatogenesis is sufficient for cryopreservation and storage of sperm. *In vitro* spermatogenesis is currently under investigation. Restoration of spermatogenesis after prolonged estrogen treatment has not been studied.

In females with GD/gender incongruence, the effect of prolonged treatment with exogenous testosterone on ovarian function is uncertain. There have been reports of an increased incidence of polycystic ovaries in transgender males, both prior to and as a result of androgen treatment (74–77), although these reports were not confirmed by others (78). Pregnancy has been reported in transgender males who have had prolonged androgen treatment and have discontinued testosterone but have not had genital surgery (79, 80). A reproductive endocrine gynecologist can counsel patients before gender-affirming hormone treatment or surgery regarding potential fertility options (81). Techniques for cryopreservation of oocytes, embryos, and ovarian tissue continue to improve, and oocyte maturation of immature tissue is being studied (82).

2.0 Treatment of Adolescents

During the past decade, clinicians have progressively acknowledged the suffering of young adolescents with GD/gender incongruence. In some forms of GD/gender incongruence, psychological interventions may be useful and sufficient. However, for many adolescents with GD/gender incongruence, the pubertal physical changes are unbearable. As early medical intervention may prevent psychological harm, various clinics have decided to start treating young adolescents with GD/gender incongruence with puberty-suppressing medication (a GnRH analog). As compared with starting gender-affirming treatment long after the first phases of puberty, a benefit of pubertal suppression at early puberty may be a better psychological and physical outcome.

In girls, the first physical sign of puberty is the budding of the breasts followed by an increase in breast and fat tissue. Breast development is also associated with the pubertal growth spurt, and menarche occurs ~2 years later. In boys, the first physical change is testicular growth. A testicular volume ≥4 mL is seen as consistent with the initiation of physical puberty. At the beginning of puberty, estradiol and testosterone levels are still low and are best measured in the early morning with an ultrasensitive assay. From a testicular volume of 10 mL, daytime testosterone levels increase, leading to virilization (83). Note that pubic hair and/or axillary hair/odor may not reflect the onset of gonadarche; instead, it may reflect adrenarche alone.

2.1. We suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment (Table 5), and are requesting treatment should initially undergo treatment to suppress pubertal development. (2 ⊕⊕◯◯)

2.2. We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty (Tanner stages G2/B2). (2 ⊕⊕◯◯)

Evidence

Pubertal suppression can expand the diagnostic phase by a long period, giving the subject more time to explore options and to live in the experienced gender before making a decision to proceed with gender-affirming sex hormone treatments and/or surgery, some of which is irreversible (84, 85). Pubertal suppression is fully reversible, enabling full pubertal development in the natal gender, after cessation of treatment, if appropriate. The experience of full endogenous puberty is an undesirable condition for the GD/gender-incongruent individual and may seriously interfere with healthy psychological functioning and well-being. Treating GD/gender-incongruent adolescents entering puberty with GnRH analogs has been shown to improve psychological functioning in several domains (86).

Another reason to start blocking pubertal hormones early in puberty is that the physical outcome is improved compared with initiating physical transition after puberty has been completed (60, 62). Looking like a man or woman when living as the opposite sex creates difficult

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 μg/kg/d
- 10 μg/kg/d
- 15 μg/kg/d
- 20 μg/kg/d
- Adult dose = 2–6 mg/d
- *In postpubertal transgender female adolescents, the dose of 17β-estradiol can be increased more rapidly:*
  - 1 mg/d for 6 mo
  - 2 mg/d

Induction of female puberty with transdermal 17β-estradiol, increasing the dose every 6 mo (new patch is placed every 3.5 d):
- 6.25–12.5 μg/24 h (cut 25-μg patch into quarters, then halves)
- 25 μg/24 h
- 37.5 μg/24 h
- Adult dose = 50–200 μg/24 h
- *For alternatives once at adult dose, see Table 11.*
- *Adjust maintenance dose to mimic physiological estradiol levels (see Table 15).*

Induction of male puberty with testosterone esters increasing the dose every 6 mo (IM or SC):
- 25 mg/m^2/2 wk (or alternatively, half this dose weekly, or double the dose every 4 wk)
- 50 mg/m^2/2 wk
- 75 mg/m^2/2 wk
- 100 mg/m^2/2 wk
- Adult dose = 100–200 mg every 2 wk
- *In postpubertal transgender male adolescents the dose of testosterone esters can be increased more rapidly:*
  - 75 mg/2 wk for 6 mo
  - 125 mg/2 wk
- *For alternatives once at adult dose, see Table 11.*
- *Adjust maintenance dose to mimic physiological testosterone levels (see Table 14).*

Adapted from Hembree *et al.* (118).

Abbreviations: IM, intramuscularly; SC, subcutaneously.

Evidence

Adolescents develop competence in decision making at their own pace. Ideally, the supervising medical professionals should individually assess this competence, although no objective tools to make such an assessment are currently available.

Many adolescents have achieved a reasonable level of competence by age 15 to 16 years (119), and in many countries 16-year-olds are legally competent with regard to medical decision making (120). However, others believe that although some capacities are generally achieved before age 16 years, other abilities (such as good risk assessment) do not develop until well after 18 years (121). They suggest that health care procedures should be divided along a matrix of relative risk, so that younger adolescents can be allowed to decide about low-risk procedures, such as most diagnostic tests and common therapies, but not about high-risk procedures, such as most surgical procedures (121).

Currently available data from transgender adolescents support treatment with sex hormones starting at age 16 years (63, 122). However, some patients may incur potential risks by waiting until age 16 years. These include the potential risk to bone health if puberty is suppressed

Table 9. Baseline and Follow-up Protocol During Induction of Puberty

Every 3–6 mo
- •Anthropometry: height, weight, sitting height, blood pressure, Tanner stages

Every 6–12 mo
- •In transgender males: hemoglobin/hematocrit, lipids, testosterone, 25OH vitamin D
- •In transgender females: prolactin, estradiol, 25OH vitamin D

Every 1–2 y
- •BMD using DXA
- •Bone age on X-ray of the left hand (if clinically indicated)

BMD should be monitored into adulthood (until the age of 25–30 y or until peak bone mass has been reached).
For recommendations on monitoring once pubertal induction has been completed, see Tables 14 and 15.

Adapted from Hembree *et al.* (118).

Abbreviation: DXA, dual-energy X-ray absorptiometry.

for 6 to 7 years before initiating sex hormones (*e.g.*, if someone reached Tanner stage 2 at age 9-10 years old). Additionally, there may be concerns about inappropriate height and potential harm to mental health (emotional and social isolation) if initiation of secondary sex characteristics must wait until the person has reached 16 years of age. However, only minimal data supporting earlier use of gender-affirming hormones in transgender adolescents currently exist (63). Clearly, long-term studies are needed to determine the optimal age of sex hormone treatment in GD/gender-incongruent adolescents.

The MHP who has followed the adolescent during GnRH analog treatment plays an essential role in assessing whether the adolescent is eligible to start sex hormone therapy and capable of consenting to this treatment (Table 5). Support of the family/environment is essential. Prior to the start of sex hormones, clinicians should discuss the implications for fertility (see recommendation 1.5). Throughout pubertal induction, an MHP and a pediatric endocrinologist (or other clinician competent in the evaluation and induction of pubertal development) should monitor the adolescent. In addition to monitoring therapy, it is also important to pay attention to general adolescent health issues, including healthy life style choices, such as not smoking, contraception, and appropriate vaccinations (*e.g.*, human papillomavirus).

For the induction of puberty, clinicians can use a similar dose scheme for hypogonadal adolescents with GD/gender incongruence as they use in other individuals with hypogonadism, carefully monitoring for desired and undesired effects (Table 8). In transgender female adolescents, transdermal 17β-estradiol may be an alternative for oral 17β-estradiol. It is increasingly used for pubertal induction in hypogonadal females. However, the absence of low-dose estrogen patches may be a problem. As a result, individuals may need to cut patches to size themselves to achieve appropriate dosing (123). In transgender male adolescents, clinicians can give testosterone injections intramuscularly or subcutaneously (124, 125).

When puberty is initiated with a gradually increasing schedule of sex steroid doses, the initial levels will not be high enough to suppress endogenous sex steroid secretion. Gonadotropin secretion and endogenous production of testosterone may resume and interfere with the effectiveness of estrogen treatment, in transgender female adolescents (126, 127). Therefore, continuation of GnRH analog treatment is advised until gonadectomy. Given that GD/gender-incongruent adolescents may opt not to have gonadectomy, long-term studies are necessary to examine the potential risks of prolonged GnRH analog treatment. Alternatively, in transgender male adolescents, GnRH analog treatment can be discontinued once an adult dose of testosterone has been reached and the individual is well virilized. If uterine bleeding occurs, a progestin can be added. However, the combined use of a GnRH analog (for ovarian suppression) and testosterone may enable phenotypic transition with a lower dose of testosterone in comparison with testosterone alone. If there is a wish or need to discontinue GnRH analog treatment in transgender female adolescents, they may be treated with an antiandrogen that directly suppresses androgen synthesis or action (see section 3.0 "Hormonal Therapy for Transgender Adults").

Values and preferences

The recommendation to initiate pubertal induction only when the individual has sufficient mental capacity (roughly age 16 years) to give informed consent for this partly irreversible treatment places a higher value on the ability of the adolescent to fully understand and oversee the partially irreversible consequences of sex hormone treatment and to give informed consent. It places a lower value on the possible negative effects of delayed puberty. We may not currently have the means to weigh adequately the potential benefits of waiting until around age 16 years to initiate sex hormones vs the potential risks/harm to BMD and the sense of social isolation from having the timing of puberty be so out of sync with peers (128).

Remarks

Before starting sex hormone treatment, effects on fertility and options for fertility preservation should be discussed. Adult height may be a concern in transgender adolescents. In a transgender female adolescent, clinicians may consider higher doses of estrogen or a more rapid tempo of dose escalation during pubertal induction. There are no established treatments yet to augment adult height in a transgender male adolescent with open epiphyses during pubertal induction. It is not uncommon for transgender adolescents to present for clinical services after having completed or nearly completed puberty. In such cases, induction of puberty with sex hormones can be done more rapidly (see Table 8). Additionally, an adult dose of testosterone in transgender male adolescents may suffice to suppress the gonadal axis without the need to use a separate agent. At the appropriate time, the multidisciplinary team should adequately prepare the adolescent for transition to adult care.

3.0 Hormonal Therapy for Transgender Adults

The two major goals of hormonal therapy are (1) to reduce endogenous sex hormone levels, and thus reduce

the secondary sex characteristics of the individual's designated gender, and (2) to replace endogenous sex hormone levels consistent with the individual's gender identity by using the principles of hormone replacement treatment of hypogonadal patients. The timing of these two goals and the age at which to begin treatment with the sex hormones of the chosen gender is codetermined in collaboration with both the person pursuing transition and the health care providers. The treatment team should include a medical provider knowledgeable in transgender hormone therapy, an MHP knowledgeable in GD/gender incongruence and the mental health concerns of transition, and a primary care provider able to provide care appropriate for transgender individuals. The physical changes induced by this sex hormone transition are usually accompanied by an improvement in mental well-being (129, 130).

3.1. We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and the criteria for the endocrine phase of gender transition before beginning treatment. (1 |⊕⊕⊕◯)

3.2. We recommend that clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment (Table 10). (1 |⊕⊕⊕◯)

3.3. We suggest that clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender. (2 |⊕⊕◯◯)

Evidence

It is the responsibility of the treating clinician to confirm that the person fulfills criteria for treatment. The treating clinician should become familiar with the terms and criteria presented in Tables 1–5 and take a thorough history from the patient in collaboration with the other members of the treatment team. The treating clinician must ensure that the desire for transition is appropriate; the consequences, risks, and benefits of treatment are well understood; and the desire for transition persists. They also need to discuss fertility preservation options (see recommendation 1.3) (67, 68).

Transgender males

Clinical studies have demonstrated the efficacy of several different androgen preparations to induce masculinization in transgender males (Appendix A) (113, 114, 131–134). Regimens to change secondary sex characteristics follow the general principle of hormone replacement treatment of male hypogonadism (135). Clinicians can use either parenteral or transdermal preparations to achieve testosterone values in the normal male range (this is dependent on the specific assay, but is typically 320 to 1000 ng/dL) (Table 11) (136). Sustained supraphysiologic levels of testosterone increase the risk of adverse reactions (see section 4.0 "Adverse Outcome Prevention and Long-Term Care") and should be avoided.

Similar to androgen therapy in hypogonadal men, testosterone treatment in transgender males results in increased muscle mass and decreased fat mass, increased facial hair and acne, male pattern baldness in those genetically predisposed, and increased sexual desire (137).

Table 10. Medical Risks Associated With Sex Hormone Therapy

Transgender female: estrogen
Very high risk of adverse outcomes:
•Thromboembolic disease
Moderate risk of adverse outcomes:
•Macroprolactinoma
•Breast cancer
•Coronary artery disease
•Cerebrovascular disease
•Cholelithiasis
•Hypertriglyceridemia
Transgender male: testosterone
Very high risk of adverse outcomes:
•Erythrocytosis (hematocrit > 50%)
Moderate risk of adverse outcomes:
•Severe liver dysfunction (transaminases > threefold upper limit of normal)
•Coronary artery disease
•Cerebrovascular disease
•Hypertension
•Breast or uterine cancer

doi: 10.1210/jc.2017-01658

Table 11. Hormone Regimens in Transgender Persons

Transgender females[a]	
Estrogen	
Oral	
Estradiol	2.0–6.0 mg/d
Transdermal	
Estradiol transdermal patch (New patch placed every 3–5 d)	0.025–0.2 mg/d
Parenteral	
Estradiol valerate or cypionate	5–30 mg IM every 2 wk 2–10 mg IM every week
Anti-androgens	
Spironolactone	100–300 mg/d
Cyproterone acetate[b]	25–50 mg/d
GnRH agonist	3.75 mg SQ (SC) monthly 11.25 mg SQ (SC) 3-monthly
Transgender males	
Testosterone	
Parenteral testosterone	
Testosterone enanthate or cypionate	100–200 mg SQ (IM) every 2 wk or SQ (SC) 50% per week
Testosterone undecanoate[c]	1000 mg every 12 wk
Transdermal testosterone	
Testosterone gel 1.6%[d]	50–100 mg/d
Testosterone transdermal patch	2.5–7.5 mg/d

Abbreviations: IM, intramuscularly; SQ, sequentially; SC, subcutaneously.

[a]Estrogens used with or without antiandrogens or GnRH agonist.

[b]Not available in the United States.

[c]One thousand milligrams initially followed by an injection at 6 wk then at 12-wk intervals.

[d]Avoid cutaneous transfer to other individuals.

In transgender males, testosterone will result in clitoromegaly, temporary or permanent decreased fertility, deepening of the voice, cessation of menses (usually), and a significant increase in body hair, particularly on the face, chest, and abdomen. Cessation of menses may occur within a few months with testosterone treatment alone, although high doses of testosterone may be required. If uterine bleeding continues, clinicians may consider the addition of a progestational agent or endometrial ablation (138). Clinicians may also administer GnRH analogs or depot medroxyprogesterone to stop menses prior to testosterone treatment.

Transgender females

The hormone regimen for transgender females is more complex than the transgender male regimen (Appendix B). Treatment with physiologic doses of estrogen alone is insufficient to suppress testosterone levels into the normal range for females (139). Most published clinical studies report the need for adjunctive therapy to achieve testosterone levels in the female range (21, 113, 114, 132–134, 139, 140).

Multiple adjunctive medications are available, such as progestins with antiandrogen activity and GnRH agonists (141). Spironolactone works by directly blocking androgens during their interaction with the androgen receptor (114, 133, 142). It may also have estrogenic activity (143). Cyproterone acetate, a progestational compound with antiandrogenic properties (113, 132, 144), is widely used in Europe. 5α-Reductase inhibitors do not reduce testosterone levels and have adverse effects (145).

Dittrich *et al.* (141) reported that monthly doses of the GnRH agonist goserelin acetate in combination with estrogen were effective in reducing testosterone levels with a low incidence of adverse reactions in 60 transgender females. Leuprolide and transdermal estrogen were as effective as cyproterone and transdermal estrogen in a comparative retrospective study (146).

Patients can take estrogen as oral conjugated estrogens, oral 17β-estradiol, or transdermal 17β-estradiol. Among estrogen options, the increased risk of thromboembolic events associated with estrogens in general seems most concerning with ethinyl estradiol specifically (134, 140, 141), which is why we specifically suggest that it not be used in any transgender treatment plan. Data distinguishing among other estrogen options are less well established although there is some thought that oral routes of administration are more thrombogenic due to the "first pass effect" than are transdermal and parenteral routes, and that the risk of thromboembolic events is dose-dependent. Injectable estrogen and sublingual

estrogen may benefit from avoiding the first pass effect, but they can result in more rapid peaks with greater overall periodicity and thus are more difficult to monitor (147, 148). However, there are no data demonstrating that increased periodicity is harmful otherwise.

Clinicians can use serum estradiol levels to monitor oral, transdermal, and intramuscular estradiol. Blood tests cannot monitor conjugated estrogens or synthetic estrogen use. Clinicians should measure serum estradiol and serum testosterone and maintain them at the level for premenopausal females (100 to 200 pg/mL and <50 ng/dL, respectively). The transdermal preparations and injectable estradiol cypionate or valerate preparations may confer an advantage in older transgender females who may be at higher risk for thromboembolic disease (149).

Values

Our recommendation to maintain levels of gender-affirming hormones in the normal adult range places a high value on the avoidance of the long-term complications of pharmacologic doses. Those patients receiving endocrine treatment who have relative contraindications to hormones should have an in-depth discussion with their physician to balance the risks and benefits of therapy.

Remarks

Clinicians should inform all endocrine-treated individuals of all risks and benefits of gender-affirming hormones prior to initiating therapy. Clinicians should strongly encourage tobacco use cessation in transgender females to avoid increased risk of VTE and cardiovascular complications. We strongly discourage the unsupervised use of hormone therapy (150).

Not all individuals with GD/gender incongruence seek treatment as described (*e.g.*, male-to-eunuchs and individuals seeking partial transition). Tailoring current protocols to the individual may be done within the context of accepted safety guidelines using a multidisciplinary approach including mental health. No evidence-based protocols are available for these groups (151). We need prospective studies to better understand treatment options for these persons.

3.4. We suggest that endocrinologists provide education to transgender individuals undergoing treatment about the onset and time course of physical changes induced by sex hormone treatment. (2 |⊕○○○)

Evidence

Transgender males

Physical changes that are expected to occur during the first 1 to 6 months of testosterone therapy include cessation of menses, increased sexual desire, increased facial and body hair, increased oiliness of skin, increased muscle, and redistribution of fat mass. Changes that occur within the first year of testosterone therapy include deepening of the voice (152, 153), clitoromegaly, and male pattern hair loss (in some cases) (114, 144, 154, 155) (Table 12).

Transgender females

Physical changes that may occur in transgender females in the first 3 to 12 months of estrogen and antiandrogen therapy include decreased sexual desire, decreased spontaneous erections, decreased facial and body hair (usually mild), decreased oiliness of skin, increased breast tissue growth, and redistribution of fat mass (114, 139, 149, 154, 155, 161) (Table 13). Breast development is generally maximal at 2 years after initiating hormones (114, 139, 149, 155). Over a long period of time, the prostate gland and testicles will undergo atrophy.

Although the time course of breast development in transgender females has been studied (150), precise information about other changes induced by sex hormones is lacking (141). There is a great deal of variability among individuals, as evidenced during pubertal development. We all know that a major concern for transgender females is breast development. If we work with estrogens, the result will be often not what the transgender female expects.

Alternatively, there are transgender females who report an anecdotal improved breast development, mood, or sexual desire with the use of progestogens. However, there have been no well-designed studies of the role of progestogens in feminizing hormone regimens, so the question is still open.

Our knowledge concerning the natural history and effects of different cross-sex hormone therapies on breast

Table 12. Masculinizing Effects in Transgender Males

Effect	Onset	Maximum
Skin oiliness/acne	1–6 mo	1–2 y
Facial/body hair growth	6–12 mo	4–5 y
Scalp hair loss	6–12 mo	—[a]
Increased muscle mass/strength	6–12 mo	2–5 y
Fat redistribution	1–6 mo	2–5 y
Cessation of menses	1–6 mo	—[b]
Clitoral enlargement	1–6 mo	1–2 y
Vaginal atrophy	1–6 mo	1–2 y
Deepening of voice	6–12 mo	1–2 y

Estimates represent clinical observations: Toorians *et al.* (149), Asscheman *et al.* (156), Gooren *et al.* (157), Wierckx *et al.* (158).

[a] Prevention and treatment as recommended for biological men.

[b] Menorrhagia requires diagnosis and treatment by a gynecologist.

Table 13. Feminizing Effects in Transgender Females

Effect	Onset	Maximum
Redistribution of body fat	3–6 mo	2–3 y
Decrease in muscle mass and strength	3–6 mo	1–2 y
Softening of skin/decreased oiliness	3–6 mo	Unknown
Decreased sexual desire	1–3 mo	3–6 mo
Decreased spontaneous erections	1–3 mo	3–6 mo
Male sexual dysfunction	Variable	Variable
Breast growth	3–6 mo	2–3 y
Decreased testicular volume	3–6 mo	2–3 y
Decreased sperm production	Unknown	>3 y
Decreased terminal hair growth	6–12 mo	>3 y[a]
Scalp hair	Variable	—[b]
Voice changes	None	—[c]

Estimates represent clinical observations: Toorians *et al.* (149), Asscheman *et al.* (156), Gooren *et al.* (157).

[a]Complete removal of male sexual hair requires electrolysis or laser treatment or both.

[b]Familial scalp hair loss may occur if estrogens are stopped.

[c]Treatment by speech pathologists for voice training is most effective.

development in transgender females is extremely sparse and based on the low quality of evidence. Current evidence does not indicate that progestogens enhance breast development in transgender females, nor does evidence prove the absence of such an effect. This prevents us from drawing any firm conclusion at this moment and demonstrates the need for further research to clarify these important clinical questions (162).

Values and preferences

Transgender persons have very high expectations regarding the physical changes of hormone treatment and are aware that body changes can be enhanced by surgical procedures (*e.g.*, breast, face, and body habitus). Clear expectations for the extent and timing of sex hormone–induced changes may prevent the potential harm and expense of unnecessary procedures.

4.0 Adverse Outcome Prevention and Long-Term Care

Hormone therapy for transgender males and females confers many of the same risks associated with sex hormone replacement therapy in nontransgender persons. The risks arise from and are worsened by inadvertent or intentional use of supraphysiologic doses of sex hormones, as well as use of inadequate doses of sex hormones to maintain normal physiology (131, 139).

4.1. We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every 3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly. (2 l⊕⊕○○)

Evidence

Pretreatment screening and appropriate regular medical monitoring are recommended for both transgender males and females during the endocrine transition and periodically thereafter (26, 155). Clinicians should monitor weight and blood pressure, conduct physical exams, and assess routine health questions, such as tobacco use, symptoms of depression, and risk of adverse events such as deep vein thrombosis/pulmonary embolism and other adverse effects of sex steroids.

Transgender males

Table 14 contains a standard monitoring plan for transgender males on testosterone therapy (154, 159). Key issues include maintaining testosterone levels in the physiologic normal male range and avoiding adverse events resulting from excess testosterone therapy, particularly erythrocytosis, sleep apnea, hypertension, excessive weight gain, salt retention, lipid changes, and excessive or cystic acne (135).

Because oral 17-alkylated testosterone is not recommended, serious hepatic toxicity is not anticipated with parenteral or transdermal testosterone use (163, 164). Past concerns regarding liver toxicity with testosterone have been alleviated with subsequent reports that indicate the risk of serious liver disease is minimal (144, 165, 166).

Transgender females

Table 15 contains a standard monitoring plan for transgender females on estrogens, gonadotropin suppression, or antiandrogens (160). Key issues include avoiding supraphysiologic doses or blood levels of estrogen that may lead to increased risk for thromboembolic disease, liver dysfunction, and hypertension. Clinicians should monitor serum estradiol levels using laboratories participating in external quality control, as measurements of estradiol in blood can be very challenging (167).

VTE may be a serious complication. A study reported a 20-fold increase in venous thromboembolic disease in a large cohort of Dutch transgender subjects (161). This increase may have been associated with the use of the synthetic estrogen, ethinyl estradiol (149). The incidence decreased when clinicians stopped administering ethinyl estradiol (161). Thus, the use of synthetic estrogens and conjugated estrogens is undesirable because of the inability to regulate doses by measuring serum levels and the risk of thromboembolic disease. In a German gender clinic, deep vein thrombosis occurred in 1 of 60 of transgender females treated with a GnRH analog and oral

Table 14. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Male

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of virilization and for development of adverse reactions.
2. Measure serum testosterone every 3 mo until levels are in the normal physiologic male range:[a]
   a. For testosterone enanthate/cypionate injections, the testosterone level should be measured midway between injections. The target level is 400–700 ng/dL to 400 ng/dL. Alternatively, measure peak and trough levels to ensure levels remain in the normal male range.
   b. For parenteral testosterone undecanoate, testosterone should be measured just before the following injection. If the level is <400 ng/dL, adjust dosing interval.
   c. For transdermal testosterone, the testosterone level can be measured no sooner than after 1 wk of daily application (at least 2 h after application).
3. Measure hematocrit or hemoglobin at baseline and every 3 mo for the first year and then one to two times a year. Monitor weight, blood pressure, and lipids at regular intervals.
4. Screening for osteoporosis should be conducted in those who stop testosterone treatment, are not compliant with hormone therapy, or who develop risks for bone loss.
5. If cervical tissue is present, monitoring as recommended by the American College of Obstetricians and Gynecologists.
6. Ovariectomy can be considered after completion of hormone transition.
7. Conduct sub- and periareolar annual breast examinations if mastectomy performed. If mastectomy is not performed, then consider mammograms as recommended by the American Cancer Society.

[a]Adapted from Lapauw *et al.* (154) and Ott *et al.* (159).

estradiol (141). The patient who developed a deep vein thrombosis was found to have a homozygous C677 T mutation in the methylenetetrahydrofolate reductase gene. In an Austrian gender clinic, administering gender-affirming hormones to 162 transgender females and 89 transgender males was not associated with VTE, despite an 8.0% and 5.6% incidence of thrombophilia (159). A more recent multinational study reported only 10 cases of VTE from a cohort of 1073 subjects (168). Thrombophilia screening of transgender persons initiating hormone treatment should be restricted to those with a personal or family history of VTE (159). Monitoring D-dimer levels during treatment is not recommended (169).

4.2. We suggest periodically monitoring prolactin levels in transgender females treated with estrogens. (2 l⊕⊕◯◯)

Evidence

Estrogen therapy can increase the growth of pituitary lactrotroph cells. There have been several reports of prolactinomas occurring after long-term, high-dose estrogen therapy (170–173). Up to 20% of transgender females treated with estrogens may have elevations in prolactin levels associated with enlargement of the pituitary gland (156). In most cases, the serum prolactin levels will return to the normal range with a reduction or discontinuation of the estrogen therapy or discontinuation of cyproterone acetate (157, 174, 175).

The onset and time course of hyperprolactinemia during estrogen treatment are not known. Clinicians should measure prolactin levels at baseline and then at least annually during the transition period and every 2 years thereafter. Given that only a few case studies reported prolactinomas, and prolactinomas were not reported in large cohorts of estrogen-treated persons, the risk is likely to be very low. Because the major presenting findings of microprolactinomas (hypogonadism and sometimes gynecomastia) are not apparent in transgender females, clinicians may perform radiologic examinations of the pituitary in those patients whose prolactin levels persistently increase despite stable or reduced estrogen levels. Some transgender individuals receive psychotropic medications that can increase prolactin levels (174).

Table 15. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Female

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of feminization and for development of adverse reactions.
2. Measure serum testosterone and estradiol every 3 mo.
   a. Serum testosterone levels should be <50 ng/dL.
   b. Serum estradiol should not exceed the peak physiologic range: 100–200 pg/mL.
3. For individuals on spironolactone, serum electrolytes, particularly potassium, should be monitored every 3 mo in the first year and annually thereafter.
4. Routine cancer screening is recommended, as in nontransgender individuals (all tissues present).
5. Consider BMD testing at baseline (160). In individuals at low risk, screening for osteoporosis should be conducted at age 60 years or in those who are not compliant with hormone therapy.

This table presents strong recommendations and does not include lower level recommendations.

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 l⊕⊕○○)

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 l⊕⊕○○)

Evidence

Transgender males

Baseline bone mineral measurements in transgender males are generally in the expected range for their pretreatment gender (188). However, adequate dosing of testosterone is important to maintain bone mass in transgender males (189, 190). In one study (190), serum LH levels were inversely related to BMD, suggesting that low levels of sex hormones were associated with bone loss. Thus, LH levels in the normal range may serve as an indicator of the adequacy of sex steroid administration to preserve bone mass. The protective effect of testosterone may be mediated by peripheral conversion to estradiol, both systemically and locally in the bone.

Transgender females

A baseline study of BMD reported T scores less than −2.5 in 16% of transgender females (191). In aging males, studies suggest that serum estradiol more positively correlates with BMD than does testosterone (192, 193) and is more important for peak bone mass (194). Estrogen preserves BMD in transgender females who continue on estrogen and antiandrogen therapies (188, 190, 191, 195, 196).

Fracture data in transgender males and females are not available. Transgender persons who have undergone gonadectomy may choose not to continue consistent sex steroid treatment after hormonal and surgical sex reassignment, thereby becoming at risk for bone loss. There have been no studies to determine whether clinicians should use the sex assigned at birth or affirmed gender for assessing osteoporosis (*e.g.*, when using the FRAX tool). Although some researchers use the sex assigned at birth (with the assumption that bone mass has usually peaked for transgender people who initiate hormones in early adulthood), this should be assessed on a case-by-case basis until there are more data available. This assumption will be further complicated by the increasing prevalence of transgender people who undergo hormonal transition at a pubertal age or soon after puberty. Sex for comparison within risk assessment tools may be based on the age at which hormones were initiated and the length of exposure to hormones. In some cases, it may be

reasonable to assess risk using both the male and female calculators and using an intermediate value. Because all subjects underwent normal pubertal development, with known effects on bone size, reference values for birth sex were used for all participants (154).

4.5. We suggest that transgender females with no known increased risk of breast cancer follow breast-screening guidelines recommended for those designated female at birth. (2 ⊕⊕◯◯)

4.6. We suggest that transgender females treated with estrogens follow individualized screening according to personal risk for prostatic disease and prostate cancer. (2 ⊕◯◯◯)

Evidence

Studies have reported a few cases of breast cancer in transgender females (197–200). A Dutch study of 1800 transgender females followed for a mean of 15 years (range of 1 30 years) found one case of breast cancer. The Women's Health Initiative study reported that females taking conjugated equine estrogen without progesterone for 7 years did not have an increased risk of breast cancer as compared with females taking placebo (137).

In transgender males, a large retrospective study conducted at the U.S. Veterans Affairs medical health system identified seven breast cancers (194). The authors reported that this was not above the expected rate of breast cancers in cisgender females in this cohort. Furthermore, they did report one breast cancer that developed in a transgender male patient after mastectomy, supporting the fact that breast cancer can occur even after mastectomy. Indeed, there have been case reports of breast cancer developing in subareolar tissue in transgender males, which occurred after mastectomy (201, 202).

Women with primary hypogonadism (Turner syndrome) treated with estrogen replacement exhibited a significantly decreased incidence of breast cancer as compared with national standardized incidence ratios (203, 204). These studies suggest that estrogen therapy does not increase the risk of breast cancer in the short term (<20 to 30 years). We need long-term studies to determine the actual risk, as well as the role of screening mammograms. Regular examinations and gynecologic advice should determine monitoring for breast cancer.

Prostate cancer is very rare before the age of 40, especially with androgen deprivation therapy (205). Childhood or pubertal castration results in regression of the prostate and adult castration reverses benign prostate hypertrophy (206). Although van Kesteren *et al.* (207) reported that estrogen therapy does not induce hypertrophy or premalignant changes in the prostates of transgender females, studies have reported cases of benign prostatic hyperplasia in transgender females treated with estrogens for 20 to 25 years (208, 209). Studies have also reported a few cases of prostate carcinoma in transgender females (210–214).

Transgender females may feel uncomfortable scheduling regular prostate examinations. Gynecologists are not trained to screen for prostate cancer or to monitor prostate growth. Thus, it may be reasonable for transgender females who transitioned after age 20 years to have annual screening digital rectal examinations after age 50 years and prostate-specific antigen tests consistent with U.S. Preventive Services Task Force Guidelines (215).

4.7. We advise that clinicians determine the medical necessity of including a total hysterectomy and oophorectomy as part of gender-affirming surgery. (Ungraded Good Practice Statement)

Evidence

Although aromatization of testosterone to estradiol in transgender males has been suggested as a risk factor for endometrial cancer (216), no cases have been reported. When transgender males undergo hysterectomy, the uterus is small and there is endometrial atrophy (217, 218). Studies have reported cases of ovarian cancer (219, 220). Although there is limited evidence for increased risk of reproductive tract cancers in transgender males, health care providers should determine the medical necessity of a laparoscopic total hysterectomy as part of a gender-affirming surgery to prevent reproductive tract cancer (221).

Values

Given the discomfort that transgender males experience accessing gynecologic care, our recommendation for the medical necessity of total hysterectomy and oophorectomy places a high value on eliminating the risks of female reproductive tract disease and cancer and a lower value on avoiding the risks of these surgical procedures (related to the surgery and to the potential undesirable health consequences of oophorectomy) and their associated costs.

Remarks

The sexual orientation and type of sexual practices will determine the need and types of gynecologic care required following transition. Additionally, in certain countries, the approval required to change the sex in a birth certificate for transgender males may be dependent on having a complete hysterectomy. Clinicians should help patients research nonmedical administrative criteria and

provide counseling. If individuals decide not to undergo hysterectomy, screening for cervical cancer is the same as all other females.

5.0 Surgery for Sex Reassignment and Gender Confirmation

For many transgender adults, genital gender-affirming surgery may be the necessary step toward achieving their ultimate goal of living successfully in their desired gender role. The type of surgery falls into two main categories: (1) those that directly affect fertility and (2) those that do not. Those that change fertility (previously called sex reassignment surgery) include genital surgery to remove the penis and gonads in the male and removal of the uterus and gonads in the female. The surgeries that effect fertility are often governed by the legal system of the state or country in which they are performed. Other gender-conforming surgeries that do not directly affect fertility are not so tightly governed.

Gender-affirming surgical techniques have improved markedly during the past 10 years. Reconstructive genital surgery that preserves neurologic sensation is now the standard. The satisfaction rate with surgical reassignment of sex is now very high (187). Additionally, the mental health of the individual seems to be improved by participating in a treatment program that defines a pathway of gender-affirming treatment that includes hormones and surgery (130, 144) (Table 16).

Surgery that affects fertility is irreversible. The World Professional Association for Transgender Health Standards of Care (222) emphasizes that the "threshold of 18 should not be seen as an indication in itself for active intervention." If the social transition has not been satisfactory, if the person is not satisfied with or is ambivalent about the effects of sex hormone treatment, or if the person is ambivalent about surgery then the individual should not be referred for surgery (223, 224).

Gender-affirming genital surgeries for transgender females that affect fertility include gonadectomy, penectomy, and creation of a neovagina (225, 226). Surgeons often invert the skin of the penis to form the wall of the vagina, and several literatures reviews have reported on outcomes (227). Sometimes there is inadequate tissue to form a full neovagina, so clinicians have revisited using intestine and found it to be successful (87, 228, 229). Some newer vaginoplasty techniques may involve autologuous oral epithelial cells (230, 231).

The scrotum becomes the labia majora. Surgeons use reconstructive surgery to fashion the clitoris and its hood, preserving the neurovascular bundle at the tip of the penis as the neurosensory supply to the clitoris. Some surgeons are also creating a sensate pedicled-spot adding a G spot to the neovagina to increase sensation (232). Most recently, plastic surgeons have developed techniques to fashion labia minora. To further complete the feminization, uterine transplants have been proposed and even attempted (233).

Neovaginal prolapse, rectovaginal fistula, delayed healing, vaginal stenosis, and other complications do sometimes occur (234, 235). Clinicians should strongly remind the transgender person to use their dilators to maintain the depth and width of the vagina throughout the postoperative period. Genital sexual responsivity and other aspects of sexual function are usually preserved following genital gender-affirming surgery (236, 237).

Ancillary surgeries for more feminine or masculine appearance are not within the scope of this guideline. Voice therapy by a speech language pathologist is available to transform speech patterns to the affirmed gender (148). Spontaneous voice deepening occurs during testosterone treatment of transgender males (152, 238). No studies have compared the effectiveness of speech therapy, laryngeal surgery, or combined treatment.

Breast surgery is a good example of gender-confirming surgery that does not affect fertility. In all females, breast size exhibits a very broad spectrum. For transgender females to make the best informed decision, clinicians should delay breast augmentation surgery until the patient has completed at least 2 years of estrogen therapy, because the breasts continue to grow during that time (141, 155).

Another major procedure is the removal of facial and masculine-appearing body hair using either electrolysis or

Table 16. Criteria for Gender-Affirming Surgery, Which Affects Fertility

1. Persistent, well-documented gender dysphoria
2. Legal age of majority in the given country
3. Having continuously and responsibly used gender-affirming hormones for 12 mo (if there is no medical contraindication to receiving such therapy)
4. Successful continuous full-time living in the new gender role for 12 mo
5. If significant medical or mental health concerns are present, they must be well controlled
6. Demonstrable knowledge of all practical aspects of surgery (*e.g.*, cost, required lengths of hospitalizations, likely complications, postsurgical rehabilitation)

laser treatments. Other feminizing surgeries, such as that to feminize the face, are now becoming more popular (239–241).

In transgender males, clinicians usually delay gender-affirming genital surgeries until after a few years of androgen therapy. Those surgeries that affect fertility in this group include oophorectomy, vaginectomy, and complete hysterectomy. Surgeons can safely perform them vaginally with laparoscopy. These are sometimes done in conjunction with the creation of a neopenis. The cosmetic appearance of a neopenis is now very good, but the surgery is multistage and very expensive (242, 243). Radial forearm flap seems to be the most satisfactory procedure (228, 244). Other flaps also exist (245). Surgeons can make neopenile erections possible by reinervation of the flap and subsequent contraction of the muscle, leading to stiffening of the neopenis (246, 247), but results are inconsistent (248). Surgeons can also stiffen the penis by imbedding some mechanical device (*e.g.*, a rod or some inflatable apparatus) (249, 250). Because of these limitations, the creation of a neopenis has often been less than satisfactory. Recently, penis transplants are being proposed (233).

In fact, most transgender males do not have any external genital surgery because of the lack of access, high cost, and significant potential complications. Some choose a metaoidioplasty that brings forward the clitoris, thereby allowing them to void in a standing position without wetting themselves (251, 252). Surgeons can create the scrotum from the labia majora with good cosmetic effect and can implant testicular prostheses (253).

The most important masculinizing surgery for the transgender male is mastectomy, and it does not affect fertility. Breast size only partially regresses with androgen therapy (155). In adults, discussions about mastectomy usually take place after androgen therapy has started. Because some transgender male adolescents present after significant breast development has occurred, they may also consider mastectomy 2 years after they begin androgen therapy and before age 18 years. Clinicians should individualize treatment based on the physical and mental health status of the individual. There are now newer approaches to mastectomy with better outcomes (254, 255). These often involve chest contouring (256). Mastectomy is often necessary for living comfortably in the new gender (256).

5.1. We recommend that a patient pursue genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically necessary and would benefit the patient's overall health and/or well-being. (1 ⊕⊕◯◯)

5.2. We advise that clinicians approve genital gender-affirming surgery only after completion of at least 1 year of consistent and compliant hormone treatment, unless hormone therapy is not desired or medically contraindicated. (Ungraded Good Practice Statement)

5.3. We advise that the clinician responsible for endocrine treatment and the primary care provider ensure appropriate medical clearance of transgender individuals for genital gender-affirming surgery and collaborate with the surgeon regarding hormone use during and after surgery. (Ungraded Good Practice Statement)

5.4. We recommend that clinicians refer hormone-treated transgender individuals for genital surgery when: (1) the individual has had a satisfactory social role change, (2) the individual is satisfied about the hormonal effects, and (3) the individual desires definitive surgical changes. (1 ⊕◯◯◯)

5.5. We suggest that clinicians delay gender-affirming genital surgery involving gonadectomy and/or hysterectomy until the patient is at least 18 years old or legal age of majority in his or her country. (2 ⊕⊕◯◯).

5.6. We suggest that clinicians determine the timing of breast surgery for transgender males based upon the physical and mental health status of the individual. There is insufficient evidence to recommend a specific age requirement. (2 ⊕◯◯◯)

Evidence

Owing to the lack of controlled studies, incomplete follow-up, and lack of valid assessment measures, evaluating various surgical approaches and techniques is difficult. However, one systematic review including a large numbers of studies reported satisfactory cosmetic and functional results for vaginoplasty/neovagina construction (257). For transgender males, the outcomes are less certain. However, the problems are now better understood (258). Several postoperative studies report significant long-term psychological and psychiatric pathology (259–261). One study showed satisfaction with breasts, genitals, and femininity increased significantly and showed the importance of surgical treatment as a key therapeutic option for transgender females (262). Another analysis demonstrated that, despite the young average age at death following surgery and the relatively larger number of individuals with somatic morbidity, the study does not allow for determination of

causal relationships between, for example, specific types of hormonal or surgical treatment received and somatic morbidity and mortality (263). Reversal surgery in regretful male-to-female transsexuals after sexual reassignment surgery represents a complex, multistage procedure with satisfactory outcomes. Further insight into the characteristics of persons who regret their decision postoperatively would facilitate better future selection of applicants eligible for sexual reassignment surgery. We need more studies with appropriate controls that examine long-term quality of life, psychosocial outcomes, and psychiatric outcomes to determine the long-term benefits of surgical treatment.

When a transgender individual decides to have gender-affirming surgery, both the hormone prescribing clinician and the MHP must certify that the patient satisfies criteria for gender-affirming surgery (Table 16).

There is some concern that estrogen therapy may cause an increased risk for venous thrombosis during or following surgery (176). For this reason, the surgeon and the hormone-prescribing clinician should collaborate in making a decision about the use of hormones before and following surgery. One study suggests that preoperative factors (such as compliance) are less important for patient satisfaction than are the physical postoperative results (56). However, other studies and clinical experience dictate that individuals who do not follow medical instructions and do not work with their physicians toward a common goal do not achieve treatment goals (264) and experience higher rates of postoperative infections and other complications (265, 266). It is also important that the person requesting surgery feels comfortable with the anatomical changes that have occurred during hormone therapy. Dissatisfaction with social and physical outcomes during the hormone transition may be a contraindication to surgery (223).

An endocrinologist or experienced medical provider should monitor transgender individuals after surgery. Those who undergo gonadectomy will require hormone replacement therapy, surveillance, or both to prevent adverse effects of chronic hormone deficiency.

Financial Disclosures of the Task Force*

Wylie C. Hembree (chair)—financial or business/organizational interests: none declared, significant financial interest or leadership position: none declared. **Peggy T. Cohen-Kettenis**—financial or business/organizational interests: none declared, significant financial interest or leadership position: none declared. **Louis Gooren**—financial or business/organizational interests: none declared, significant financial interest or leadership position: none declared. **Sabine E. Hannema**—financial or business/organizational interests: none declared, significant financial interest or leadership position: Ferring Pharmaceuticals Inc. (lecture/conference), Pfizer (lecture). **Walter J. Meyer**—financial or business/organizational interests: none declared, significant financial interest or leadership position: none declared. **M. Hassan Murad****—financial or business/organizational interests: Mayo Clinic, Evidence-based Practice Center, significant financial interest or leadership position: none declared. **Stephen M. Rosenthal**—financial or business/organizational interests: AbbVie (consultant), National Institutes of Health (grantee), significant financial interest or leadership position: Pediatric Endocrine Society (immediate past president). **Joshua D. Safer, FACP**—financial or business/organizational interests: none declared, significant financial interest or leadership position: none declared. **Vin Tangpricha**—financial or business/organizational interests: Cystic Fibrosis Foundation (grantee), National Institutes of Health (grantee), significant financial interest or leadership position, Elsevier *Journal of Clinical and Translational Endocrinology* (editor). **Guy G. T'Sjoen**—financial or business/organizational interests: none declared, significant financial interest or leadership position: none declared.* Financial, business, and organizational disclosures of the task force cover the year prior to publication. Disclosures prior to this time period are archived.**Evidence-based reviews for this guideline were prepared under contract with the Endocrine Society.

Acknowledgments

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Disclosure Summary: See Financial Disclosures.

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EXHIBIT 11

IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF TENNESSEE
NASHVILLE DIVISION

L.W. et al., *by and through her parents and next friends, Samantha Williams and Brian Williams,*	)	
Plaintiffs,	)	No. 3:23-cv-00376 JUDGE RICHARDSON
v.	)	
JONATHAN SKRMETTI et al.,	)	
Defendants.	)	

DECLARATION OF CHLOE COLE

I, Chloe Cole, declare as follows:

1. I am 18 years old and am not a party to this action. I have actual knowledge of the following facts and, if called upon to testify to them, could and would do so competently. I am submitting this Declaration in support of Defendants' Opposition to Plaintiffs' Motion for a Preliminary Injunction.

2. Tennessee's law prohibiting medical procedures performed on minors "for the purpose of: (A) Enabling a minor to identify with, or live as a purported identity inconsistent with the minor's sex, or (B) Treating purported discomfort or distress from a discordance between the minor's sex and asserted identity," Tenn. Code Ann. § 68-33-101, *et seq.*, is a necessary and potentially life-saving regulation to protect vulnerable young people from the heartbreaking regret, irreversible physical changes, and emotional pain I have experienced.

3. I am a detransitioned woman from California who medically transitioned as a child. I grew up with ideal conditions for transitioning. I lived in an area where medical transition was easily accessible, had the support of family and a group of friends, and started treatment as young as possible. Yet, my transitioning was still a failure.

4. I began puberty very young, no older than 8 or 9. I had a lot of discomfort around my developing body. I was afraid to grow from a girl into a woman and experience things like periods, childbirth, and menopause. I only hear about how scary and painful being a woman was from other girls and older women. I never really had any strong female role models, and I never felt like I fit in with other girls, but I had a tomboyish streak influenced by my older brothers.

5. At the age of 12, I began to believe that I was transgender. I became obsessed about the idea of becoming a boy. I believed that my insecurities and anxieties about being a hypersexualized and vulnerable girl would magically disappear if I transitioned. At school, I also

had trouble making friends but saw the praise that coming out as "trans" gave people on Instagram and social media. I started socially transitioning from a girl into a male identity.

6. Soon after, I was diagnosed with gender dysphoria by a "gender specialist." The gender specialist told my parents that children know their gender from a young age, and I know what's best for myself. The mental health professionals did not try to dissuade me from my beliefs. At no point did anyone explore why I did not want to be a girl.

7. The doctors treated me like an adult who could make informed lifelong decisions. Yet, I was in 8th grade. I had no concept of what it would mean to me as an adult to have children someday. But this decision would affect every area of my life, from socialization and relationships to sexual function, and my ability to have children. I cannot imagine a doctor asking a child this and expecting them to make a mature judgment.

8. When speaking to my parents, the gender specialist cited the suicide rate, stating, "If you don't affirm your child, she will commit suicide." The provider asked, "Would you rather have a dead daughter or live son?" They did not present any other option to treat my dysphoria to me or to my parents. My distraught parents wanted me alive, so they listened to my doctors. However, I wasn't suicidal until I underwent treatments.

9. Like many dysphoric children, I suffered from several mental health conditions, such as ADHD, and comorbidities, including undiagnosed autism and body dysmorphia.

10. Because I am autistic, I have more masculine behaviors and am more object-oriented than most girls. I have some social, cognitive, and sensory processing differences that made school and going through puberty a little more difficult. These struggles were all normal but were misrepresented as problems having to do with my gender.

11. Six months after my gender dysphoria diagnosis, I started puberty blockers. A month later, I was put on testosterone. I stayed on puberty blockers for a year and on testosterone for three years. When I received the hormones, the endocrinologist cited some of the risks, including vaginal atrophy and the inability to have children. However, I did not really understand what that would mean and didn't realize that it could involve other pelvic structures.

12. After I started the hormones, I began having severe hot flashes, like those in menopause. My entire body got very itchy. After a while I would sometimes hear loud cracks in my neck and back. The hormones caused an atrophy of my urinary tract. I suffered from urinary tract infections and blood clots in my urine. I also developed digestive problems. I also experienced a very heightened libido which was very difficult to deal with at such a young age. This caused me to make a lot of regrettable sexual decisions. However, I did not want to discontinue testosterone because I wanted to continue to be treated as a boy.

13. At 13, I started binding my breasts. A classmate groped me in 8th grade, and I never wanted it to happen again. After two years of binding, I began seeking a mastectomy to have my breasts removed. This process took only six months and did not require a psychological evaluation. I was simply referred to a surgeon by a gender specialist.

14. At 15, just after my sophomore year of high school ended, I had a double mastectomy. I had serious complications from the surgery. I have to wear bandages over my chest every day because the areola grafts on my mastectomy started to fail and leak fluid two years post-op.

15. About 11 months after my surgery, I began experiencing grief. I realized this was a mistake, that I had lost a part of my body. I won't be able to breastfeed my future children. While

doctors warned me about this, no teenager can grasp what that really means. I will never be able to bond in an important way with any future children. I might not be able to have children.

16. I became extremely depressed to the point of my grades and school attendance dropping, and I experienced severe paranoia and suicidal ideation. I had to drop out of high school several times. The longer I was on my medications, the worse my mental health became. I felt alienated and started to become suicidal for the first time. Although I did not act on my thoughts, they were taking a toll on me.

17. I broke down one night as it all came to a head and made the decision to stop the testosterone. I also dropped the male identification and began to identify again as female.

18. At first some things got worse. I had more UTIs, blood clots and sometimes tissue in my urine, and worse digestive issues. That has since gone away, but I still experience frequent urination, dehydration, and occasionally infections.

19. I was very emotionally volatile, and my suicidal ideation got worse. I became very sick and lost a lot of weight. My overall mental health got worse. I had to drop out of school and get a GED because I couldn't perform at school.

20. Over time my body began to readjust. My features resoftened. The fat in my body and body shape began to return to a female form and I have regained the weight.

21. Currently, my mental health is stable. The treatments were just band aids for my mental health issues. I still struggle, but my depression and anxiety have improved.

22. It should not have been an option for me to be prescribed hormone treatments that caused me harm and may have affected my fertility, or to have my healthy breasts removed at the age of 15.

23. The complications from puberty blockers, testosterone, and surgery still impact my day-to-day life in ways that I didn't even know were possible. The puberty blockers gave me joint and back pain, and the testosterone caused me to develop issues in my urinary tract. The status of my fertility is currently unknown.

24. I still experience gender dysphoria to this day. The only thing that has improved it long term was simply living in my body with no intervention or medication.

25. Tennessee's law banning these treatments is a crucial step in protecting children and their right to grow up into healthy adults who are able to live fulfilling lives.

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

Executed on May 19, 2023.

*/s/ Chloe Cole*_____
Chloe Cole

EXHIBIT 12

IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF TENNESSEE
NASHVILLE DIVISION

L.W. et al., *by and through her parents and next friends, Samantha Williams and Brian Williams,*	)	
Plaintiffs,	)	No. 3:23-cv-00376 JUDGE RICHARDSON
v.	)	
JONATHAN SKRMETTI et al.,	)	
Defendants.	)	

DECLARATION OF HELENA KERSHNER

I, Helena Kershner, declare as follows:

1. I am 24 years old. I have actual knowledge of the following facts and if called upon to testify to them could and would do so competently. I am submitting this Declaration in support of Defendants' Opposition to Plaintiffs' Motion for a Preliminary Injunction and Complaint.

2. I am a detransitioned female from Ohio who would have transitioned as a minor if my mother consented to "gender affirming" medical treatment: giving me testosterone. Thankfully, she did not. Tennessee's law prohibiting minors' medical transitioning is a necessary regulation that will allow kids to grow up and mature before changing their bodies forever.

3. I was conventionally feminine when I was young and had no discomfort with being a girl. However, I was an introvert, and found it difficult to fit in with other girls.

4. My home life was challenging. My mom worked many hours, so my aunt became my main caretaker. After my aunt moved out of the country, I spent more time surrounded by babysitters than family. I struggled with depression and started seeing a therapist.

5. When I was 13, I started using the social media site Tumblr and spent a lot of time online. On Tumblr, I became completely immersed in the "topics" I read about. As a socially struggling teen, this had a big effect on me. When I read about self-harm, I started to self-harm. When I read about eating disorders, I developed an eating disorder.

6. Around the time I turned 14, I found Tumblr's "social justice" communities that harshly stigmatized people who were straight, white, and not transgender. I found myself in an environment where being a cis-white female was the absolute worst form of human, and being trans was normal. I read that if a person did not like their body and if they suspected that they might be trans, they are probably trans.

7. Based on the content I saw and the materials I read, I started to interpret my social, emotional, and body image difficulties as signs of gender dysphoria. I believed that by becoming trans, I could become a desirable, accepted, not evil white cis-person that caused all of the pain of the world. Soon, I began to identify as nonbinary.

8. When I was 15, I started to identify as transgender. I started socially transitioning, changing my pronouns, cutting my hair, and changing my clothing. I received more positivity and encouragement than I had ever experienced. With each change, I received positive affirmation on the internet.

9. By age 17, I identified as a "trans boy" and was fully convinced that my only chance at living a happy life would be to take hormones and undergo surgeries to change my body. I became obsessed with my weight and believed that taking testosterone would transform my body into the ideal I dreamed I could become: thin, tall, sporty, androgynous.

10. My school counselor and therapist both agreed with my beliefs. The psychologist told my mother that I was at risk of suicide if she would not agree to testosterone treatments. Thankfully, my mom did not allow it.

11. I went to a Planned Parenthood clinic in Chicago a few weeks after my 18th birthday and asked for testosterone to medically transition. No clinician asked me what was behind my desperation to change my body. The clinician prescribed me testosterone that day without any blood work or medical evaluation because I seemed "so sure" about my decision. I told the clinicians that I wanted a high dose so I would see more changes in my body. They agreed and prescribed me 100mg of testosterone per week.

12. The mental health effects of testosterone were profound. I began experiencing uncontrollable episodes of rage and paranoia, where I was a danger to myself and others. I self-harmed more and became suicidal. Due to this, I was hospitalized twice. No prescribing ever mentioned these side effects of testosterone. Instead, I was prescribed a litany of psychiatric drugs. This time was so dark that it caused me to question the original promises of a joyful trans life.

13. In February 2018, I stopped taking testosterone and began the journey of detransitioning. My mysterious mental illness went away soon after and has never returned.

14. I am grateful that I spent only a short time on testosterone and am fortunate I haven't experienced any obvious physical injuries. But the impact this experience has had on my life cannot be understated. I became a danger to myself and others under the influence of testosterone. I struggled to process my new reality and face these mental health issues.

15. I am very thankful that my mother did not consent to giving me testosterone as a teenager. If I had transitioned as a minor, I could have spent a lot more time taking it. Because of her decision, I can now have a healthy relationship with my body.

16. Tennessean children are lucky that its legislature has seen these dangers of "gender affirmation" and created a law to allow kids to grow into their natural bodies first before making a life-altering decision.

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

Executed on May 19, 2023.

/s/ Helena Kershner
Helena Kershner

EXHIBIT 13

IN THE UNITED STATES DISTRICT COURT FOR THE MIDDLE DISTRICT OF TENNESSEE NASHVILLE DIVISION

L.W., et al.,	)	
	)	
Plaintiffs,	)	
	)	
v.	)	No. 3:23-cv-00376
	)	Judge Richardson
JONATHAN SKRMETTI, et al.,	)	
	)	
Defendants.	)	

DECLARATION OF PRISHA MOSLEY

I, Prisha Mosley, declare as follows:

1. I am a 25-year-old woman who has suffered severe and lasting injuries because I was subjected to so-called "gender-affirming care" as a minor. This "care" included medical intervention to make my body appear as that of a male.

2. I support the legislation under challenge in this case known as Senate Bill 1.

3. If legislation like Senate Bill 1 had been in place when I was a minor in my home state of North Carolina, I would have been protected from the healthcare providers who irreversibly harmed my body in order to make it look more like a boy's.

4. As a teenager, I suffered from a number of mental health issues, including anorexia, obsessive-compulsive disorder, borderline personality disorder, anxiety, and depression. I also engaged in self-harm and suffered trauma from sexual assault.

5. At age 17, after meeting with me for a matter of minutes, a counselor told me that I was actually a boy and that changing my body to be more like a boy's would fix my mental health issues. Around that same time, a doctor prescribed testosterone for me as "gender-affirming care" to make my body look more like a boy's body.

6. Less than six months later, while I was still 17, a surgeon familiar with breast reduction surgery for women met with me and expressed eagerness in performing gender-affirming "top surgery" on me. At age 18, the surgeon performed a double mastectomy, removing my healthy breasts.

7. These healthcare providers, whom I trusted to take care of me, misled me into believing that changing my body to look more like a boy's body would solve my mental/psychological problems.

8. As a result of these healthcare providers' actions, I have suffered severe and lasting injuries. These injuries are both psychological and physical in nature.

9. My body did not develop the way it should have and does not function normally. I am unable to nurse a child and I do not know if I will be able to conceive and give birth to a child.

10. I suffer from chronic pain and a host of additional medical issues and psychological and emotional anguish as a result of the medical and surgical abuse that I was led into by the healthcare providers who were supposed to take care of me.

11. I feel strongly that what happened to me should not have happened, and it should not happen to anyone else. That is why I support Senate Bill 1.

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

Executed on ___05/19/2023_____.
Date

___s/Prisha Mosley_____
Prisha Mosley

EXHIBIT 14

IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF TENNESSEE
NASHVILLE DIVISION

L.W. et al., *by and through her parents and next friends, Samantha Williams and Brian Williams*,	)	
Plaintiffs,	)	No. 3:23-cv-00376 JUDGE RICHARDSON
v.	)	
JONATHAN SKRMETTI et al.,	)	
Defendants.	)	

DECLARATION OF BARBARA F.

I, Barbara F.,1 declare as follows:

1. I am over the age of 18 years and am not a party to this action. I have actual knowledge of the following facts and, if called upon to testify to them, could and would do so competently. I am submitting this Declaration in support of Defendants' opposition to Plaintiffs' Motion for a Preliminary Injunction.

2. Tennessee recently passed a law prohibiting hormonal and surgical procedures "for the purpose of: (A) Enabling a minor to identify with, or live as a purported identity inconsistent with the minor's sex, or (B) Treating purported discomfort or distress from a discordance between the minor's sex and asserted identity," Tenn. Code Ann. § 68-33-101, *et seq*. This Act will protect parents against confused children, ex-spouses, and providers' coercive tactics to obtain consent to medical interventions "affirming" a child's professed discordant gender identity—through methods such as threatening alienation or loss of a child through suicide.

3. There is no such parent and child-protective law in my home state, where "gender-affirming" providers and clinicians have blatantly disregarded my decisions related to my child's medical and mental health. Tennessee's law will prevent its parents and children from suffering harm like mine and my daughter's.

4. When my daughter, B, was young, her father (my ex-husband) gave B's brother preferential treatment. B's father also ridiculed her for having traits similar to mine, such as the way we both laugh.

1 Declarant is submitting this Declaration using a pseudonym to protect the privacy of her children and other family members.

5. When B was 11 years old, she told me she identified as a boy and wanted me to call her by a male name she had chosen. B's father championed her new "male" identity and harassed me for not affirming it. He accused me of emotional abuse and called child protection services against me. B's father convinced B to avoid visiting me under our custody agreement unless I affirmed the discordant identity.

6. Shortly after B announced that she identified as a boy, I acted on the advice of our family physician and took B to a gender clinic. I naively believed that the clinic's psychologist would evaluate and provide counseling to discuss B's sudden identification as a boy before medical intervention to "affirm" her choice.

7. When we arrived at the clinic, the staff psychologist did an evaluation. However, the psychologist also said she did not have time to see B regularly for more in-depth psychological help. I told the clinic staff that B needed psychological counseling before starting any medical interventions (i.e., seeing an endocrinologist). As a parent, I was confused why there were two different offices: Why would we visit with an endocrinologist if the psychologist (as a gatekeeper) isn't prioritizing seeing my child regularly? I was instantly troubled by the clear lack of any regard for my child's underlying comorbidities. I could picture my child on a conveyor belt, as if she was just one more coin in their purse.

8. That same day, the clinic left me alone in a room for 2 hours. While I waited, I thought the psychologist was talking to my child, and then my ex-husband. However, it turned out that B and her father secretly met with the clinic's endocrinologist without my knowledge or consent to discuss starting her puberty blockers. After their secret meeting, the endocrinologist returned to my room to speak with me and my daughter to "get me on board" with the treatment.

9. I had researched puberty blockers and cross-sex hormone therapy and was concerned about their unproven safety and efficacy. When I raised these concerns, the endocrinologist said no studies show that the drugs aren't safe. She also told me in front of my daughter that I needed "to get on board if I don't want my daughter to commit suicide."

10. My ex-husband and I have shared decision-making authority for our children's medical care. I have repeatedly notified clinic staff, orally and in writing, that I do not consent to them treating B. The clinic staff ignored my directions.

11. The clinic and B's father have continued with regular consultations with my daughter without my consent. I have reviewed documents from the clinic where staff noted that they plan to "convince me" to consent to the medical interventions. The notion of "informed consent" or parental decision-making was non-existent.

12. The availability and promotion of "gender-affirming" medical intervention for minors were used to drive a wedge between B and me, preventing B from receiving counseling for underlying mental health issues and exposing her to unknown long-term medical and mental health consequences without my consent.

13. Tennessee's Act prevents such coercive manipulation and potential harm against its vulnerable children and should be upheld to protect children and their families.

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

Executed on May 18, 2023.

*/s/ Barbara F.*_____
Barbara F. (pseudonym)

EXHIBIT 15

IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF TENNESSEE
NASHVILLE DIVISION

L.W. et al., *by and through her parents and next friends, Samantha Williams and Brian Williams,*	)	
Plaintiffs,	)	No. 3:23-cv-00376 JUDGE RICHARDSON
v.	)	
JONATHAN SKRMETTI et al.,	)	
Defendants.	)	

DECLARATION OF JOHN STILES

I, John Stiles,[1] declare as follows:

1. I am over the age of 18 years and am not a party to this action. I have actual knowledge of the following facts and, if called upon to testify to them, could and would do so competently. I am submitting this Declaration in support of Defendants' opposition to Plaintiffs' Motion for a Preliminary Injunction.

2. Tennessee recently passed a law prohibiting medical procedures performed on minors "for the purpose of: (A) Enabling a minor to identify with, or live as a purported identity inconsistent with the minor's sex, or (B) Treating purported discomfort or distress from a discordance between the minor's sex and asserted identity," Tenn. Code Ann. § 68-33-101, *et seq*. This Act will provide parents with necessary protections against manipulation and coercion on the part of health care providers, ex-spouses, and confused children to comply with demands for medical and surgical interventions aimed at "affirming" a child's professed discordant gender identity under threats of alienation or loss of a child to suicide.

3. No such parent and child-protective law exists in my home state. Providers have blatantly disregarded my decisions for my child's medical and mental health. Tennessee's Act will prevent its parents and children from suffering similar harm. It will restore the rights of all parents, not only those who agree with demands for "gender-affirming" medical interventions.

4. I am the father of an 18-year-old son, C (pseudonym), who had received medical treatment from the University of California San Francisco ("UCSF") Child & Adolescent Gender Center as a minor. UCSF had actively worked to prevent my participation in my son's care to the

[1] Declarant is submitting this Declaration using a pseudonym for himself and his son to protect the privacy of his child and family.

point of providing information to the attorney representing my son in family court aimed at stripping me of custody because I would not affirm my son in a discordant gender identity.

5. In fact, I knew nothing about my son receiving life-altering medical interventions until I received a statement from my insurance carrier showing that it had paid more than $209,000 to a child and adolescent gender clinic at UCSF. He was 17 years old. Even then, I did not know what the payment was for until I asked my ex-wife. She emailed me that she was "pleased" to report that our son had been given an implant of Supprelin (used to suppress testosterone) and was receiving estradiol (estrogen) pills.

6. My research on these substances showed that they chemically castrate patients and are even used specifically for that purpose in some cases for sex offenders. Yet, here my 17-year-old son was receiving these drugs from the gender clinic ostensibly to improve his health and well-being.

7. I have learned that Supprelin, a popular method for administering puberty blockers for adolescents like my son, requires surgical implantation. It is a surgical intervention administered to children under the age of 18, which is contrary to any testimony that surgical interventions are not prescribed for minors and not recommended by the "Standards of Care."

8. The surgical implantation of Supprelin into my son violated the family court's custody order, which stated that my son was not permitted to "undergo any gender identity related surgery" until he turned 18, absent a written agreement of both parents or order of the court, which UCSF had a copy of and made a record of the family court's custody order in C.'s patient notes. I did not agree to the surgical implantation, nor is there any court order permitting it. Yet, C.'s records show a surgical procedure performed on him to insert the Supprelin.

9. After UCSF surgically implanted my 17-year-old son with Supprelin LA (without my knowledge or consent, but paid for by my health insurance), UCSF clinicians discussed follow-up surgical options with him without both parents present, including breast implants, facial feminization, and bottom surgery. At the time, my son was 17 years and 5 months old.

10. C.'s patient notes state that his "family was involved in complex family custody case" and that I "adamantly opposed C.'s transition." This is not true. I would not oppose C.'s transition if it were medically safe for him to do so. However, my research showed significant evidence that medical transitioning is very unsafe.

11. I sought the information necessary to make an informed decision on my son's treatment. I asked UCSF clinicians about the safety of these treatments, citing the alarming research I found concluding that puberty blockers when administered to a minor, cause permanent damage to the child. The providers did not attempt to respond to my questions. UCSF failed to ease my concerns in the face of this glaring evidence that the treatments cause permanent harm when administered to minors. Instead of receiving an answer, UCSF squarely aimed to strip me of custody by apprising the family court that I questioned its protocols.

12. Similarly, I emailed UCSF's lead physician, providing him with research that I had found which suggests that puberty blockers can cause cognitive harm. After one year had passed, the physician finally acknowledged my email but still failed to provide me with any substantial feedback about my concerns for my son's safety.

13. UCSF concluded that C. gave informed consent. Yet, the form the clinicians provided C., my then 16-year-old son, did not indicate that permanent and irreversible sterility is a potential and likely outcome of the recommended treatment, particularly when puberty blockers

are combined with estrogen, as is the case with C. The form merely indicated that the treatments "might" impact his fertility.

14. However, the day after C. gave UCSF his "informed consent," they banked his sperm: collecting, freezing, and storing his sperm for future use. I contend that UCSF's actions were motivated by the possibility that these treatments would make C. infertile.

15. My experiences with UCSF point to an ideologically driven conveyor belt onto which vulnerable children like my son are placed and processed without the safeguards usually inherent in medical procedures.

16. Parental participation is tolerated only so long as it affirms the ideology. If, as in my case, the parent asks questions instead of immediately affirming the agenda, then that parent is disregarded even to the point, as in my case, of having their rights stripped away. Parent participation assists in closing the significant power differential between physicians and minors.

17. The availability of "gender-affirming" medical interventions for vulnerable children experiencing distress about changes in their bodies enables the ideological conveyor belt to proceed unhindered, leaving in its wake sterilized, drug-dependent and dysfunctional young adults, shattered relationships, and distrust in the medical profession.

18. Tennessee's efforts through its recent legislation to ban these treatments for minors is necessary to prevent the irreversible and incalculable harms caused by the unchecked gender medicine machine. The Act will save Tennessee families from similar devastation.

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

Executed on May 19, 2023.

/s/ John Stiles
John Stiles (pseudonym)

EXHIBIT 16

IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF TENNESSEE
NASHVILLE DIVISION

L.W. et al., *by and through her parents and next friends, Samantha Williams and Brian Williams,*	)	
Plaintiffs,	)	No. 3:23-cv-00376 JUDGE RICHARDSON
v.	)	
JONATHAN SKRMETTI et al.,	)	
Defendants.	)	

DECLARATION OF KELLIE C.

I, Kellie C.,[1] declare as follows:

1. I am over the age of 18 years and am not a party to this action. I have actual knowledge of the following facts and, if called upon to testify to them, could and would do so competently. I am submitting this Declaration in support of Defendants' opposition to Plaintiffs' Motion for a Preliminary Injunction.

2. Tennessee recently passed a law prohibiting medical procedures performed on minors "for the purpose of: (A) Enabling a minor to identify with, or live as a purported identity inconsistent with the minor's sex, or (B) Treating purported discomfort or distress from a discordance between the minor's sex and asserted identity," Tenn. Code Ann. § 68-33-101, *et seq*. This Act will provide parents with necessary protections against manipulation and coercion on the part of health care providers, ex-spouses, and confused children to comply with demands for medical and surgical interventions aimed at "affirming" a child's professed discordant gender identity under threats of alienation or loss of a child to suicide.

3. No such parent and child-protective law exists in my home state. Providers have used coercion and manipulation to obtain my consent or blatantly disregarded my decisions for my child's medical and mental health. Tennessee's Act will prevent its parents and children from suffering similar harm. It will restore the rights of all parents, not just those who agree with demands for "gender-affirming" medical interventions, to make medical and mental health care decisions for their children following their natural, healthy development.

4. My daughter, D., became involved in fan fiction at age 11, around the time she began puberty. By age 13, D. had diagnosed herself with gender dysphoria and began identifying

[1] Declarant is submitting this Declaration using a pseudonym to protect the privacy of her children and other family members.

as a 17-year-old male character from Harry Potter. For several years, D. celebrated the birthday of the fictional identity and, at age 17, identified as a 23-year-old male.

5. D. underwent a psychiatric evaluation which found that she is delusional and incapable of caring for herself. She is on the autism spectrum and has OCD and possibly ADHD, but she is not psychotic. The evaluation team admits that D. identifies as a 23-year-old man and proclaims that she has Dissociative Identity ("multiple personality") Disorder. The psychiatric team does not believe she has DID, but that D. has researched DID and is using it as a maladaptive coping tool for working through the childhood trauma of being sexually assaulted at age 13 or 14.

6. D. is in a residential treatment center. The treatment team has not engaged in therapy with D. to address her underlying issues. Instead, they have embraced her delusion that she is a 23-year-old fictional male character with a transgender identity. The therapists reiterate that they want D. to feel "safe," so they will not address any underlying issues unless D. brings it up on her own.

7. D. has asked for puberty blockers and testosterone. Despite her myriad co-morbidities and unaddressed sexual trauma, the treatment team said that D. is ready for "gender-affirming" medical interventions. The therapists and psychologists have told me that if I do not consent, I "will have a dead daughter instead of a 'live son.'" The providers constantly tell me I must "get on board" with what D wants.

8. The therapists and D.'s father told her that my refusal to consent was the only thing standing in the way of her getting those treatments. As a result, my daughter has alienated me, and I have been banned from knowing her medical status.

9. Today, D. is 19. As far as I know, D. never received puberty blockers or cross-sex hormones. Five months ago, D's younger brother, age 17, told me that D. no longer identifies as the 17-year-old fictional character from Harry Potter. Now, D bounces back and forth to multiple characters, calling herself "AND-I." It's expected that everyone embraces D.'s ever-changing pronouns and various personas, including the "transgender" aspect of any given character.

10. Tennessee's Act protects its vulnerable children by making these medical interventions unavailable. The Act will also prevent the harm inflicted on parents who fight to defend their mentally disturbed children from irresponsible healthcare providers. It is a necessary regulation that should be upheld for the protection of children and their families.

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

Executed on May 18, 2023.

*/s/ Kellie C.*_____
Kellie C. (pseudonym)

EXHIBIT 17

IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF TENNESSEE
NASHVILLE DIVISION

L.W. et al., *by and through her parents and next friends, Samantha Williams and Brian Williams,*	)	
Plaintiffs,	)	No. 3:23-cv-00376 JUDGE RICHARDSON
v.	)	
JONATHAN SKRMETTI et al.,	)	
Defendants.	)	

DECLARATION OF ROBERT ROE

I, Robert Roe,[1] declare as follows:

1. I am over the age of 18 years and am not a party to this action. I have actual knowledge of the following facts and, if called upon to testify to them, could and would do so competently. I am submitting this Declaration in support of Defendants' opposition to Plaintiffs' Motion for Preliminary Injunction.

2. I am an Alabama resident and the father of a son who said he was gender dysphoric, socially transitioned at school without my or my wife's knowledge, and was referred for "gender transition" medical treatments.

3. Tennessee's law prohibiting medical procedures performed on minors "for the purpose of: (A) Enabling a minor to identify with, or live as a purported identity inconsistent with the minor's sex, or (B) Treating purported discomfort or distress from a discordance between the minor's sex and asserted identity," Tenn. Code Ann. § 68-33-101, *et seq*., will protect vulnerable children from providers and third parties secretly interfering in their medical care decisions like I experienced.

4. My son, J, was diagnosed with ADHD and anxiety. He never expressed any distress about his sex until middle school. During that time, J spent a lot of time online and was interested in anime and role-playing games. He also became friends with a girl who identified as transgender.

5. Between 8th and 9th grade, J left a note for his mother stating that he was "transgender" and signed it "your daughter." Later, J told his mother that he "felt more female than male." J left me a similar note saying he had gender dysphoria for as long as he could remember.

1 Declarant is submitting this Declaration using a pseudonym to protect the privacy of his children and other family members.

6. During a therapy session, J said he started feeling that he was transgender in the 8th grade and that his "research" online confirmed his feelings. I learned that this "research" consisted of watching YouTube videos of internet trans influencers, and that he had self-diagnosed by answering online questionnaires.

7. In 9th grade, J's public school facilitated J's social transition to a female gender identity without my or my wife's knowledge or consent. The school began calling J by a female name and referring to J by female pronouns. I learned, by accident, through communication with a teacher about an art project.

8. I believe that the school instituted its own therapy plan for J by interfering with his gender questioning. However, parents should agree on any therapy plans for minors before implementing them.

9. We took J to a therapist, who diagnosed him with OCD, anxiety, depression, and ADHD. The therapist did not do a psychological evaluation on J.

10. During a family therapy session, the therapist focused solely on gender dysphoria and did not mention J's other comorbidities. The therapist printed out a handout from an advocacy group. The therapist said that kids have a sense of their gender identity by age 3 or 4. She tried to convince my wife and me to let J take the lead on the diagnosis and medical treatment.

11. After the third or fourth visit, the therapist recommended that we take J to a gender clinic to receive puberty blockers or cross-sex hormones. While J was present, the therapist told us that kids are more likely to attempt suicide and run away from home if their parents do not affirm their chosen identity.

12. We cut ties with the therapist and did not follow her recommendation. Afterward, I got tired of attempting to find a therapist to look at the big picture instead of focusing only on J's gender issues. As many parents in my situation will say, "No therapy is better than bad therapy."

13. J struggled with self-esteem, and I believe his comorbidities amplified this. It was not clear that medical intervention would solve his underlying issues. I thought the interventions were permanent changes with life-long consequences to J's body for a problem that a less invasive route could solve.

14. Today, J is 19 years old. He has never received puberty blockers or cross-sex hormones. While he still identifies as transgender, he maintains conventionally masculine mannerisms and features. J has not shown any interest in medical transitioning even though he is an adult and could get the hormones by going to any Planned Parenthood or local gender clinic.

15. I hope J lives as his biological sex until his prefrontal cortex fully develops. That way, he can develop into a healthy body before deciding to medically transition.

16. A total ban on these treatments for children, such as provided in Tennessee's Act, is necessary to regulate medical professionals' protocol and to prevent adolescents from harming themselves and their future.

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

Executed on May 18, 2023.

*/s/ Robert Roe*_____
Robert Roe (pseudonym)

EXHIBIT 18

IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF TENNESSEE
NASHVILLE DIVISION

L.W. et al., *by and through her parents and next friends, Samantha Williams and Brian Williams,*	)	
Plaintiffs,	)	No. 3:23-cv-00376 JUDGE RICHARDSON
v.	)	
JONATHAN SKRMETTI et al.,	)	
Defendants.	)	

DECLARATION OF YVONNE YOE

I, Yvonne Yoe,[1] declare as follows:

1. I am over the age of 18 years and am not a party to this action. I have actual knowledge of the following facts and, if called upon to testify to them, could and would do so competently. I am submitting this Declaration in support of Defendants' opposition to Plaintiffs' Motion for a Preliminary Injunction.

2. Tennessee recently passed a law prohibiting medical procedures performed on minors "for the purpose of: (A) Enabling a minor to identify with, or live as a purported identity inconsistent with the minor's sex, or (B) Treating purported discomfort or distress from a discordance between the minor's sex and asserted identity," Tenn. Code Ann. § 68-33-101, *et seq*. This Act will provide parents with necessary protections against manipulation and coercion on the part of health care providers, ex-spouses, and confused children to comply with demands for medical interventions aimed at "affirming" a child's professed discordant gender identity under threats of alienation or loss of a child to suicide.

3. I am a resident of the State of Tennessee. My daughter, Z, received treatment from a local eating disorder therapist who encouraged me to affirm her discordant gender identity. I fear that my daughter's medical providers will blatantly disregard my decisions for my child's medical and mental health. Tennessee's Act will prevent parents, like me, and children, like my daughter, from suffering harm. It will restore the rights of all parents, not just those who agree with demands for "gender-affirming" medical interventions, to make medical and mental health care decisions for their children following their natural, healthy development.

[1] Declarant is submitting this Declaration using a pseudonym to protect the privacy of her children and other family members.

4. Growing up, my daughter, Z, never hinted that she had issues with her gender identity. However, Z suffers from several comorbidities, including learning disabilities, anxiety, depression, self-harm, anorexia, and body dysmorphia. She also suffered from bullying and online sexual abuse.

5. In 2020, Z saw an eating disorder therapist. She was battling anorexia and was near the point of being hospitalized.

6. Around that time, Z announced that she was transgender. She was 12 years old. I was completely blindsided, so I spoke with her therapist privately. The therapist told me that Z suggested she had felt she was transgender for 3 years. The therapist hinted that I should affirm her.

7. My daughter has severe dyscalculia, a learning disability that causes her to struggle understanding space in time. Therefore, 3 years could mean 10 years or even 3 weeks.

8. My daughter had never hinted that she had gender dysphoria before this announcement.

9. The therapist was aware that Z had never questioned her gender before. I was shocked that the therapist blindly took her word for it knowing about her comorbidities.

10. I poured myself into research and was completely horrified that no randomized clinical trials on gender-affirming therapy and medical procedures existed. There is absolutely no data to support the safety of these medical treatments on minors. I quickly realized that because I questioned my daughter's trans identity, I was considered closed-minded and bigoted. I could be accused of psychological abuse for not 100% affirming Z's new identity.

11. I became paralyzed trying to find Z the help she needed. I was scared to speak to her Vanderbilt-affiliated pediatrician and afraid to have her sit one-on-one with a therapist. I felt so betrayed by the medical profession. I felt that, at every corner, a provider or clinician would encourage my daughter to transition, ultimately ending with unnecessary and harmful medical treatments without my consent.

12. I ended up cutting ties with the eating disorder therapist. I knew it was a gamble because Z was so new to her eating disorder recovery. Still, I did not want to risk more damage that may be caused by her beloved therapist affirming her while I was non-affirming due to my own research of the literature.

13. As a parent who understands the current research available, I am infuriated that I cannot obtain the help my child needs based on the same rigors necessary to establish a standard of care in every other area of medicine. Through developing relationships and connections with parents like me, I ultimately found a therapist in Dublin, Ireland, to work with her. Z saw the therapist via Zoom for about a year.

14. Today, Z is well and only needs to see her therapist on an as-needed basis. However, I fear her needing further care for her anorexia or any other health issue that may pop up due to the current gender-affirming political and clinical environment.

15. I also cannot get the mental health care I need to process this challenging situation emotionally. Every single parent I have met in Tennessee dealing with this feels the same way. We are struggling to find help.

16. Tennessee's Act protects its vulnerable children by making these medical interventions unavailable. The Act will also prevent the harm inflicted on parents who fight to

defend their mentally disturbed children from irresponsible healthcare providers. It is a necessary regulation that should be upheld for the protection of children and their families.

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

Executed on May 19, 2023.

*/s/ Yvonne Yoe*_____
Yvonne Yoe (pseudonym)

EXHIBIT 19

IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF TENNESSEE
NASHVILLE DIVISION

L.W. et al., *by and through her parents and next friends, Samantha Williams and Brian Williams,*	)	
Plaintiffs,	)	No. 3:23-cv-00376 JUDGE RICHARDSON
v.	)	
JONATHAN SKRMETTI et al.,	)	
Defendants.	)	

DECLARATION OF JOHN NOAKES

I, John Noakes,[1] declare as follows:

1. I am over the age of 18 years and am not a party to this action. I have actual knowledge of the following facts and, if called upon to testify to them, could and would do so competently. I am submitting this Declaration in support of Defendants' opposition to Plaintiffs' Motion for a Preliminary Injunction.

2. Tennessee recently passed a law prohibiting hormonal and surgical procedures "for the purpose of: (A) Enabling a minor to identify with, or live as a purported identity inconsistent with the minor's sex, or (B) Treating purported discomfort or distress from a discordance between the minor's sex and asserted identity," Tenn. Code Ann. § 68-33-101, *et seq*. This Act will protect parents against confused children, ex-spouses, and providers, whose coercive tactics to obtain consent to medical interventions "affirming" a child's professed discordant gender identity include threatening alienation or loss of a child through suicide.

3. I am a resident of the State of Tennessee, along with my 20-year-old daughter, B, who recently identified as transgender. However, B had never suggested that she had issues with her gender before. She was a "girly girl." She did gymnastics and ballet, and happily wore a pink tutu.

4. Growing up, my daughter, B, and I had a good relationship. However, my relationship with B changed after her mother and I divorced. B was about 13 years old at this time. Initially, visitation was regular and normal. However, as time went on, I did not see her as much due to the distance created by the divorce.

[1] Declarant is submitting this Declaration using a pseudonym to protect the privacy of his children and other family members.

5. After B turned 16, I saw her only a handful of times the following year. It became increasingly difficult for B to deal with her mother whenever she visited me.

6. I invited B over right before she was about to turn 17 years old to celebrate her birthday. It was the first time I had seen her in months. When B arrived, I was completely shocked. She had given herself a buzz cut and was dressed like a boy.

7. B announced that she was transgender. She told me that she identified as a boy and wanted me to call her by a new name she had chosen. This was the first time I learned that B was experiencing issues with her gender identity.

8. B handed me papers from the Vanderbilt University Medical Clinic ("VUMC"). She had been to VUMC's gender clinic and saw Dr. Cassandra Brady. My ex-wife had taken her and had not informed me about the appointment. B's mother supported her new male gender identity.

9. B told me she wanted me to sign these papers, giving my consent and approval for her to receive testosterone shots from Vanderbilt. Her request overwhelmed me, and I wanted to speak with her doctor.

10. B and my ex-wife pressured me to sign immediately. Dr. Brady had told them about the risk of suicide if they chose not to administer medical treatments. They both told me that if B committed suicide, it would be all my fault. However, I needed more information before signing. My gut told me that something was not right. B and her mother said everything would make sense once I talked to Dr. Brady.

11. So, I called Dr. Brady at VUMC. Dr. Brady told me she was "so sure" that B was a good candidate. Dr. Brady said that kids as young as 5 to 7 years old come to the clinic and that the physicians know right away if the kids are good candidates for medical treatments.

12. Dr. Brady said that kids question their gender as early as 5 to 7 years old, and when these kids come into the clinic, the physicians know right away if the kids are good candidates for medical treatments. The concept that a child would know they are transgender that young was completely absurd. Still, I challenged Dr. Brady's suggestion and told her that when B was younger, she never acted like a boy, did girly things, and never suggested she was uncomfortable in her body. I ended the call when it became clear that Dr. Brady did not care about my experiences with and observations of B as a child that clearly identified as female.

13. Ultimately, I could not agree to the medical treatments. I was concerned about the permanent harm it might have on her body. I wanted to wait for her at least to turn 18 so she could have more time to develop. The possibility that she might change her mind was very real. This change happened so quickly that she could easily change her mind.

14. Dr. Brady's promotion of "gender-affirming" medical intervention for minors was used to drive a wedge between me and my daughter. For the next year, until B turned 18, B and her mother harassed me for not affirming her gender or consenting to the treatments. B has since completely alienated me from her life. I have no idea if she has received medical treatments or continues to visit VUMC.

15. Tennessee's law will prevent its parents from suffering harm like mine. It will also help prevent coercive manipulation and potential harm against its vulnerable children and should be upheld to protect children and their families.

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

Executed on May 19, 2023.

/s/ John Noakes
John Noakes (pseudonym)

EXHIBIT 20

IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF TENNESSEE
NASHVILLE DIVISION

L.W. et al., *by and through her parents and next friends, Samantha Williams and Brian Williams*,	)	
Plaintiffs,	)	No. 3:23-cv-00376 JUDGE RICHARDSON
v.	)	
JONATHAN SKRMETTI et al.,	)	
Defendants.	)	

DECLARATION OF JAMIE REED

I, Jamie Reed, declare as follows:

1. I am an adult, I am under no mental incapacity or disability, and I know that the following facts set forth are true because I have personal knowledge of them. I am submitting this Declaration in support of Defendants' Opposition to Plaintiffs' Motion for a Preliminary Injunction and Complaint.

2. Tennessee's law prohibiting hormonal and surgical procedures "for the purpose of: (A) Enabling a minor to identify with, or live as a purported identity inconsistent with the minor's sex, or (B) Treating purported discomfort or distress from a discordance between the minor's sex and asserted identity," Tenn. Code Ann. § 68-33-101, *et seq*., is necessary to support children's health and welfare and to protect the medical profession's integrity and public respect.

3. I hold a Bachelor of Arts in Cultural Anthropology from the University of Missouri St. Louis and a Master of Science in Clinical Research Management from Washington University. I have worked at Washington University for seven years. I initially worked with HIV-positive patients, caring for many transgender individuals. From 2018 until November 2022, I worked as a case manager at the Washington University Pediatric Transgender Center ("the Center") at St. Louis Children's Hospital. My duties included meeting with patients two to three days a week and completing the screening triage intake of patients referred to the Center.

4. I have experience and expertise working with transgender individuals and pediatric populations. I accepted the job at the Center because I firmly believed I could provide quality care for children there. Instead, I personally witnessed children experience shocking injuries from puberty blockers and cross-sex hormones, which often were prescribed to them without complete informed parental consent or an accurate assessment of the child's needs. To my knowledge, the

Center did not track patients' adverse outcomes post-discharge. I left the Center in November 2022 after having raised concerns internally for years.

5. During my time at the Center, I was required to schedule patients to the Endocrinology or Adolescent Medicine practice based on their age and stage of puberty. Generally, Psychology was primarily only available to write patients' letter of support for medical transition treatments instead of ongoing therapy. Psychiatry was limited to patients "not too severe" to avoid the already overburdened emergency room for patients suffering suicidal ideations and self-harm or requiring inpatient eating disorder treatment.

6. On my own initiative, I tracked certain patients on a case-by-case basis. I was concerned that Center doctors were prescribing cross-sex hormones and puberty blockers to children who were not good candidates. I created a "red flag" list of children where other staff and I had concerns. Ultimately, Center doctors sent these children to our in-house therapists, and those therapists inevitably provided letters to the doctors. Center doctors told me I had to stop raising these concerns, and I was no longer allowed to maintain the red flag list. I also wanted to track the number of our patients who detransitioned, attempted suicide, or committed suicide. The Center would not make these tracking systems a priority.

7. From 2020 to 2022, the Center initiated medical transition for more than 600 children and adolescents. Approximately 74% of these patients were assigned female at birth. One biologically female patient on cross-sex hormones called the Center after having sexual intercourse and experiencing severe vaginal lacerations as a result. Patient bled through a pad, pants, and a towel wrapped around their waist. Ultimately, Patient required surgical treatment in St. Louis Children's Hospital emergency room. I have heard from minor patients given testosterone that

their clitorises have grown so large that they now constantly chafe against their pants, causing them pain when they walk.

8. Nearly all children and adolescents who came to the Center presented with severe comorbidities, including autism, ADHD, depression, anxiety, PTSD, trauma histories, OCD, and eating disorders. Many were prescribed puberty blockers or cross-sex hormones. For example:

a. Patient came to the Center identifying as a "communist, attack helicopter, human, female, maybe nonbinary." Patient was in poor mental health and reported early on that they had no idea of their gender identity. The Center prescribed Patient cross-sex hormones. Patient subsequently reported that their mental health worsened.

b. Patient was in a residential sex offender treatment facility in state custody. Patient had previously sexually abused animals and had stated that they would do so again when released. There were questions about the consistency of gender history. The Center prescribed Patient cross-sex hormones.

c. Patient had severe Obsessive Compulsive Disorder and threatened to self-harm their genitals. Patient did not have a trans or other incongruent gender identity. The Center prescribed Patient cross-sex hormones to reduce libido and sexual arousal chemically.

d. Patient had a history of sexual abuse and notified the psychologist of this. Documented in the letter of support were Patient's concerns about the changes that testosterone would cause to their genitals. The Center prescribed Patient testosterone.

e. Patient had severe mental health concerns and was prescribed psychiatric medications. Patient failed to take these prescriptions. The Center nonetheless prescribed Patient cross-sex hormones.

f. Patient had significant autism with unrealistic expectations, struggled to answer questions, and wanted questions provided ahead of time. The Center prescribed Patient feminizing hormones.

g. Patient had a mental health history that included violent tendencies. Parent forced Patient to cross-dress. The Center prescribed Patient feminizing hormones.

h. Patient was on cross-sex hormones and had decompensating mental health, outlandish name changes, and a self-diagnosis of multiple personalities. The Center continued prescribing Patient cross-sex hormones.

i. Patient believed that their prescribed testosterone was poisoning them and stopped for a period. Patient had significant serious mental health issues. The Center continued prescribing Patient testosterone.

j. A 17-year-old Patient arrived at the Center with non-relative man who had been living with Patient. One year later, the Center prescribed Patient hormones. Patient's mental health deteriorated. Patient visited the Emergency Department and disclosed that the non-relative man that had brought them to the clinic had been sexually and physically abusing them. The Center continued Patient's medical transition treatment.

k. Patient was in residential facility, in foster care. The Center convinced the facility staff to allow Patient to start testosterone. Patient ran away numerous times from the facility and began having unprotected intercourse while on testosterone. The Center continued prescribing Patient testosterone.

l. Patient admitted that their parent encouraged them to start taking testosterone at 11-years-old because they were moving to a state that the parent believed would restrict

Patient's care in the future. Patient had desisted in male identity to a vague nonbinary. Patient changed their name numerous times and struggled with thoughts about desistence, even saying they wanted breast development. The Center continued prescribing Patient testosterone.

m. Patient on cross-sex hormones was evaluated for OCD and a somatization disorder with "seizure" activity. The Center continued prescribing Patient cross-sex hormones.

n. Patient on cross-sex hormones stopped taking their schizophrenia medications without consulting a doctor. The Center continued prescribing Patient cross-sex hormones.

9. I witnessed puberty blockers worsen patients' mental health. Several children that had never contemplated suicide attempted suicide after taking puberty blockers. Similarly, many patients with depression and anxiety symptoms became more severe after starting cross-sex hormones. The Center did not require children to continue with mental health care after they prescribed cross-sex hormones or puberty blockers. The Center continued treatment despite patients reporting worsening mental health.

10. The Center had four basic requirements to place a child on puberty blockers or cross-sex hormones: age or puberty stage, therapist letter, parental consent, and a clinical visit. In practice, every patient who met these minimum criteria was prescribed cross-sex hormones or puberty blockers.

11. First, the Center required that the child be at a certain age or stage of puberty. Puberty stages were measured according to the Tanner Stage system. When I was at the clinic, the World Professional Association for Transgender Health ("WPATH") Standard of Care Version 7

recommended that children be at least 16 years old before starting cross-sex hormones. The Center routinely prescribed cross-sex hormones to children as young as 13.

12. Second, the Center required the child to have a therapist referral letter authorizing medical treatment. Supposedly, this requirement ensured that two independent professional clinicians agreed that medical transition was appropriate before giving the child medication. The Center would recommend therapists it knew would offer children a letter supporting medical transition. If the child did not receive a letter from an outside therapist authorizing puberty blockers or cross-sex hormones, we would send the patient to the Center's in-house therapists. I was instructed to draft and send language to the therapists for them to use for letters supporting medical transition. Most therapists had a template letter drafted by the Center. Many therapists on the Center's list would return letters supporting medical transition after 1-2 hours with a patient.

13. Third, the Center required parental consent. But parents routinely said they felt they were pressured to consent. I was present during visits where Center doctors obtained consent by telling the parent of a child assigned female at birth, "You can either have a living son or a dead daughter," or parents of a child assigned male at birth, "You can either have a living daughter or dead son."

14. The Center did not inform parents or children of all known side effects before placing children on cross-sex hormones or puberty blockers. Center doctors knew that many of its former patients had stopped taking cross-sex hormones and were detransitioning. Doctors did not share this information with parents or children. The Center nurse and I expressed concerns about one patient's intellectual function and ability to provide informed consent. Patient attended a school district for special education needs, could not identify where they lived, and could not

explain what kind of legal documents or identification they possessed. The provider dismissed our concerns and prescribed hormones. In a follow-up appointment, Patient stated that they were possibly interested in having biological children. Patient never saw the fertility department and the Center never discussed fertility questions with Patient.

15. Fourth, the Center required that the child attend a consultation with the Endocrinology or Adolescent Medicine practices. On several occasions, I witnessed Center doctors mention that they did not have time in the meeting to discuss everything they would have liked to.

16. During my four years working at the clinic, I witnessed only two instances where doctors chose not to prescribe cross-sex hormones or puberty blockers for a child who met the four basic criteria. Both cases involved patients with severe developmental delays. In one of those cases, the doctors did not prescribe cross-sex hormones or puberty blockers, despite recommending the medications, solely because the parents would not agree to monitor the child's medication administration.

17. Toward the end of my time at the Center, I saw a large increase in children seeking transition treatment. When I started in 2018, the Center received between 5 and 10 calls a month. When I left, the Center had received more than 40 calls a month. Many children reported that they learned of their gender identities from TikTok.

18. Center doctors would prescribe puberty blockers or cross-sex hormones even if the child had severe comorbidities or was influenced by social media.

19. Children had come into the clinic using pronouns of inanimate objects like "mushroom," "rock," or "helicopter;" asking for hormones because they do not want to be gay;

changing their identities on a day-to-day basis; and under clear pressure by a parent to identify in a way inconsistent with the child's actual identity.

20. In hundreds of other cases, Center doctors regularly issued puberty blockers or cross-sex hormones despite concerns raised by the child's individual circumstances. For example:

a. Patient's gender identity shifted day-to-day. Patient changed preferred name and at one point changed to non-binary identity. Center doctors continued prescribing Patient cross-sex hormones.

b. 19-year-old Patient, initially seen as a minor, had a mastectomy at St. Louis Children's Hospital. Three months after the surgery, Patient contacted the surgeon and asked for their breasts to be "put back on."

c. Doctors placed a biologically female patient on cross-sex hormones. Later, I discovered that Patient desired cross-sex hormones only to avoid becoming pregnant.

d. I witnessed a call between an outside psychiatrist and the Center's endocrinologist. Psychiatrist recommended that Patient not start cross-sex hormones due to the child's serious mental health issues. Patient had threatened to commit suicide by jumping off a roof. The Center's endocrinologist yelled at the psychiatrist and spoke down to this provider.

e. At intake, Patient identified as "blind," even though vision tests revealed that the child could see. Patient also identified as transgender. The Center dismissed the child's blindness claim as a somatization disorder but accepted Patient's statement about gender. The Center prescribed that child drugs for medical transition without

confirming the length or persistence of the condition. The Center provided no concurrent mental health.

21. I have personally witnessed staff say they were uncomfortable with how the Center requested that they code bills sent to publicly funded insurance programs. I witnessed staff ask providers for clarification on billing questions and have providers dismiss the concerns and prioritize patients' coverage. I personally witnessed staff report that they were aware that patients had been coded incorrectly, coding for precocious puberty for a puberty blocker prescription when the child did not have the condition.

22. In my role we had direct ties to the Vanderbilt Gender Center in Nashville, Tennessee, early in my tenure. We were aware of a program that Vanderbilt started called the TransBuddy Program. We extensively researched this program, one of my students had contact with a staff member at Vanderbilt and we worked for a period to pilot the same program at St Louis Children's Hospital. We were interested in piloting this program in part because we knew that Vanderbilt's gender program was very similar in practice to our own program. We were similarly embedded in a university research-based hospital system and shared the same structural values in treating transgender children. The TransBuddy program itself is based on the same fundamental principles that transgender children require special medical care that is kept protected from any medical staff questions or true assessment. It is my assessment having spent hours working to reproduce the program that Vanderbilt created that the same or very similar systematic issues, ethical concerns, and maltreatment would be found in both centers.

23. Washington University School of Medicine's Pediatric Transgender Center at St Louis Children's Hospital is not an outlier in its practices. It is just like the vast majority if not all other pediatric gender centers in the United States. I know this to be true for the following reasons:

a. Our clinical co-director was trained in gender care by Dr. Steven Rosenthal, the Medical Director of the Children and Adolescent Gender Center at the University of California San Francisco at Benioff Children's Hospital. UCSF is known as a leading institution in pediatric gender care. UCSF recently hosted the 2023 National Transgender Health Summit. Our clinical co-director, Dr. Chris Lewis continued to seek out Dr. Rosenthal's clinical expertise on a regular basis through my tenure at the center and would state that he wanted to discuss cases with his mentor. Even after those discussions clinical decisions like I described above were made.

b. Our center multidisciplinary team attended numerous national conferences. We attended as a group the Philadelphia Trans Wellness Conference at the Mazzoni Center. We also attended as a group the Gender Odyssey Conference in San Diego. In these conference sessions we were never challenged with any information or clinical practices that demonstrated that our clinical practices were outside of the norm. If anything, we were presented with information that demonstrated that our clinical care was potentially more conservative than the prevailing norms at the coastal centers. For example, the conference in San Diego had an entire session on the use of the cancer drug bicalutamide and our provider, Dr Chris Lewis, was using this drug on a regular basis. This drug was not found in any WPATH or Endocrine Society formal 'guidelines' and yet was clearly being used by other gender centers treating children around the country.

c. Our center's multidisciplinary team was active in an online email national group that linked together pediatric gender care providers. Although I never completed the steps to join that group, in part because I already had enough email to manage, I heard from the providers comments that our practices were actually more conservative than what they were seeing on the group chats. Casey Lofquest, our center's nurse practitioner even commented once to me about this chat saying that if I think our center is going too far and not following the 'guidelines' that I would be appalled at some of the other clinical practices who do not even know that 'guidelines' even exist.

d. We had patients who transferred their care to our center from centers in other states. Upon reviewing the records from other centers I found that other centers did not even attempt to determine who the legal guardians are for children in their care. I found that other centers did not even request a letter of support at all before starting children on cross sex hormone treatment. I also found in one case that a child transferred to our center who was started on testosterone at the age of 11. It was apparent that other centers, within the United States, were operating well outside of any standard of care.

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

Executed on May 18, 2023

/s/ Jamie Reed
Jamie Reed