# EXHIBIT 41

Ex. 14


SPECIAL ARTICLE

# Consensus Statement on the Use of Gonadotropin-Releasing Hormone Analogs in Children

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## ABSTRACT

OBJECTIVE. Gonadotropin-releasing hormone analogs revolutionized the treatment of central precocious puberty. However, questions remain regarding their optimal use in central precocious puberty and other conditions. The Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology convened a consensus conference to review the clinical use of gonadotropin-releasing hormone analogs in children and adolescents.

PARTICIPANTS. When selecting the 30 participants, consideration was given to equal representation from North America (United States and Canada) and Europe, an equal male/female ratio, and a balanced spectrum of professional seniority and expertise.

EVIDENCE. Preference was given to articles written in English with long-term outcome data. The US Public Health grading system was used to grade evidence and rate the strength of conclusions. When evidence was insufficient, conclusions were based on expert opinion.

CONSENSUS PROCESS. Participants were put into working groups with assigned topics and specific questions. Written materials were prepared and distributed before the conference, revised on the basis of input during the meeting, and presented to the full assembly for final review. If consensus could not be reached, conclusions were based on majority vote. All participants approved the final statement.

CONCLUSIONS. The efficacy of gonadotropin-releasing hormone analogs in increasing adult height is undisputed only in early-onset (girls <6 years old) central precocious puberty. Other key areas, such as the psychosocial effects of central precocious puberty and their alteration by gonadotropin-releasing hormone analogs, need additional study. Few controlled prospective studies have been performed with gonadotropin-releasing hormone analogs in children, and many conclusions rely in part on collective expert opinion. The conference did not endorse commonly voiced concerns regarding the use of gonadotropin-releasing hormone analogs, such as promotion of weight gain or long-term diminution of bone mineral density. Use of gonadotropin-releasing hormone analogs for conditions other than central precocious puberty requires additional investigation and cannot be suggested routinely. *Pediatrics* 2009;123:e752–e762

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**Key Words**
precocious puberty, GnRH analogs, development

**Abbreviations**
GnRHa—gonadotropin-releasing hormone analog
CPP—central precocious puberty
ESPE—European Society for Pediatric Endocrinology
LWPES—Lawson Wilkins Pediatric Endocrine Society
AH—adult height
BA—bone age
CA—chronological age
LH—luteinizing hormone
FSH—follicle-stimulating hormone
SDS—SD score
GH—growth hormone
BMD—bone mineral density
PCOS—polycystic ovarian syndrome
ISS—idiopathic short stature
SGA—small for gestational age
CAH—congenital adrenal hyperplasia

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GONADOTROPIN-RELEASING HORMONE ANALOGS (GnRHas) are standard of care for treatment of central precocious puberty (CPP). However, despite a favorable record of safety and efficacy, significant questions remain regarding their use. The European Society for Pediatric Endocrinology (ESPE) and the Lawson Wilkins Pediatric Endocrine Society (LWPES) convened a consensus conference to examine GnRHa therapy in pediatric patients. We did not address whether historically defined normal ages for the onset of puberty should be modified but used the

operational definition of precocious puberty as puberty beginning before 8 years of age in girls and 9 years of age in boys.

## METHODS

### Participant Selection

Consideration was given to equal representation from North America (United States and Canada) and Europe, an equal male/female ratio, and a balanced spectrum of professional seniority and expertise.

### Process

Thirty participants were put into 1 of 6 groups with assigned topics and designated chairpersons. Each participant prepared a summary of the literature regarding a question that was distributed before the conference (held over 3 days in November 2007). Each group revised the summaries and presented them to the full conference. If consensus could not be reached, conclusions were made on the basis of a vote of all participants. This report is organized around the questions that were addressed; it has been approved by the participants and endorsed by the LWPES and ESPE.

### Evaluation of Evidence

Preference was given to articles written in English with long-term outcome data published between 1990 and 2007. The US Public Health grading system[1] was used to grade the evidence and strength of the recommendations.* Grading was reviewed by the full conference under the guidance of a methodologist/biostatistician. This report is a not a practice guideline; nonetheless, we aimed to adhere to modified appraisal of guidelines research and evaluation (AGREE) criteria.[2]

## INITIATION OF GnRHa THERAPY FOR CPP

### Clinical Criteria

The most important clinical criterion for GnRHa treatment is documented progression of pubertal development, which is based on the recognition that many patients with CPP have a slowly progressive or nonprogressive form and achieve adult height (AH) within their target range without GnRHas.[3–7] Accelerated growth velocity and skeletal maturation are other features of sustained and/or rapidly progressing CPP.[8] However, some patients with slowly progressive CPP and advanced bone age (BA) reach normal AH without intervention.[3]

Conclusions: Progressive pubertal development and growth acceleration should be documented over a 3- to 6-month period before GnRHa therapy. This observational period may not be necessary if the child is at or past Tanner stage III (breast), particularly with advanced skeletal maturation (CIII).

*The qualities of evidence are I (data from ≥1 properly randomized, controlled trial), II (data from other clinical studies), and III (data from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees), and the strengths of recommendation are A (good evidence to support use), B (moderate evidence to support use), C (poor evidence to support recommendation), D (moderate evidence against use), and E (strong evidence against use).

### Chronological Age and Psychosocial Criteria

Common reasons for GnRHa therapy are potential for compromise in adult stature, inability to adapt oneself to menarche, and psychosocial difficulties. Most of the evidence concerns height outcomes (predicted versus actual AH) and age at initiation of therapy, but no randomized, controlled trials quantifying the effect of therapy on AH are available. The Bayley-Pinneau method is commonly used to predict AH and is likely better than other prediction methods[9]; however, in some instances, it may overpredict height by several centimeters.[10,11]

The greatest height gain has been observed in girls with onset of puberty at <6 years (average gain 9–10 cm, but with variation among studies[6,12–16]). Girls with onset between 6 and 8 years comprise a heterogeneous group that may have a moderate benefit ranging from 4.5 ± 5.8[13] to 7.2 ± 5.3 cm.[6] Insufficient data exist to relate CA to height outcomes among boys.[17]

Data regarding the psychosocial impact of untreated or treated CPP are inconclusive, and whether delaying puberty with GnRHas may improve social functioning is still an open question. Early menarche in the general population is associated with risk-taking behavior,[18] but it is unclear whether such data can be generalized to CPP. In patients with severe developmental delay, CPP may be associated with inappropriate behavior. If suppression of menses is the primary goal, GnRHas are only one of several therapeutic options, including progestogens, that could be considered.[19]

Conclusions: Girls with onset of progressive CPP before 6 years of age benefit most in terms of height from GnRHas. The decision to initiate therapy in girls with onset after the age of 6 should be individualized (BII). Treatment should be considered for all boys with onset of progressive CPP before 9 years of age who have compromised height potential (CIII). The use of GnRHas solely to influence the psychosocial consequences of CPP or to delay menarche should be considered carefully given the absence of convincing data (CIII). Additional studies to evaluate the effects of GnRHa therapy on quality of life and psychosocial functioning are needed.

### Adopted Children

Boys and girls adopted internationally are at risk of CPP, although data are limited for boys.[20,21] Response to GnRHas in adopted girls with precocious or early normal puberty seems comparable with that seen in nonadopted girls.[22] Adopted children may be at increased risk of emotional and behavioral problems,[23] but no data are available to demonstrate that GnRHa therapy improves psychological well-being.[24]

Conclusions: Although international adoption constitutes a risk factor for CPP, adopted children should be treated no differently than nonadopted children with CPP (CIII).

### Hormonal Criteria

Luteinizing hormone (LH) measurements are the most valuable biochemical parameter for the diagnosis of CPP.

**TABLE 1 Characteristics of GnRHas**

| | Rapid Acting | Monthly Depot | 3-mo Depot | 12-mo Implant |
|---|---|---|---|---|
| Dosing | 3–4 times daily (intranasal) or every day (subcutaneous) | Every 28 d | Every 90 d | Every year |
| Peak serum concentrations | 10–45 min | 4 h | 4–8 h | 1 mo |
| Onset of therapeutic suppression | 2–4 wk | 1 mo | 1 mo | 1 mo |
| Advantage | Quick on/off | Dosing and efficacy well studied | Fewer injections and fewer compliance concerns | No injections needed |
| Disadvantage | Multiple daily doses needed/ compliance very difficult | Painful injections/suboptimal compliance | Painful injection | Requires surgical procedure for insertion and removal |

Because prepubertal LH levels are <0.1 IU/L, LH assays used should have a detection limit near 0.1 IU/L.[25–27] In 1 study of normal children, basal LH levels distinguished prepubertal (LH < 0.2 IU/L) and pubertal males with 100% sensitivity and specificity, but 50% of the girls with Tanner stage 2 breasts had levels in the prepubertal range.[27]

LH can be measured after stimulation with GnRH (single serum sample at 30–40 minutes[27–29]) or with a GnRHa such as aqueous leuprolide (single sample at 60 minutes[30,31]). Peak LH values show an overlap between prepubertal and early pubertal children. As with basal LH, variability among assays and paucity of normative data have hampered the development of diagnostic cutoffs for CPP, although an (assay-specific) prepubertal limit of peak LH at 3.3 to 5.0 IU/L has been suggested.[25,27,28]

LH levels provide more information than those of follicle-stimulating hormone (FSH). However, the stimulated LH/FSH ratio may help differentiate progressive CPP (which tends to have higher LH/FSH ratios) from nonprogressive variants that do not require GnRHa therapy.[32–34]

For estradiol, the most sensitive measurements (tandem mass spectrometry) have shown that prepubertal levels may be <1 pg/mL (3.7 pmol/L) and undetectable with commonly available assays.[35] Thus, in non–mass spectrometry assays, measurable estradiol only confirms relatively advanced puberty. Similarly, testosterone assays with detection limits of >10 ng/dL may not discriminate prepubertal from early pubertal levels.[36] For estradiol and testosterone, the laboratory used must have a defined prepubertal range.

Conclusions: Sensitive assays with pediatric norms should be used and stimulation results interpreted depending on the agent used (BII). The same caveats are important if hormonal testing is used to monitor therapy (see below). Basal LH levels are useful screening tests and may be diagnostic (BII). Stimulated LH levels are important, but interpretation suffers from assay variability and absence of clear diagnostic cutoffs (BII). Gonadal sex-steroid levels can add information in support of the diagnosis but are not sufficient (BII).

### Pelvic Ultrasound

Female patients with CPP have increased ovarian and uterine dimensions compared with prepubertal controls and girls with premature thelarche.[37] For CPP, cutoff values for uterine length range from 3.4 to 4.0 cm. The presence of an endometrial echo is highly specific (~100%) but less sensitive (42%–87%).[34] The cutoffs for a pubertal ovarian volume range between 1 and 3 mL (volume = length × width × height × 0.5233).[38]

Conclusions: Pelvic ultrasound is helpful in differentiating CPP from premature thelarche as an adjunct to GnRH stimulation (BII).

### Central Nervous System Imaging

CPP may be a sign of central nervous system pathology. Unsuspected intracranial pathology has been reported in 8% of girls[39,40] and 40% of boys[41] without neurologic findings or neurofibromatosis. The percentage of children with unsuspected intracranial pathology decreases with age.[39–41] Only 2% to 7% of girls who have onset of CPP between the ages of 6 and 8 years have unsuspected pathology, and only ~1% have a tumor such as a glioma or astrocytoma.[39,40] Factors that may decrease the likelihood of finding a tumor include racial/ethnic background, family history of CPP, and adoption.

Conclusions: All boys with CPP and girls with CPP at <6 years of age should have a head MRI. It is controversial whether all girls who develop CPP between 6 and 8 years of age require head MRI. Girls with neurologic findings and rapid pubertal progression are more likely to have intracranial pathology and require an MRI examination (BII).

## AVAILABLE GnRHas AND THERAPEUTIC REGIMENS FOR CPP

### Currently Available Therapeutic Regimens

All available GnRHas are effective despite their different routes of administration, dosing, and duration of action (Tables 1–3).[42,43] The depot preparations are preferred be-

**TABLE 2 Rapid-Acting Formulations of GnRHa**

| GnRHa | Administration | Starting Dose, per day |
|---|---|---|
| Nafarelin | Nasal spray | 800 μg twice |
| Buserelin | Nasal spray | 20–40 μg/kg |
| Buserelin | Subcutaneous | 1200–1800 μg |
| Leuprolide | Subcutaneous | 50 μg/kg |
| Deslorelin | Subcutaneous | 4–8 μg/kg |
| Histrelin | Subcutaneous | 8–10 μg/kg |
| Triptorelin | Subcutaneous | 20–40 μg/kg |

**TABLE 3 Depot GnRHa Formulations**[42,47,48]

| Depot Preparation | Brand Name | Starting Dose |
|---|---|---|
| Goserelin | Zoladex LA | 3.6 mg every month or 10.8 mg every 3 mo |
| Buserelin | Suprefact depot | 6.3 mg every 2 mo |
| Leuprolide | Enantone or Lupron-depot | 3.75 mg every month or 11.25 mg every 3 mo |
| | Prostap SR | 3.75 mg every month |
| | Lupron depot PED | 7.5, 11.25, or 15 mg every month (0.2–0.3 mg/kg per mo) or 11.25 mg every 3 mo[a] |
| Triptorelin | Decapeptyl, Gonapeptyl | 3 or 3.75 mg every month or 11.25 mg every 3 mo |
| Histrelin | Supprelin LA | 50 mg implant every year |

[a] No data are available on the use of the 22.5-mg 3-month depot in children.

cause of improved compliance.[44–46] In most children, monthly injections adequately suppress the gonadotropic axis, but some children require more frequent injections or higher-than-standard doses. The 3-month formulations are comparable with monthly dosing, but no randomized comparative trial is available.[42,47–49] In 1 prospective trial, 7.5 mg of leuprolide monthly suppressed LH more effectively than 11.25 mg every 3 months, although sex-steroid concentrations were equally inhibited.[50] The 50-mg histrelin-acetate implant provides sustained suppression for 12 months.[51,52]

Conclusions: A variety of GnRHa formulations are available and efficacious. The choice of a particular agent depends on patient and physician preference and on local marketing approval (CIII).

### Treatment Monitoring

Progression of breast or testicular development is suggestive of treatment failure,[52–56] but progression of pubic hair may indicate normal adrenarche. Growth velocity, height SD score (SDS), and BA advancement should decline during treatment. Vaginal bleeding may occur after the first administration of GnRHas, but subsequent bleeding suggests lack of efficacy or incorrect diagnosis. Markedly decreased growth velocity (less than or equal to a −2 SDS) or rapid BA advancement should also prompt reassessment. BA can be used to update AH prediction understanding that the Bayley-Pinneau method may overestimate AH.[57] If elevated, random LH levels obtained by using an ultrasensitive assay indicate lack of suppression. Stimulated LH values (using GnRH, aqueous GnRHas, or the free GnRHas contained in depot preparations) can also be used to assess effectiveness. FSH levels are not normally used to monitor suppression. If measured, testosterone and estradiol levels should be in a prepubertal range for the assay used.[44,51,53–56,58] No long-term data have provided compelling support for any specific short-term monitoring scheme.

Conclusions: GnRHa-injection dates should be recorded and adherence with the dosing interval monitored (BII). Tanner stage and growth should be assessed every 3 to 6 months, and BA should be monitored periodically (BII). There was no consensus about the routine use of random or stimulated measurements of gonadotropins or sex steroids for monitoring therapy. For patients with suboptimal clinical response, there was consensus about need for comprehensive reassessment (CIII). Additional information on the relationship between on-treatment measures of gonadotropic axis suppression and outcomes are needed.

### Adverse Events

GnRHas are generally well tolerated in children and adolescents. Systemic complaints such as headaches or hot flashes occur occasionally but are usually short-term and do not interfere with therapy. Local adverse events occur in ~10% to 15% of patients and necessitate a change in agent when persistent, because they can result in sterile abscesses in a fraction of the patients.[54,55,59] Although exceedingly rare, anaphylaxis has been described.

### Potential New Therapeutic Agents for the Treatment of CPP

GnRH antagonists cause immediate and direct inhibition at the level of pituitary GnRH receptors.[60] Theoretical advantages over GnRHas include eliminating the initial "flare" in gonadotropic axis activation and rapid recovery of suppression once therapy is withdrawn. Depot and nonpeptide orally active GnRH antagonists are under development[61] and could be evaluated in children with CPP in the future.

### Therapeutic Agents That Can Be Combined With GnRHas for the Treatment of CPP

Adjunctive therapies that may improve outcomes (AH, for example) of GnRHa therapy include pure or selective estradiol estrogen receptor blockers, aromatase inhibitors,[62] pure antiandrogens, sex steroids,[63] or nonaromatizable anabolic steroids.[64] The addition of oxandrolone increased AH compared with GnRHas alone in a small ($n = 10$) nonrandomized study.[64] The addition of growth hormone (GH) increased AH compared with GnRHas alone in girls with CPP and slow growth velocity in small ($n = 10$ and 17) nonrandomized series.[65,66] The addition of GH increased height outcome in a randomized, controlled study ($n = 46$) of adopted girls with precocious or early puberty.[22] However, to date, no large-scale randomized, controlled trials evaluating the addition of GH to GnRHas for CPP have been performed.

Conclusions: The addition of GH or oxandrolone to GnRHas cannot be routinely recommended. These adjunctive therapies require validation by larger studies with consideration for potential adverse effects (CIII).

## DISCONTINUATION OF GnRHa THERAPY IN CPP

Factors that could influence the decision to stop GnRHa treatment depend on the primary goal(s) of therapy, including maximizing height, synchronizing puberty with peers, ameliorating psychological distress, and facilitating care of the developmentally delayed child. Available data only permit analysis of factors that affect AH among girls.

### Treatment Duration

Several studies have reported a direct relationship between treatment duration and AH[14,15,67–69] and an inverse relationship between age at pubertal onset or at initiation of therapy and AH.[6,14,67–69] However, deciphering the respective influences of age at onset of puberty, age at initiation of therapy, and treatment duration is problematic, because these variables are interrelated. Undue delay in initiation of therapy (>1–2 years) may compromise AH.

### Parent/Patient Preference, Anticipated Time of Menarche, CA, and BA

In the studies we examined, wishes of the patient and family and the physician's decision were stated as deciding factors for cessation of treatment.[13,15,68,70–73] The mean age at treatment discontinuation ranged from 10.6 to 11.6 years, with mean BA ranging from 12.1 to 13.9 years and mean age at menarche of ~12.3 years. Discontinuation at a CA of ~11.0 years[13] and a BA of ~12.0 years[14,67] has been associated with maximum AH. However, BA is not an appropriate single variable, because a BA of ~12.0 years can be observed at different CAs and because BA is unreliable for predicting height gain after treatment.[12–15,72] One study has suggested that height gain after treatment may be higher for those with early (<6 years) versus late treatment.[6]

### Height and Growth Velocity

Although growth velocity during therapy[6,13–15,67–69,71,72] and height at interruption of therapy are positively associated with AH,[6,13,14] they cannot be used as independent factors for deciding when to stop treatment. For a child with unexplained marked deceleration of growth, consideration might be given to stopping treatment or to introducing adjunct therapies.

Conclusions: There is insufficient evidence to rely on any one clinical variable (CA, duration of therapy, BA, height, target height, growth velocity) to make the decision to discontinue treatment (CIII). Therefore, it is reasonable to consider these parameters and informed parent and patient preferences, with the goal of menarche occurring near the population norms (CIII).

## OUTCOMES OF GnRHa THERAPY FOR CPP

### Reproductive Function

Follow-up studies have been performed with girls in their late teens[68,69,74–76] and women up to 31 years in 1 study[77] and have reported that ovarian function was not impaired.[68,69,74,75,78,79] Menses began 2 to 61 months (mean: ~16 months) after the end of treatment.[69,74–77] Regular ovarian cycles occurred in 60% to 96% of the patients, without differences from reference populations.[69,74–77] Infertility has not been reported. Of 28 reported pregnancies,[69,74,75,77] 7 were terminated and 21 resulted in healthy children.[69,75,77] Three small studies showed no differences from controls in gonadal function for boys at the ages of 15 to 18 years.[68,78,79] Paternity rates have not been reported.

Conclusions: The available data suggest that gonadal function is not impaired in girls treated with GnRHas (BII). Nevertheless, available data are limited. Long-term data on fecundity and ovarian reserve of treated patients with CPP are needed.

### BMI and Correlates of Metabolic Syndrome

Childhood obesity is associated with earlier pubertal development in girls, and early sexual maturation is associated with increased prevalence of overweight and obesity. There has been concern that GnRHa therapy may affect BMI. Eleven studies addressed BMI outcome in girls with CPP,[6,12,49,69,75,80–85] 2 included boys,[78,80] and 1 included girls with early puberty (onset at the ages of 8 and 9 years).[86] Before GnRHa treatment, mean BMI SDS was above average in girls with CPP in all studies, whereas results were split in boys.[78,80] The combined analysis indicates that BMI SDS did not increase after treatment irrespective of age at presentation. At AH, mean BMI SDS ranged from 0.1 to 1.7, with an overall slight decrease from pretreatment BMI. No reports regarding metabolic syndrome and GnRHa treatment were identified.

Conclusions: Above-average BMI is frequent at diagnosis of CPP. Long-term GnRHa treatment does not seem to cause or aggravate obesity, as judged from BMI (BII). Studies of body composition and fat distribution are needed.

### Bone Mineral Density

Bone mineral density (BMD) may decrease during GnRHa therapy. However, subsequent bone mass accrual is preserved, and peak bone mass does not seem to be negatively affected by treatment.[12,82,87] There is some suggestion that discontinuation of treatment in girls with a BA of ≤11.5 years may lead to greater BMD[87] and that, as in all adolescents, optimum calcium and vitamin D intake and skeletal-loading exercise may positively influence bone mass.[82]

Conclusions: Young adults treated with GnRHas for CPP in childhood ultimately accrue BMD within the normal range for age (BII).

### Risk of Polycystic Ovarian Syndrome

The possibility that CPP is a first manifestation of polycystic ovarian syndrome (PCOS) has been raised.[88] PCOS occurred in 0% to 12% of girls with CPP followed prospectively[12,89–91] compared with 5% to 10% in the general population.[92] Single studies have reported (1) an increased average ovarian size after CPP resulting from hypothalamic hamartoma,[75] (2) a higher prevalence of exaggerated adrenarche in patients with CPP than in controls,[93] and (3) the occurrence of signs of PCOS 0.5 to 4.0 years after menarche.[94]

Conclusions: Follow-up of treated or untreated girls with CPP into the midteenage years suggests that the development of PCOS (BII) or polycystic ovary morphology (CIII) is not clearly different from that in the general population. Premature adrenarche and early childhood insulin resistance are potential risk factors for PCOS, but it is not clear if the presence of these conditions along

with CPP increases the eventual risk of PCOS (CIII). Longitudinal data through adolescence are needed.

## PSYCHOSOCIAL DEVELOPMENT

Potential psychological consequences of CPP, including risk for emotional distress and problem behavior, are often used to justify treatment with GnRHas.[95,96] Hormonally induced behavioral changes (eg, aggression, sexuality) that occur during normal puberty[97] may occur earlier in children with CPP, perhaps consistent with the hormonal effects on brain development observed in rodents.[98]

Limited data are available regarding psychological consequences of CPP, and the few existing studies have limitations that have yielded inconsistent conclusions.[99] In 2 studies examining psychological functioning in girls with CPP before and after treatment,[24,100] no consistent patterns of change were observed. GnRHas have been suggested to adversely affect mood and cognition in adults,[101] but similar effects have not been evaluated in children.

Conclusions: There is little evidence to show whether CPP leads to psychological or behavioral problems or whether treatment with GnRHas are associated with improved psychological outcome (CIII). Thus, no recommendations related to psychosocial outcomes are possible. Controlled studies with standardized instruments are needed.

## USE OF GnRHas FOR CONDITIONS OTHER THAN CPP

### Gonadal Protection for Children Undergoing Chemotherapy

Infertility represents one of the main long-term consequences of chemotherapy. Studies that evaluated the effects of ovarian suppression by GnRHas during chemotherapy in adult and adolescent patients have yielded inconsistent results.[102–104] Prospective, randomized trials in adult women are ongoing (see NCT00196846, NCT0090844, NCT00380406, NCT00068601 at http://clinicaltrials.gov/).

Conclusions: Routine use of GnRHas for gonadal protection in children undergoing chemotherapy cannot be suggested (CIII).

### Increasing AH of Children With Idiopathic Short Stature

The effect of GnRHa therapy on AH has been evaluated in girls with idiopathic short stature (ISS) and normal puberty (8–10 years of age), with a mean gain compared with predicted height of 0 to 4.2 cm.† In boys with rapidly progressing puberty, GnRHa therapy increased AH compared with predicted height.[5] The effects of combined GH and GnRHa therapy in children with ISS are controversial,[111] with mean gains of 4.4 to 10 cm with combination therapy versus −0.5 to 6.1 cm in untreated controls.[112,113] In these studies, one cannot definitively separate the effects of GH from GnRHas. In 2 randomized studies of adopted girls with normal puberty, GnRHas plus GH was compared with GnRHas alone, with a 3-cm height gain demonstrated with combination therapy.[22,114] Disadvantages of the use of GnRHas in children with ISS include absence of pubertal growth acceleration, delayed puberty with potential psychosocial disadvantage, and decreased BMD. Long-term follow-up studies are lacking.

Conclusions: GnRHa therapy alone in children with ISS and normally timed puberty is minimally effective in increasing AH, may compromise BMD, and cannot be suggested for routine use (DII). Combined GnRHa and GH therapy leads to a significant height gain but may have adverse effects. Routine use of GnRHas in children with ISS being treated with GH cannot be suggested (CIII).

### Increasing AH of Children Born Small for Gestational Age

Short children born small for gestational age (SGA) usually have a normal pubertal timing, although some of them have rapidly progressing puberty, and may be treated with GH.[92,115] Data on the additional effect of GnRHas are limited.[113]

Conclusions: Routine use of the combination of GnRHas and GH in children born SGA cannot be suggested (CIII).

### Increasing AH of Children With Severe Hypothyroidism

Some children with severe hypothyroidism are at risk for rapid progression through puberty and diminished AH. In the only study available, combined GnRHas and levothyroxine and levothyroxine alone produced similar gains in height SDS.[116]

Conclusions: Routine use of combined therapy with GnRH and levothyroxine cannot be suggested (CIII).

### Increasing AH of Children With GH Deficiency

Some children with GH deficiency are short at the start of puberty and at risk for short adult stature. Retrospective studies that evaluated the addition of GnRHas to GH involved a limited number of subjects and provided controversial results.[117–119] Three prospective studies that reported near-AH or AH have shown an ~1-SD height gain,[120–122] possibly without detrimental effect on BMD.[123]

Conclusions: Routine use of combined therapy with GnRH and GH in GH-deficient children with low predicted AH at onset of puberty cannot be suggested (CIII).

### Increasing AH of Children With Congenital Adrenal Hyperplasia

One nonrandomized study examined the effect of combined GH and GnRHa treatment on AH in 14 children with congenital adrenal hyperplasia (CAH) and normal or precocious puberty and found a 1-SD increase in AH in comparison with standard treatment for CAH.[124]

Conclusions: Additional studies are needed to determine if GnRHa therapy alone or in combination with GH should be used in children with CAH and low predicted AH. Routine use of GnRHas for CAH cannot be suggested (CIII).

### Children With Autism

Conclusions: Despite 1 controversial article reporting that GnRHas may benefit behavioral symptoms in chil-

†Refs 6, 14, 15, 57, 69, 71, 73, and 105–110.

dren with autism,[125] the consensus is that there is no current evidence for GnRHa therapy for this indication (CIII).

## CONCLUSIONS

Several important observations emerged from this conference. Despite a considerable body of literature on the use of GnRHas, few rigorously conducted and controlled prospective studies are available from which to derive evidence-based recommendations. Most of our conclusions are categorized as CIII, a level of evidence that underscores the need for additional research in key areas such as the psychosocial effects of GnRHa treatment for CPP. The efficacy in increasing AH is undisputed only in early-onset progressive CPP, which highlights the need to increase our knowledge of the pathophysiology and normal limits of puberty and of the physical and psychosocial consequences of treated and untreated CPP. Our systematic review also highlighted the lack of objective support for commonly voiced concerns such as the propensity for GnRHas to promote weight gain or to lead to long-term diminution of BMD. Use of GnRHas for conditions other than CPP requires additional investigation and cannot be routinely suggested.

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Guidelines

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# Use of Gonadotropin-Releasing Hormone Analogs in Children: Update by an International Consortium

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**Keywords**
Gonadotropin-releasing hormone analogs · Children · Adolescents · Precocious puberty · Transgender

**Abstract**
This update, written by authors designated by multiple pediatric endocrinology societies (see List of Participating Societies) from around the globe, concisely addresses topics related to changes in GnRHa usage in children and adolescents over the last decade. Topics related to the use of GnRHa in precocious puberty include diagnostic criteria, globally available formulations, considerations of benefit of treatment, monitoring of therapy, adverse events, and long-term outcome data. Additional sections review use in transgender individuals and other pediatric endocrine related conditions. Although there have been many significant changes in GnRHa usage, there is a definite paucity of evidence-based publications to support them. Therefore, this paper is explicitly not intended to evaluate what is recommended in terms of the best use of GnRHa, based on evidence and expert opinion, but rather to describe how these drugs are used, irrespective of any qualitative evaluation. Thus, this paper should be considered a narrative review on GnRHa utilization in precocious puberty and other clinical situations. These changes are reviewed not only to point out deficiencies in the literature but also to stimulate future studies and publications in this area.



## Introduction

Gonadotropin-releasing hormone analogs (GnRHa) have been used primarily in the treatment of central precocious puberty (CPP), in other conditions in which adult stature is compromised (those with a growth hormone [GH] deficiency, those with idiopathic short stature, or those who are small for gestational age [SGA]), or when pubertal hormone suppression is a part of the treatment regimen (transgender individuals). Noteworthy is the fact that the diagnosis of CPP appears to have become more common since the availability of GnRHa, similar to GH deficiency when biosynthetic GH first became available.

The goal of this update, which has been written by members designated by multiple, global pediatric endocrine societies (see List of Participating Societies), is to

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concisely address topics related to changes in GnRHa usage during childhood and adolescence since the previous consensus statement was published in 2009 [1]. It is not a consensus statement and hence has not been endorsed by any of the societies that designated participating authors. Clinical care using GnRHa has changed dramatically in recent years based on unpublished knowledge and discussions in numerous settings regarding daily clinical practice. This has been driven by many factors, most of which involve current demands for health care delivery, without verification by publications or controlled studies. Hence the need for a publication such as this.

Examples of changes include:

1. The lack of evidence for weight-based dosing previously recommended for depot forms of GnRHas
2. Change in the assessment of pituitary gonadotropins, with updated laboratory criteria
3. Fewer GnRH/GnRHa stimulation tests and a greater use of unstimulated luteinizing hormone (LH) concentrations that are above the prepubertal range, with less frequent insistence on stimulation testing by insurance companies in the USA
4. Less hormonal monitoring during therapy, particularly among patients on chronic therapy when other parameters including linear growth rates, lack of pubertal progression, and slowed progression of skeletal age are consistent with suppression, confirming efficacy
5. A shift to longer-acting forms
6. A lack of agreement regarding use of the 11.25-mg and 30-mg 12-week preparation, again raising unanswered questions of how much suppression is needed for efficacy
7. Giving long-acting injections subcutaneously rather than intramuscularly with similar efficacy and much less pain
8. The additional cost of the minor surgical procedures to place and remove the implant at many locations
9. Continued lack of long-term outcome studies even though available information continues to support safety and efficacy
10. Greater usage of GnRHa among older patients with CPP despite advanced skeletal age X-rays as well as in those with borderline early puberty or normally timed puberty, those with a short stature for their age, short pubertal GH-deficient individuals, and short pubertal individuals born SGA after pubertal onset
11. Use among transgender individuals including concerns mentioned above and highlighting concerns regarding impacts on bone mineral density and infertility.

Thus, this publication is considered timely and pertinent since clinical practitioners need to be aware of how GnRHa are being used. Hopefully, these topics will stimulate future prospective studies.

Sections include diagnostic criteria, formulations of GnRHa available globally for therapy, considerations of which patients will benefit from treatment, monitoring of GnRHa therapy, adverse events, long-term outcome data, and use in transgender individuals as well as usage for other situations. The primary focus is to highlight management changes since the 2009 update.

This project was initiated by the European Society for Pediatric Endocrinology (ESPE) Clinical Practice Committee (CPC) and the International Clinical Guidelines Committee (iCGC) at the 2016 ESPE meeting. E. Charmandari and P.A. Lee were asked to coordinate a GnRHa clinical update rather than a consensus statement. It was envisioned that this would be an effort from numerous interested pediatric endocrinology societies and that it would be accomplished via e-mails rather than face-to-face meetings. K. Bangalore Krishna agreed to work as coordinator, provide e-mail communications as needed, and develop a repository of pertinent publications that were made available to all. The project leaders developed an outline and identified potential authors who then chose leaders for each outlined section. These in turn invited additional authors, aiming for representative participation from each society. Each subgroup was responsible for reviewing pertinent literature and writing their own section using knowledge of current practices and primarily recent publications. The section leads were given the responsibility of negotiating content among section authors. In addition, a writing committee was designated to integrate the sections and achieve agreement among the section leaders, and when necessary among section authors.

Grading of evidence was performed by a subgroup of the writing committee. The majority of literature citations have levels of evidence (LoE) graded at level 4 (uncontrolled cohort and case studies) or level 5 (expert opinions, case reports, and personal observations). References with higher levels of evidence are indicated by notations for LoE 1 (homogenous randomized control trials), 2 (meta-analyses or heterogeneous prospective trials), and 3 (case-control studies and retrospective cohorts) [2]. For each topic, an average LoE for the cited references was calculated as follows: section 1: 4.5; section 2: 3.9; section 3: 4.2; section 4: 4.5; section 5: 4.5; section 6: 4.3; section 7: 4.5; and section 8: 4.0.

**Table 1.** LH is the most valuable biochemical parameter used to diagnose CPP

| | Sensitivity, % | Specificity, % | Formulation | Subjects, *n* (sex) | Method | Study |
|---|---|---|---|---|---|---|
| Unstimulated LH (IU/L) | | | | | | |
| >0.3 | 77 | 100 | – | 49 (F) | ICMA | Neely et al. [7] |
| <0.3 (prepubertal)<br>>0.83 (clearly pubertal)<br>>0.3 but <0.83 (overlap of prepubertal and pubertal) | 93 | 100 | | 25 (F) | ICMA | Houk et al. [8] |
| <0.2 (prepubertal)<br>>0.2 (pubertal) | 91 | 100 | | 59 (F) | ICMA | Harrington et al. [10] |
| Peak LH (IU/L) | | | | | | |
| 5 (+2 SD in Tanner stage 1) | NA | NA | GnRH | 8 (F) | ICMA | Neely et al. [21] |
| 4.1 (+2 SD in Tanner stage 1) | NA | NA | | 10 (M) | ICMA | Resende et al. [22] |
| 3.3 (+2 SD in Tanner stage 1) | NA | NA | | 10 (F) | ICMA | |
| >4.9 | 78 | 79 | | 80 (F) | ICMA | Pasternak et al. [23] |
| >6.7 | 94 | 100 | | 46 (F) | ECLIA | Freire et al. [14] |
| Stimulated LH (IU/L) (sample time) | | | GnRHa | | | |
| >9.2 (pubertal) (30 min) | NA | NA | Leuprolide | 14 (F) | ICMA | Houk et al. [24] |
| <4.9 (prepubertal) (30 min) | NA | NA | (20 μg/kg) | 21 (F) | ICMA | |
| >5 (2 h) | 78 | 100 | | 39 (F) | ICMA | Sathasivam et al. [13] |
| Adding stimulated estradiol >50 pg/mL (24 h) | 100 | 100 | | | | |
| >5.5 (3 h) | 93 | 100 | Leuprolide (500 μg) | 61 (F) | ECLIA | Carretto et al. [25] |
| >6 (60 min) | 89 | 91 | Triptorelin (0.1 mg) | 101 (F) | ICMA | Poomthavorn et al. [26] |
| >8 (3 h) | 76 | 100 | Triptorelin | 46 (F) | ECLIA | Freireet al. [14] |
| Adding estradiol >80 pg/mL (24 h) | 94 | 100 | (0.1 mg/m$^2$) | | | Freire et al. [27] |

## Section 1: CPP – Diagnosis, Assessment, Natural History, and Racial Differences

Challenges in diagnosing CPP involve: (1) differences in the normal age range of onset of puberty for different racial groups and (2) the decreasing age at onset of breast development in the general population [3]. Regarding (1), since patients from African-American and Hispanic racial and ethnic groups have an earlier normal range of onset of puberty, different age criteria should be considered when diagnosing CPP. Concerning (2), the earlier onset of breast development may not be progressive as typically occurs in CPP, and it is not necessarily caused by hypothalamic pituitary gonadal (HPG) activation. Thus, the documented decline in the age of thelarche over the past 5 decades does not mean that puberty is occurring earlier. To verify this, clinical progression and documentation of pubertal HPG activation are necessary. Since the age of menarche has decreased only minimally during this interval [4, 5], it appears that earlier breast development in most instances is due to premature thelarche, which may be related to increased rates of obesity. Nevertheless, an increase in body mass index (BMI) may be one of many factors that accelerate biologic maturation and thus pubertal progression and menarche [4]. Internationally adopted children may have a greater likelihood (10- to 20-fold) of developing CPP [6].

LH is the best biochemical parameter used to diagnose CPP. When measured in ultrasensitive assays (ICMA with a sensitivity of 0.01 U/L or ECLIA with a sensitivity of 0.1 IU/L), randomly obtained serum LH concentrations within the pubertal range confirm the diagnosis of CPP [7–9]. The most recent analyses suggest that a value >0.2 IU/L can be considered a pubertal value [10] (Table



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1). However, in the setting of clinically progressive puberty, LH concentrations below the pubertal range do not exclude CPP, suggesting the need for GnRH or GnRHa stimulation testing. Likewise, there is still an overlap between prepubertal and pubertal levels reported by others, i.e., between 0.3 and 0.83 IU/L [11], suggesting the need for stimulation testing if the clinical presentation is not definitive. With stimulation testing, specific cut-offs for LH concentrations that indicate a pubertal HPG axis depend on the use of GnRH or GnRHa as the stimulus, the sampling time, and the assay employed (Table 1). Caution should be exercised when interpreting gonadotropin concentrations in children younger than 2 years, since baseline and peak LH concentrations are higher during infancy and can lead to a misdiagnosis of CPP [11, 12]. Random estradiol concentrations may not verify pubertal activation but may improve the sensitivity of stimulation testing when obtained 18–24 h after GnRH/a administration [13, 14].

Findings from transabdominal pelvic ultrasonography are not a diagnostic criterion for CPP. Nonetheless, uterine and ovarian enlargements are consistent with precocious puberty because uterine growth reflects estrogen stimulation, while gonadotropin stimulation is required for growth of the ovaries. Uterine lengths >3.5–4 cm and ovarian volumes >2 mL are consistent with puberty [15, 16].

In children diagnosed with CPP, central nervous system magnetic resonance imaging (MRI) should be performed in all boys and at least in all girls who are 6 years or younger to exclude intracranial pathology, which has been reported to occur in up to 6.3% of girls [17] and 38% of boys [18] with CPP. However, a meta-analysis of MRI findings in CPP demonstrated that only 1.6% of girls had CNS abnormalities that required an intervention [19]. The goal of imaging is to identify pathologic causes of CPP, which are less likely when there is a family history, genetic findings, or an international adoption, particularly from the developing world. A consequence of obtaining MRI is that there may be incidental findings of unknown significance. Current recommendations are to discuss the pros and cons of MRI scanning with the parents to assist them in making an informed decision [20].

LH is the most valuable biochemical parameter used to diagnose CPP. Studies have shown the specificity and sensitivity of stimulated and unstimulated LH concentrations in diagnosing CPP (Table 1) [7, 8, 10, 13, 14, 21–27].

## Section 2: Available GnRHa and Current Therapeutic Regimens

Long-acting GnRHa are the standard of care for the treatment of CPP. They generally have been understood to exert their effect by occupying the GnRH receptor resulting in a desensitization of pituitary gonadotrophs [28] with subsequent suppression of gonadal steroid secretion. Interestingly, animal studies have shown that the total number of membrane receptors during GnRHa treatment does not decrease to below 30% of baseline values, which should result in a normal sensitivity of the gonadotrophs to native GnRH. It has been shown that there are sustained increased levels of free α-subunit during LH and follicle-stimulating hormone suppression by the histrelin implant as well as monthly depot GnRHa preparations [29]. Thus the GnRH receptors are not totally suppressed, but rather they alter their function to produce increased amounts of free α-subunit instead of both components of the glycoprotein hormones [30].

Previously, monthly (4-week) depot GnRHa were most frequently used. However, additional 3-monthly (12-week) and 6-monthly (24-week) formulations, as well as subcutaneous implants, have become available over the past ~10 years. The depot options (leuprolide and triptorelin) are sustained-release formulations administered in various doses and intervals, whereas the subcutaneous histrelin implant requires a minor surgical procedure for insertion and removal and is marketed for annual use. This implanted preparation has been shown to be effective longer, which has the potential to decrease the cost and number of procedures [31]. The starting dose of monthly depot leuprolide acetate approved for pediatric use in the USA ranges from 7.5 to 15 mg and for the 12-week preparation is either 11.25 or 30 mg. Doses are increased if needed to achieve adequate suppression. In Europe and Asia, leuprolide dosing is standardized at 3.75 mg i.m. every 28 days [32, 33]. Weight-based dosing is no longer recommended for the depot forms of leuprolide acetate. The starting dose of triptorelin pamoate is typically 3.75 mg every 28 days and may be titrated up as necessary (to 11.25 mg) [34, 35]. Triptorelin pamoate (22.5 mg) administered at 6-month intervals is effective, but long-term outcome data are not yet available [36]. Prospective extension studies during therapy have demonstrated HPG axis suppression within days of histrelin implant insertion [37], within weeks for higher doses of depot forms, and within 3 months for lower doses and longer-acting depot forms [34, 36, 38]. Biochemical efficacy may be demonstrated by measuring unstimulated

**Table 2.** Available GnRHa preparations (may vary in different countries)

| GnRHa preparation | | Dosing |
|---|---|---|
| Leuprolide acetate | 1-month depot | 3.75 mg |
| | | 7.5 mg |
| | | 11.25 mg |
| | | 15 mg |
| | 3-month depot | 11.25 mg |
| | | 30 mg |
| Triptorelin pamoate (embonate) | 1-month depot | 3.75 mg |
| | | 11.25 mg |
| | 6-month depot | 22.5 mg |
| Histrelin acetate | 12-month implant | 50 mg (65 µg/day) |

ultrasensitive LH or stimulated LH concentrations or sampling after a therapeutic depot injection. However, it is important to note that unstimulated LH concentrations above the prepubertal range commonly do not indicate a lack of suppression [39]. Clinical evidence of efficacy includes a slowing growth velocity, regression or lack of progression of clinical signs of puberty, a progressive decrease in the ratio of BA to CA (BA/CA), and an increase in the predicted adult height (PAH). However, the extent of suppression required for clinical efficacy remains unclear. No differences in clinical indices of pubertal progression were seen in studies comparing monthly preparations and 2 doses of the 3-monthly preparations of leuprolide depot [34, 40]. Prospective comparison studies are needed to establish whether there are differences in efficacy among the GnRHa in use today. Clinicians should discuss all of the available options with patients and families, including the expected duration of the therapy, the frequency of administration, and potential short-term and long-term side effects. Considerations may include an implant for patients with an extreme needle phobia and those with special needs, whereas others may opt for extended-release injectable formulations. The sustained-release GnRHa preparations are similar in annual cost and may improve compliance. Table 2 contains a summary of the most commonly used GnRHa preparations.

### Section 3: Considerations for GnRH Analog Therapy in Children with CPP: to Treat or Not to Treat

The onset of thelarche in 7- to 8-year-old females is increasingly common [41, 42] and it is frequently associated with obesity [3]; however, pubertal gonadotropin secretion in these girls has not been clearly documented. The physical changes of puberty at this age may be temporary, commonly followed by a slow progression or development within the range of normal puberty, and they culminate in achievement of a normal adult height (AH) without therapeutic intervention [43].

Early GnRHa studies treating CPP primarily included patients who were young (e.g., mean age of onset: 6 years) [44] and also demonstrated a rapid progression of pubertal changes. Subsequently, GnRHa use has considerably expanded to include those with a minimally early onset of puberty (e.g., girls ages 7–9 years) who may not necessarily derive similar significant clinical benefits from treatment.

To determine the benefit of GnRHa treatment for individual patients, the following factors should be considered:

1. Girls younger than 7 years and boys younger than 9 years showing progressive central puberty, or who are more advanced in pubertal development (e.g., sexual maturation rating [SMR; i.e., Tanner stage] 3 breast or genital development) with rapid linear growth apparent at their first visit merit GnRHa treatment. A brisk tempo of pubertal progression increases the risk of adult short stature.
2. For girls older than 7 years with SMR 2 breast development, an observation period of 4–6 months is suggested to assess the tempo of pubertal progression before offering treatment. Height outcomes are much less clear for girls with pubertal onset at age 7 years or older. The increase in AH over the predicted height at the onset of therapy varied in one comprehensive review summarizing 29 studies, i.e., from 2 to 10 cm [43], suggesting that some but not all patients benefit from therapy starting at this age. Another report, i.e., a meta-analysis of 6 studies involving 332 girls treated between the ages of 7 and 10 years reported no increase in AH [45]. In fact, most untreated girls with CPP who were not treated with GnRHa reached a normal AH [46–48], although some were shorter than their mid-parental height range.
3. There have been concerns about psychological morbidity of CPP with early menses, but adverse behavioral profiles occurring with early maturation may not be as common as earlier described [49, 50]. Families should be informed that, when puberty starts close to age 8 years or later, menarche usually does not occur for another 2.5–3 years, so an onset before age 10 years is unlikely [4, 51, 52]. Preparation of early-maturing girls for the onset of menses by a calm and reassuring

parent is a key aid to lessening psychological distress. Suppression of menses can still be an option if menarche occurs early and is stressful for the child.

The following are suggestions for an informed discussion of possible GnRHa treatment for an early-maturing girl (onset: 7–9 years of age):

1. If the height is above average, with a skeletal age that is not markedly advanced, the AH will probably be normal and may not significantly improve with treatment.
2. Adverse psychosocial stress may not occur from early puberty but, if it does, GnRHa treatment may not alleviate such stress.
3. Puberty may progress slowly so that menses may not occur as early as feared. Observation for 4–6 months will help to decide whether a child's puberty is progressing rapidly.
4. Treatment is expensive, and in addition there is the stress associated with having a condition requiring a pharmacologic intervention, clinic visits, and periodic injections or implant insertion/removal, among other factors.
5. Several studies have failed to find any benefit in terms of height in girls treated after age 8 years, and some girls may even lose height as a result of treatment [53–59].

Discussion with the parents and child about the goals of treatment (or not) encourages thoughtful consideration of therapeutic restraint, reassurance, and observation, since the benefit of treatment may be uncertain in this age group [60].

Among males, a similar rationale could be applied in consideration of treatment among those who have a borderline early pubertal onset. Regarding height, unless the skeletal age is markedly advanced, it is unclear whether the adult stature will be increased by GnRHa therapy, especially if the treatment interrupts a robust pubertal growth spurt.

## Section 4: Monitoring GnRHa Treatment

The goals of GnRHa therapy for patients with CPP are to halt pubertal progression and progressive physical development, including height for age and differences from age- and sex-matched peers, and to preserve or reclaim the AH potential. Short-term clinical assessment should occur every 3–6 months to evaluate for stabilization of physical changes [36, 61, 62]. The height change velocity generally slows to prepubertal rates within months of the onset of therapy [63, 64]. The development of pubic hair may stabilize or regress but it is not an accurate indicator of HPG axis suppression since adrenarche may have occurred. The rate of skeletal age advancement should decrease after 6 months of therapy, with a concomitant gradual increase in the PAH, assuming a reasonable growth rate. The HPG axis can be evaluated by measuring unstimulated or stimulated (following GnRH or GnRHa administration) serum LH, sex steroids, or urinary gonadotropin concentrations [24, 65–68]. It is recognized that unstimulated LH concentrations above the prepubertal range do not necessarily indicate a lack of suppression, while concentrations within the prepubertal range likely indicate suppression. However, the lack of correlation between biochemical measurements during treatment and AH outcomes does not support routine biochemical testing in all patients [39, 61, 69].

Indicators of treatment failure, including clinical pubertal progression, a lack of growth deceleration, and continued excessive bone age advancement, should prompt reassessment. Treatment failure may be confirmed on clinical grounds alone or verified by GnRHa-stimulated LH concentrations minimally >4 IU/L [39, 69]. The adherence to and timing of GnRHa administration should be assessed when treatment fails, with confirmation that the precocity is CPP rather than a GnRH-independent cause. If increasing the dose of GnRHa is indicated, decreasing the dosing interval is an option.

### *Discontinuation of GnRHa Therapy in CPP*

No single clinical variable can determine the best age to discontinue GnRHa. The decision to discontinue treatment should be individualized, and it is appropriate to inquire about the parents' and the patient's perceptions of readiness to stop, since it can be anticipated that pubertal maturation will resume within months. Menses may occur from several months to more than 2 years after stopping GnRHa treatment. It is reasonable to discontinue therapy at a time such that puberty progresses concurrently with that of the child's peers. Increased AH has been associated with longer treatment [56, 70–72]. However, at some point further GnRHa therapy does not produce further gains in AH, and treatment beyond a bone age of 12.5 years in girls and 14.0 years in boys may at best result in a minimal increase in height [43, 56, 71, 73]. Hence, the timing of GnRHa treatment discontinuation is based on patient readiness for resumption of puberty, recent growth rates and shifts in height prediction rather than on bone age alone. The patient's AH typically ends

up being greater than the AH predicted when the GnRHa treatment is initiated but less than the predicted height when the therapy is discontinued [71–74].

### Section 5: GnRHa Adverse Effects

Adverse effects of GnRHa therapy are rare, and the associations of most reported adverse events with the GnRHa molecule itself are unclear. Decades of experience have shown that GnRHa treatment is both safe and efficacious. The following comments relate to specific adverse events:

1. Allergic or local reactions to GnRHa preparations occur rarely and have been inadequately documented. Local reactions associated with suspensions and histrelin implants occur infrequently. Sterile abscess formation after depot injections is likely a reaction to the inert polymer [53, 75]. Fracture of implants on removal, including the risk of leaving active drug, occurs in 22–28% of cases, more frequently after implants have been left in place for longer than 2 years [31, 62, 76, 77].
2. Withdrawal bleeding due to falling estrogen concentrations may occur after the initiation of GnRHa treatment in girls having a significant endometrial lining. Occurrence beyond 2 months of treatment suggests that gonadotropin suppression has not been achieved or another etiology.
3. Hot flashes are occasionally seen in the initial phases of GnRHa treatment in girls with CPP. This is due to declining estrogen concentrations, but it resolves quickly.
4. Convulsions have been reported in patients receiving GnRHa in postmarketing reports and have included patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies, or tumors and patients on concomitant medications that have been associated with convulsions, such as bupropion and selective serotonin reuptake inhibitors. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above. The data in the literature are limited, consisting of sporadic case reports [78].
5. A prolonged QT interval associated with GnRHa has not been reported in women or children. This has been reported in adult males treated with GnRHa for prostate cancer, attributed to changes in circulating testosterone concentrations and postulated to be related to congenital long QT syndrome, increased body weight, a reduction in insulin sensitivity, dyslipidemia, concomitant medications, cardiac disease, electrolyte abnormalities, and diuretic therapy [79, 80]. For pediatric cases, a screening ECG is recommended only if the individual is receiving other medications known to cause a prolonged QT interval, has a history of congenital heart disease, arrhythmia, or long QT syndrome, has a family history of long QT syndrome or sudden cardiac death, or has symptoms suggestive of long QT syndrome, including syncope [81][1].
6. Slipped capital femoral epiphysis has been reported in a small number of patients, occurring during GnRHa treatment or after cessation of GnRHa therapy [82]. As during normally timed puberty, slipped capital femoral epiphysis may be related to a lack of adequate sex hormone exposure at a critical period of bone formation. Prompt evaluation and management are indicated.
7. Pituitary apoplexy is a rare complication reported in men with prostate cancer treated with GnRHa for androgen deprivation and it develops within hours after the GnRHa administration [83]. In 14 males and 1 female, all were found to have pathologic gonadotropin secreting adenomas, suggesting the potential to precipitate pituitary apoplexy. There have been no reported cases of pituitary apoplexy in children or adolescents.

### Section 6: Long-Term Outcomes

*General Health and Wellness*

While studies indicate that early normal puberty is associated with more frequent risk-taking behaviors and functional symptoms in older adolescents [84], there is insufficient data to determine whether those with CPP with or without GnRHa therapy show such behaviors. GnRHa therapy for early puberty may have adverse metabolic profiles as reported among girls with early normal puberty [84, 85]. These girls with early normal puberty, assumed to be related to a longer chronic estrogen exposure, have an increased risk of breast cancer [86] and unverified increased risks of obesity, type 2 diabetes mellitus, cardiovascular disease, and other malignancies [87]. These reports do not control for secular trends in obesity

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and exposure to endocrine disrupting chemicals. The impact of the addition of GnRHa therapy on these risks is unknown.

*Reproductive Function and Fertility*

There is no substantiated evidence that GnRHa treatment for CPP impairs reproductive function or reduces fertility. In most girls, gonadal function is restored promptly after cessation of therapy, with subsequent menarche and regular ovulatory menstrual cycles [32, 58, 88]. Using structured interviews among 135 adult women with CPP treated with GnRHa, 61 women with untreated CPP, and 466 controls matched for age, education, marital status, and parity [89], pregnancy was uneventful in 90% of all 3 groups. Unassisted pregnancy rates were similar in GnRHa-treated women with CPP and controls (>90%), while, in this series, untreated women with a history of CPP were more likely to require assisted fertility therapy. In another group of 46 women with CPP (aged 19.0–31.3 years), 71% experienced regular, spontaneous menstrual cycles, with normal fertility and offspring. The menstrual history is reported to be normal in all women previously treated with GnRHa for CPP, except for those with organic causes such as anterior pituitary lesions [56]. The outcomes of 113 pregnancies included 97 uneventful pregnancies with healthy children, 5 elective abortions, and 11 early miscarriages.

Limited data exist on reproductive function in males treated for CPP but they include normal serum testosterone [32, 90], gonadotropin concentrations, and semen analysis [90]. Data on paternity rates and fertility are not available.

*Polycystic Ovary Syndrome*

There is no clear evidence that girls with treated or untreated CPP are more likely to develop polycystic ovary syndrome (PCOS) than their age-matched peers [55, 84, 89, 91–96]. Reports include a significant incidence of PCOS in former CPP patients [97], with a lower prevalence of PCOS in GnRHa-treated girls than in nontreated girls (17.2%, $n$ = 33, vs. 30.8%, $n$ = 14), with elevated DHEAS and androstenedione concentrations in 56% of those receiving GnRHa versus 23.6% among those who did not [55]. Another report using single logistic regression analysis found that GnRHa treatment correlated with PCOS ($p$ = 0.03) when comparing 36% of 25 girls diagnosed with PCOS who had been previously treated with GnRHa for CPP with 14.5% of 55 girls who had had CPP untreated with GnRHa [95]. However, these percentages are high and it is unclear whether there was representative sampling and whether diagnostic criteria fit published incidence studies that indicate a lower frequency [98]. Further, since data do not determine whether hyperandrogenemia preceded the diagnosis or treatment of CPP, it is possible that this is a preselected biased group. Future studies should use the Recent International Consortium Update [99] to classify both treated and untreated CPP subjects.

*Psychological Outcome*

Some early studies suggested that psychological and social problems occur among girls with CPP [100–102], citing anxiety about breast development and other physical differences from peers. Subsequent reports have not substantiated such findings. A study of 19 girls with CPP, 22 girls with premature adrenarche, and 21 girls with early normal puberty found no significant differences in peer acceptance or child psychological adjustment [103]. No significant differences in anxiety, depression, somatization, attention deficit, offensive behavior, or academic performance were found before or after 24 weeks of GnRHa treatment in those with CPP. Using adaptation profiles, social competency was not significantly higher than that of peers before treatment onset [101]. Another report did not show significantly more behavior problems in girls with CPP than in age-matched healthy controls [50]. In contrast, another report found that GnRHa-treated girls with CPP had higher total scores of physical and psychological stress with a depressive component before GnRHa treatment, and stress scores were reduced in all patients after a year of GnRHa treatment [104]. The lack of uniformity regarding the psychological impact of GnRHa treatment in children with CPP is not surprising since individuals are unique, with both innate and environmental factors influencing responses to pubertal changes. Thus, there is no basis for expecting a different incidence of psychological problems among those who had CPP with or without therapy than in the general population, although more research is needed.

*Impact on Weight*

Although it has been suggested that weight gain occurs with GnRHa treatment of CPP [105–108], a reduction in BMI has also been reported [109]. Long-term studies have not supported the concept of treatment-related weight gain when comparing BMI SD scores before and after therapy, even though there is an increased prevalence of being overweight and obese at diagnosis [58, 109–112]. The weight status of women who had CPP resembles that of the general population [113]. A higher

BMI percentile at presentation and during therapy was associated with being overweight or obese during young adulthood. Thus, GnRHa treatment appears not to influence the long-term progression of these children toward obesity during adolescence or adulthood.

*Bone Mineral Density*

Children with CPP often have an elevated bone mineral density (BMD) for their age at diagnosis. GnRHa treatment slows mineral accrual, but after discontinuation BMD appears not to be significantly different from that of their peers by late adolescence. Reports of BMD among children and adolescents verified a decrement in BMD at the achievement of near AH, while accrual resumed after therapy, regardless of whether or not calcium supplementation was given. By late adolescence, all subjects had BMD within the normal range [114, 115]. A recent report of assessment during therapy suggested structural alterations, but those adolescents were not evaluated after stopping therapy [116]. Data suggest that, while children treated with GnRHa have a diminished bone accrual during treatment, it is likely that BMD is within the normal range after cessation of therapy by late adolescent ages.

## Section 7: Use of GnRHa in the Management of Transgender Adolescents

Current guidelines include criteria for initiating treatment with GnRHa [117, 119]. Therapy should only be initiated after the individual has begun clinical puberty (breast or genital SMR 2 and testicular volume ≥4 mL) [117]. In transgender boys, GnRHa may be continued until subsequent testosterone therapy has resulted in serum concentrations within the adult reference range. In contrast, adult dose estrogens frequently do not suppress testosterone production in transgender girls, so GnRHa therapy may be continued if the testes remain in situ [117]. Initial treatment of young transgender adolescents with GnRHa is commonly recommended to prevent the development of undesired secondary sex characteristics [117, 118]. Such reversible treatment enables an extended diagnostic phase for gender clarification before electing to proceed with further gender-affirming hormone treatment [119, 120].

GnRHa suppress the HPG axis, resulting in a decreased testicular volume and the cessation of menses [121, 122]. Additional changes include a decrease in height SDS and BMD along with alterations in body composition consisting of increased body fat and a decreased lean body mass [121]. The impact on BMD is concerning since lumbar spine Z-scores at age 22 years were found to be lower than those observed prior to treatment [122, 123], suggesting a possible permanent decrement in BMD. Thus, it is unclear how long GnRHa can safely be administered. The effects of GnRHa on adolescent brain maturation are unclear. GnRHa therapy prevents maturation of primary oocytes and spermatogonia and may preclude gamete maturation, and currently there are no proven methods to preserve fertility in early pubertal transgender adolescents. Care for each adolescent must be individualized, with awareness of gender fluidity and ethical guidelines [124].

## Section 8: Use of GnRHa in Other Conditions

*GH Deficiency*

In GH-deficient children, the addition of GnRHa may be considered in 2 situations:

1. Children treated for malignancy with a resultant GH deficiency and CPP. In this group of patients, GnRHa and GH therapy increases the PAH and the AH [125–128].
2. Children with a GH deficiency who have not experienced catch-up growth at the onset of puberty since an insufficient height at pubertal onset will result in a short AH. Therapeutic combinations in this situation have involved increased GH doses [129], the addition of aromatase inhibitors [130], and the addition of GnRHa to halt pubertal progression and allow more GH-augmented prepubertal growth. The addition of a GnRHa to GH at the onset of puberty and treatment for at least 2 years resulted in gains of AH ranging from 6 to 9 cm (~1–1.5 SD) [131, 132]. These situations are not the usual practice for patients diagnosed with an isolated GH deficiency and treated in a timely manner with GH. Such use of GnRHa or aromatase inhibitors remains controversial and is not standard of care.

*Non-GH-Deficient Short Stature*

Adolescent growth has been the focus of several interventions aimed at increasing the amplitude of the adolescent growth spurt. Favorable results with GnRHa in precocious puberty have encouraged attempts to increase the duration of the adolescent growth spurt by delaying normal puberty in short subjects using GnRHa with or without GH treatment. Controlled prospective [133,

134], uncontrolled prospective [135], and retrospective analyses [136] indicate that the use of GnRHa alone in these cases lacks efficacy. In a randomized, placebo-controlled trial in short adolescents with normally timed puberty (most having idiopathic short stature), 18 boys and 32 girls with baseline predicted AH of −3.3 ± 1.2 SD were randomized to receiving either placebo or GnRHa. Those who received GnRHa had a 0.6 SD increase in AH (~4.2 cm, range 1.7–6.7 cm) compared to the predicted AH at baseline ($p$ = 0.01) after a mean duration of 3.5 ± 0.9 years; however, they also demonstrated a significant reduction in BMD [115]. A recent study of GnRHa treatment of idiopathic short stature during puberty reported that AH in treated girls was significantly greater than among untreated girls but not boys [137]. It should be noted, however, that the treated (21 girls and 7 boys) and untreated (14 girls and 17 boys) groups were not matched, with the latter group being those offered but declining GnRHa therapy. There was considerable variation in response to therapy, and the group size for girls may have been sufficiently large to yield a statistically significant response, while the group of boys may have been too small. Some studies have shown that combined GH and GnRHa treatment for 3 or more years may result in a greater increase in AH [138–142], particularly in adopted girls [140, 141].

However, a recent publication regarding combined therapy found that, not unexpectedly, patients treated with the combination grew more slowly than those receiving GH alone during the first 2–3 years of treatment. Statistical comparison of near AH SDS between the 2 groups was not possible [143]. In addition to height, the cost-benefit of such invasive treatments should also be considered, and further larger, long-term, and adequately powered clinical trials, focusing on efficacy, safety, and clinical significance, are needed to fully evaluate the combination of GH and GnRHa in short adolescents. Meanwhile, these approaches should be considered as experimental.

*Small for Gestational Age*

Pubertal height gain is less than expected in children born SGA, as a result of an earlier onset of puberty, an earlier peak height velocity, and accelerated bone maturation [144, 145]. Evidence suggests that combined GH and GnRHa treatment may increase AH in SGA children who are short at the start of puberty (<140 cm) and who have a subnormal PAH [146]. The mean height gain from the onset of puberty until AH, including the height gain during 2 years of GnRHa treatment, was 25.4 cm in girls and 33.0 cm in boys, i.e., 6.6 cm more than girls and boys treated with GH alone [147]. Hence, although the data are limited, it is appropriate to consider the potential advantages and disadvantages of treatment with GH and GnRHa in this population.

*Fertility Preservation*

GnRHa treatment has been administered just before and during chemotherapy to minimize the risk of premature ovarian insufficiency by reducing exposure to cytotoxic agents and protecting the developmental process of primordial follicles [148]. Systematic reviews and meta-analyses show a higher recovery rate of cyclic ovarian function after chemotherapy in patients treated with GnRHa before and during chemotherapy than untreated groups [149–154]. However, the results were mixed depending on the type of tumor [155–159]. Additionally, there are no long-term randomized, controlled studies. Thus, the efficacy of fertility preservation by GnRHa in adults is still controversial. Furthermore, there are few efficacy data in adolescent girls [160, 161]. Because primordial follicles and eggs do not originally have receptors for GnRH and thus GnRHa cannot directly protect primitive follicles from chemotherapy toxicity [160], and because the efficacy of fertility preservation of GnRHa is still controversial, the use of GnRHa before and during chemotherapy for all adolescents with malignancies is currently not recommended outside of clinical trials.

*Autism, Problematic Behavior, and Developmental Impairment*

GnRHa treatment cannot be recommended for autism as there is no validated evidence of efficacy. A single article reported that GnRHa usage in both prepubertal and pubertal children with autism improved behavioral symptoms (e.g., reduced aggressiveness and inappropriate sexual behavior) in the short term [162]. Attempts to replicate these data have not been successful. There is no evidence of any longstanding improvement in patients' inappropriate behavior or use of such therapy in children with autism [163]. Although GnRHas have been used to treat patients with developmental problems (i.e., males who masturbate in public and females unable to care for themselves during menstruation), preventing pubertal progression can be seen, at best, as a temporary measure.

## Conclusion

While much of the information discussed above is not published in well-controlled studies or even published at all, this concise summary has included items that are pertinent to the diagnosis and care of those treated with GnRHa. It is clear that many changes have occurred in the clinical use of GnRHa without the benefit of peer-reviewed publications. These changes appear to have been driven by an understanding that detailed testing may not be necessary to diagnose CPP or to monitor GnRHa therapy as well as the demands for pragmatic clinical approaches. Hence, when a single LH verifies pubertal secretion or when the clinical findings for patients on treatment are consistent with suppression, additional testing may be considered unnecessary. Nevertheless, carefully conducted outcome studies, preferably prospective controlled studies, are needed to verify dosing, monitoring, and long-term outcomes. Likewise, research is required to determine a basis for weight-based dosing of depot preparations, to compare efficacy and safety profiles of depot injections, and to assess subcutaneous versus intramuscular administration, as well as to examine other unpublished changes that are listed in the Introduction.

## Disclosure Statement

The authors declare no conflict of interests relevant to this paper.

## List of Participating Societies

Pediatric Endocrine Society (PES), ESPE, Australasian Pediatric Endocrine Group (APEG), Asia Pacific Paediatric Endocrine Society (APPES), African Society for Paediatric and Adolescent Endocrinology (ASPAE), Japanese Society for Pediatric Endocrinology (JSPE), Sociedad Latinoamericana de Endocrinologia Pediatrica (SLEP), Chinese Society for Pediatric Endocrinology and Metabolism (CSPEM), Indian Society for Paediatric and Adolescent Endocrinology (ISPAE), Canadian Pediatric Endocrine Society (CPES), and Sociedad Mexicana de Endocrinología Pediátrica (SMEP).

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**Scientific Statement**



# Endocrine Health and Health Care Disparities in the Pediatric and Sexual and Gender Minority Populations: An Endocrine Society Scientific Statement

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## Abstract

Endocrine care of pediatric and adult patients continues to be plagued by health and health care disparities that are perpetuated by the basic structures of our health systems and research modalities, as well as policies that impact access to care and social determinants of health. This scientific statement expands the Society's 2012 statement by focusing on endocrine disease disparities in the pediatric population and sexual and gender minority populations. These include pediatric and adult lesbian, gay, bisexual, transgender, queer, intersex, and asexual (LGBTQIA) persons. The writing group focused on highly prevalent conditions—growth disorders, puberty, metabolic bone disease, type 1 (T1D) and type 2 (T2D) diabetes mellitus, prediabetes, and obesity. Several important findings emerged. Compared with females and non-White children, non-Hispanic White males are more likely to come to medical attention for short stature. Racially and ethnically diverse populations and males are underrepresented in studies of pubertal development and attainment of peak bone mass, with current norms based on European populations. Like adults, racial and ethnic minority youth suffer a higher burden of disease from obesity, T1D and T2D, and have less access to diabetes treatment technologies and bariatric surgery. LGBTQIA youth and adults also face discrimination and multiple barriers to endocrine care due to pathologizing sexual orientation and gender identity, lack of culturally competent care providers, and policies. Multilevel interventions to address these disparities are required. Inclusion of racial, ethnic, and LGBTQIA populations in longitudinal life course studies is needed to assess growth, puberty, and attainment of peak bone mass. Growth and development charts may need to be adapted to non-European populations. In addition, extension of these studies will be required to understand the clinical and physiologic consequences of interventions to address abnormal development in these populations. Health policies should be recrafted to remove barriers in care for children with obesity and/or diabetes and for LGBTQIA children and adults to facilitate comprehensive access to care, therapeutics, and technological advances. Public health interventions encompassing collection of accurate demographic and social needs data, including the intersection of social determinants of health with health outcomes, and enactment of population health level interventions will be essential tools.

**Key Words:** health disparities, health care disparities, health equity, sexual and gender minority, pediatric endocrine, growth, puberty, diabetes mellitus, obesity

**Abbreviations:** 25OHD, 25-hydroxyvitamin D; AIAN, American Indians and Alaskan Natives; API, Asians and Pacific Islanders; BMD, bone mineral density; CDGP, constitutional delay of growth and puberty; CGM, continuous glucose monitoring; DKA, diabetic ketoacidosis; DSD, Disorders of Sexual Development; DSM, Diagnostic and Statistical Manual of Mental Disorders; DXA, dual-energy x-ray absorptiometry; EDC, endocrine disrupting chemical; ESR1, estrogen receptor alpha; GAHT, gender-affirming hormone therapy; GHD, growth hormone deficiency; GnRHa, gonadotropin releasing hormone agonist; GWAS, genome-wide association study; ICD, International Classification of Diseases; ISS, idiopathic short stature; LGBTQIA, lesbian gay bisexual transgender queer intersex and asexual; NHB, non-Hispanic Black; NHW, non-Hispanic White; QOL, quality of life; RED-S, relative energy deficit syndrome; SDoH, social determinants of health; SGA, small for gestational age; SGM, sexual and gender minority; SES, socioeconomic status; SNP, single nucleotide polymorphism; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; WHO, World Health Organization.

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Recognizing that health disparities exist among population subgroups with respect to disease burden, comorbidities, and outcomes, the Endocrine Society released its inaugural scientific statement on health disparities in 2012. These disparities continue to be pervasive throughout the world, making inequities in health and health care among the most pressing issues facing science and medicine today. Our expanded understanding of factors that contribute to these disparities recognizes that biological differences associated with poor disease outcomes in marginalized communities result from unequal access to high-quality health care and social conditions and policies that perpetuate health inequities. In 2008, the World Health Organization (WHO) Committee on Social Determinants of Health (SDoH) published a report proposing the ambitious goal of achieving health equity within a generation stating "Social injustice is killing people on a grand scale" (1).

Given endocrinology's expansive scope, the inaugural statement focused on health disparities in highly prevalent endocrine conditions in adults. These included type 2 diabetes mellitus (T2D) and related conditions (prediabetes and diabetes complications), gestational diabetes, metabolic syndrome with a focus on obesity and dyslipidemia, thyroid disorders, osteoporosis, and vitamin D deficiency. A high-level summary of findings from the 2012 scientific statement is included in Table 1. The statement reported that that for certain endocrine disorders (1) there were discrepancies between incidence and mortality by race/ethnicity and sex; (2) obesity and body fat distribution were important contributors to race/ethnic and sex differences in disease incidence and outcomes; (3) heterogeneity in subgroups of Hispanic American and Asian American people resulted in disparities within these groups, and (4) genetic differences were not significant contributors to disparities. Several themes emerged in the statement, including a need for basic science and translational studies to explore underlying molecular mechanisms that may contribute to endocrine health disparities, in addition to the need to explore the etiology in clinical, population-based, and health services research studies.

Since publication of the 2012 scientific statement, health and health care disparities have continued to plague our societies globally, as highlighted by the COVID-19 pandemic. Endocrine conditions, particularly diabetes and obesity, have been highlighted as enhancing mortality risk among people with COVID-19. Because these endocrine disorders are highly prevalent in Black, Hispanic, Native American, and Pacific Islander communities, people in these groups have experienced higher mortality rates in the setting of COVID-19. The disproportionate impact of health disparities on these populations again highlights the importance of addressing the underpinnings of these disparities and working to eradicate them. Most recently, medical societies have acknowledged that race is a social and not biological construct, and gender "inhabits a complex social system that structures the life experience of human beings"(2, 3). Several medical societies, including the Endocrine Society, have called for the reexamination, if not elimination, of race-based medicine (4).

Several endocrine conditions and vulnerable populations were not addressed in the inaugural statement due to insufficient data. However, over the last 10 years, new information has drawn attention to additional populations where disparities in endocrinology also exist. This updated scientific statement will examine disparities in and barriers to care in pediatric endocrine health disorders and endocrine care of adult and pediatric sexual and gender minority populations (SGM; eg, lesbian, gay, bisexual, transgender, queer/questioning [LGBTQ] persons). We will also conceptualize contributors to health and health care disparities with an eye toward multilevel interventions that have been shown to reduce disparities and improve clinical outcomes. While the bulk of the information presented here reflects United States (US) populations, international data will be addressed in conditions where sufficient information exists.

Research suggests that many health disparities experienced in adulthood are rooted in early childhood. For instance, exposure to stressors (in pediatrics often described as adverse childhood experiences) can negatively affect health over a person's lifetime, disrupting metabolic, neurological and immunological systems, and contributing to poor developmental outcomes (5). There are race/ethnic/sex differences in adverse childhood experiences. Health disparities in pediatrics may negatively contribute to and complicate care for children with chronic endocrine conditions and further negatively exacerbate downstream adult morbidity and mortality. Examination of health disparities in pediatric endocrine disorders must also consider the unique characteristics of child developmental stages and the impacts of health disparities at each of these junctures, many of which are believed to be critical "windows," biologically and psychosocially. Moreover, infants, children, and teenagers do not function as independent agents of their own health care; they are subject to the ability of parents or guardians to function effectively in the health care system and society at large, and are thus characterized as vulnerable populations.

In SGM populations, health disparities exist in cardiovascular disease, malignancies, fertility, and in the ability to access necessary, timely, and appropriate high-quality medical care. We will examine how these disparities may be exacerbated by the intersection of racism, transphobia, and sexism (6). Restrictive environments, where care is expressly prohibited, are especially deleterious for both physical and mental health outcomes for SGM populations.

In addition to examining the biological consequences of race, ethnicity, and sex in pediatric endocrine and SGM populations, we include an overview of structural factors that contribute to health disparities in these populations. With the COVID-19 pandemic, modalities of care expanded and new avenues opened for routine care of endocrine patients, such as telehealth. As noted in the 2022 Appropriate Use of Telehealth Visits in Endocrinology: Policy Perspective of the Endocrine Society, careful consideration will need to be given about how to use these tools to improve health equity, not exacerbate existing injustices (7). The 2003 Institute of Medicine report, "Unequal Treatment," (8) did not include SGM and pediatric populations as data then were scarce; however, issues perpetuating health disparities related to the health care system, the provider, and the patient continue to hold true for multiple marginalized populations almost 20 years after its publication.

## Literature Search Strategy

We conducted a comprehensive English language literature search of PubMed to identify international and US population-based studies, systematic reviews, and meta-analyses. To identify literature focused on race/ethnic and

**Table 1. Major race/ethnic and sex disparities in adults**

| | |
|---|---|
| Discrepancies in endocrine disease incidence and mortality | Compared with non-Hispanic White (NHW) populations, non-Hispanic black (NHB) populations have worse outcomes and higher mortality from certain disorders despite having a lower (eg, macrovascular complications of diabetes mellitus and osteoporotic fractures) or similar (eg, thyroid cancer) incidence of these disorders<br>• Inadequate access to high-quality health care among minoritized populations |
| | NHBs with diabetic nephropathy have lower mortality on dialysis than NHW despite higher incidence of end-stage renal disease |
| Contributions of obesity to endocrine disease disparities | Obesity is an important contributor to diabetes risk in minority populations and to sex disparities in thyroid cancer, suggesting that interventions targeting weight loss may favorably impact multiple endocrine disorders. |
| | There are important implications regarding the definition of obesity in different race/ethnic groups, including potential underestimation of disease risk in Asian Americans and overestimation in NHB women<br>• Ethnic-specific thresholds for central obesity should be determined so that clinicians can adequately assess metabolic risk |
| Sex differences in endocrine disorders | Sex disparities exist in certain endocrine disorders, with autoimmune thyroid disease and cardiovascular complications of diabetes being more common in women than men |
| Identifying heterogeneity in race/ethnic groups | A major gap in our current understanding of race/ethnic disparities in endocrine disorders is a failure of most studies to specify Hispanic American and Asian American subgroups<br>• Where these data are available, clear ethnic-specific differences exist within Hispanic and Asian subgroups, particularly related to diabetes and obesity risk |
| | In general, there are few data on endocrine disorders in AIAN |
| Genetic contributors to endocrine disorder disparities | There is little evidence that genetic differences contribute significantly to race/ethnic disparities in the endocrine disorders examined, but significant heterogeneity and admixture[a] among populations may mask genetic differences in GWAS studies |

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[a]Refers to being biracial or multiracial.
Abbreviations: AIAN; GWAS.

sex disparities in pediatric endocrine disorders, we used a combination of Medical Subject Headings (MeSH, controlled vocabulary) terms, keywords, and phrases to develop search algorithms for 3 concepts: the first was a search filter defining racial, ethnic, and sex differences for specific populations; the second defined pediatric and adolescent populations; and the third described a specific endocrine disorder or condition. We applied the algorithm to each disorder to optimize search consistency. To identify literature focused on disparities in endocrine disorders in SGM in pediatric and adult populations, we used a combination of MeSH terms and keywords and phrases to develop search algorithms to identify 2 concepts: a filter defining the LGBTQIA group and a second defining the endocrine disorder or condition. Through these searches we identified systematic reviews, meta-analyses, large cohort and population-based studies, as well as original studies that focused on the prevalence and determinants of disparities in endocrine disorders.

## Definitions of Race and Ethnicity

As in our prior scientific statement (9), we use Williams' definition of ethnicity as "a complex multidimensional construct reflecting the confluence of biological factors and geographical origins, culture, economic, political and legal factors, as well as racism" (10). Although there are many ethnicities and nationalities, in the United States, ethnicity denotes the presence or absence of Hispanic, Latinx, or of Spanish origin (9). By contrast, race is a social construct—a created set of categories based on arbitrary physical attributes such as skin color, hair color/texture, and facial and other physical features (9).

There was significant variation in the terms used to define specific race/ethnic groups in the literature reviewed for this Statement. For consistency, we used the terms non-Hispanic Black (NHB), non-Hispanic White (NHW), Hispanic American, Asian American, and Native American as defined in Table 2. We acknowledge that these categories may be arbitrary, often contain heterogeneous groups, and may not fully account for biracial individuals. We indicated in the text when studies were more specific in defining ethnic subgroups, particularly for Black, Asian, and Hispanic individuals. We also recognize that some individuals within each ethnic subgroup may be a mix of foreign/native born and may have a racial and ethnic identity and other groups (eg, those from the Middle East and North Africa) do not self-identify as White or Black.

## Definitions of Sex, Gender, Gender Identity, and Sexual Orientation

In this statement we expand the term "sex differences" to describe health outcomes specific to being male or female according to reproductive organs and chromosomal complement (13, 14), as well as "gender identity," reflecting a person's internal sense of being male, female, both, or neither (15). Sex and gender are umbrella terms that reference biological characteristics, gender identification, and the presence or absence of behaviors considered stereotypically masculine or feminine (15). Cisgender describes persons whose gender identity is aligned with their sex recorded at birth; however, there are several descriptors for gender incongruent persons whose gender identity is not aligned with their recorded sex at birth (see Table 3). The lexicon describing sexual orientation and gender identity continues to evolve, with increased emphasis on diversity of possible sexual orientations or gender identities that people may attribute to themselves (16).

**Table 2. Definitions of race and ethnic groups**

| | Race/ethnic groups |
|---|---|
| Non-Hispanic Black (NHB) | Individuals with descent from any of the Black racial groups of Africa (eg, African American, African, Afro-Caribbean) |
| Non-Hispanic White (NHW) | Nonminoritized individuals of White European descent but not of Hispanic ethnicity |
| Hispanic | Individuals with descent from Cuba, Mexico, Puerto Rico, South or Central America, or other Spanish culture or origin, regardless of race |
| Asian | Individuals with descent from the following regions:<br>• Central Asia (Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan)<br>• East Asia (China [including Macau and Hong Kong], Japan, Mongolia, North Korea, South Korea, Taiwan)<br>• South Asia (Afghanistan, Bangladesh, Bhutan, India, the Maldives, Nepal, Pakistan, and Sri Lanka)<br>• Southeast Asia (Burma, Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, Timor-Leste, and Vietnam)<br>• Western Asia (Armenia, Azerbaijan, and Georgia) |
| Middle Eastern and North African (MENA) | Individuals with descent from the following regions:<br>• Middle East (Bahrain, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Oman, Palestine Qatar, Saudi Arabia, Syria, United Arab Emirates, Yemen<br>• North Africa (Algeria, Egypt, Libya, Morocco, Sudan, Tunisia) |
| Indigenous Peoples | • American Indians and Alaska Natives—individuals with descent in any of the original peoples of North and South America (including Central America) born and/or residing in the United States and who maintains tribal affiliation or community attachment<br>• Non-American indigenous individuals |
| Native Hawaiian/Other Pacific Islander | Individuals with descent from the original peoples of Polynesia, Micronesia, and Melanesia<br>• Polynesia includes American Samoa, Hawaii, Samoa, , Tahiti, Tokelau, and Tonga<br>• Micronesia includes Chuuk, Guam, Kiribati, Kosrae, Mariana Islands, Marshall Islands, Palau, Pohnpei, Saipan, and Yap<br>• Melanesia includes Fiji, Papua New Guinea, Solomon Islands, and Vanuatu |

United States Census Bureau. *Office of Management and Budget (OMB) Standards*. 2020. United States Census Bureau. Washington, DC.; *Defining Diaspora: Asian, Pacific Islander, and Desi Identities*. 2021. Cross-Cultural Center, California State University, San Marcos (11, 12).

Given that most individuals identify as straight/heterosexual and cisgender, the term *sexual and/or gender minority* has been used in medical literature to describe individuals with either a sexual orientation or gender identity which diverges from this majority group, highlighting that this minority status may place members of a sexual and/or gender minority at increased risk for health disparities. The term *LGBTQ*, an acronym for lesbian, gay, bisexual, transgender, queer (or questioning) has been used in both medical and nonmedical settings to describe this population. An alternative acronym, *LGBTQIA*, highlights the inclusion of *intersex*, *asexual*, and *agender* individuals. We will therefore also describe variation in health outcomes for endocrine disorders by sexual orientation, which describes the pattern of romantic or sexual attraction to other people, independent of gender identity (18) (see Table 4). Throughout the statement we use the term "sexual and gender minorities" (SGM) to describe disparities in health outcomes and health care among members of LGBTQIA populations.

## A Conceptual Framework for Race/Ethnic and Sex Disparities in Pediatric Endocrine Disorders

We build on the conceptual framework adapted from Warnecke et al included in our 2012 Scientific Statement. It combines a population health framework with a quality of care framework to guide our understanding of the multilevel contributors to disparities in endocrine disorders, which can help to inform interventions (9, 19). We describe the contributors to disparities in each section of our current statement in the context of this framework and note where gaps persist in our current understanding. This framework recognizes population-level determinants of health outcomes as distinct from, but intertwined with, individual-level determinants of health (Fig. 1) (9, 19). The model identifies proximate, intermediate, and distal factors that influence health. Proximate determinants of health include biological and genetic pathways, biological responses, individual health behaviors, and individual demographic and social factors. Genetic ancestry, epigenetic changes induced by environmental stress and adverse childhood experiences, and allostatic load induce biological responses that may increase disease risk (9). Biological responses include poor glycemic control, obesity, hyperlipidemia, poor blood pressure control, and longer-term complications of diabetes, including cardiovascular disease, renal disease, and stroke. Behaviors that influence disease risk or outcomes include diet, tobacco and alcohol use, medication adherence, and disease self-management (9). Individual-level demographic characteristics affecting a person's capacity to respond to environmental challenges include age, race/ethnicity, language, literacy, cultural beliefs, education, income, social support, and acculturation (9).

The intermediate determinants of health include neighborhood- or community-level physical and social environments, as well as the health care delivery environment (9). The physical context, influenced by past policies such as redlining, includes factors such as neighborhood stability, accessible recreational facilities, and healthy foods. The social

**Table 3. Gender identity definitions**

| Descriptor | Definition |
|---|---|
| Cisgender | Person whose gender identity aligns with the sex recorded at birth |
| Transgender/ Trans | • Used umbrella terms describing gender identity that is not cisgender<br>Transgender Female/Transfeminine/Trans woman<br>• Person recorded male at birth but who has a gender identity on the feminine spectrum<br>Transgender Male/Transmasculine/Trans man<br>• Person who was recorded female at birth but who has a gender identity on masculine spectrum |
| Genderqueer | Person whose gender identity and/or gender expression falls outside of the masculine/feminine gender binary |
| Nonbinary | Person who does not exclusively have a gender identity that is either male or female |
| Agender | Person who does not identify with any gender |
| Intersex | General term for conditions in which a person is born with reproductive or sexual anatomy that does not fit the typical definition of male or female (also known as differences in sexual differentiation). Intersex individuals may incorporate their being intersex as an important element of identity similar to sexual orientation and gender identity (17) |

Safer JD & Tangpricha V. *N Engl J Med*. 2019; 381(25):2451-2460; Shumer DE et al. *Adv Pediatr*. 2016; 63(1):79-102. (15, 16)

**Table 4. Sexual orientation definitions**

| Descriptor | Definition |
|---|---|
| Straight | Person who identifies as a heterosexual and is attracted to members of the opposite gender in a binary view of gender such as men attracted to women and vice versa (not lesbian or gay) |
| Lesbian | A woman who is emotionally, romantically, sexually, affectionately, or relationally attracted to other women or who identifies as lesbian |
| Gay | A person who is emotionally, romantically, sexually, affectionately, or relationally attracted to others of the same sex or who identifies as being gay. The term is often used to describe when men are attracted to men. However, the term is also used by some as an umbrella term to encompass all sexual minority groups, including those who are lesbians and bisexual |
| Asexual | Person who does not experience sexual attraction towards other people and who identifies as asexual. May still have romantic, emotional, affectional, and relational attractions to other people |
| Bisexual | A person who is emotionally, romantically, sexually, affectionately, or relationally attracted to both men and women or who identifies as bisexual |
| Pansexual | A person who is emotionally, romantically, sexually, affectionately, or relationally attracted to other people regardless of their gender identity |

Reprinted from *GLAAD Media Reference Guide*, 11th Edition. 2022. Glossary of Terms: LGBTQ. (18)

context includes factors such as community-level poverty, resource availability, and social interactions, and the health care delivery context includes access to care, quality of care, provider characteristics, availability of interpretation services, and diverse aspects of the patient–provider relationship (eg, adequate clinical and cultural training to care for diverse patient populations) (9). We hypothesize that it is through these intermediate determinants that distal social and policy factors influence individual behavior (9) (Fig. 2). Finally, distal factors include population social conditions (eg, poverty, discrimination, prejudice) and policies that affect social conditions, and the organizations and institutions that determine or influence these policies.

As reviewed recently, many of our health care and social conditions and policies in the United States have long-standing historical context, which has adversely impacted the metabolic health of certain communities (Fig. 2) (9). Hundreds of years of unconsented medical and research experimentation on vulnerable groups and perpetuation of eugenics theory (purporting that certain racial and ethnic groups were biologically inferior to others) in the early 20th century violated patients' trust, leaving residual health care provider biases toward minority patients, ultimately driving poor quality health care (9). Employment discrimination diminished access to high-quality jobs with adequate health insurance, and farm and domestic labor were excluded from Social Security benefits of New Deal legislation, disproportionately impacting Black, Hispanic, immigrant, and female workers (21). Discriminatory housing and lending policies resulted in residential segregation and neighborhoods with substandard housing, limited access to healthy foods, recreational resources for physical activity, educational resources, and economic investments. Taken together, these forces laid the foundation for our present-day SDoH (Fig. 2) (20). In the Native American community, the Homestead Act of 1862 and Desert Land Act of 1877 led to the drying up of the Gila River resulting in the reliance of Native Americans on reservations established in the prior century (another form of racial residential segregation) and government subsidies. In turn, this led to reduced physical activity and access to healthy nutrition due to disruptions in traditional agriculture and hunting practices (21).

Discrimination in the educational system and the resulting school to prison pipeline impair opportunities for higher education and future job prospects for minoritized youth, cementing poverty as adults (22). Black and Latinx children and adolescents are more likely to be suspended or expelled from school and to be referred to the juvenile justice system than White children (23). As discussed throughout this Statement, understanding these historical and present-day contextual contributors to disparities in endocrine disorders will lay the foundation for describing what interventions are needed to address and eliminate them.

## Pediatric Growth Disorders

Worrisome growth is among the most common problems encountered by pediatric endocrinologists. It can be a symptom

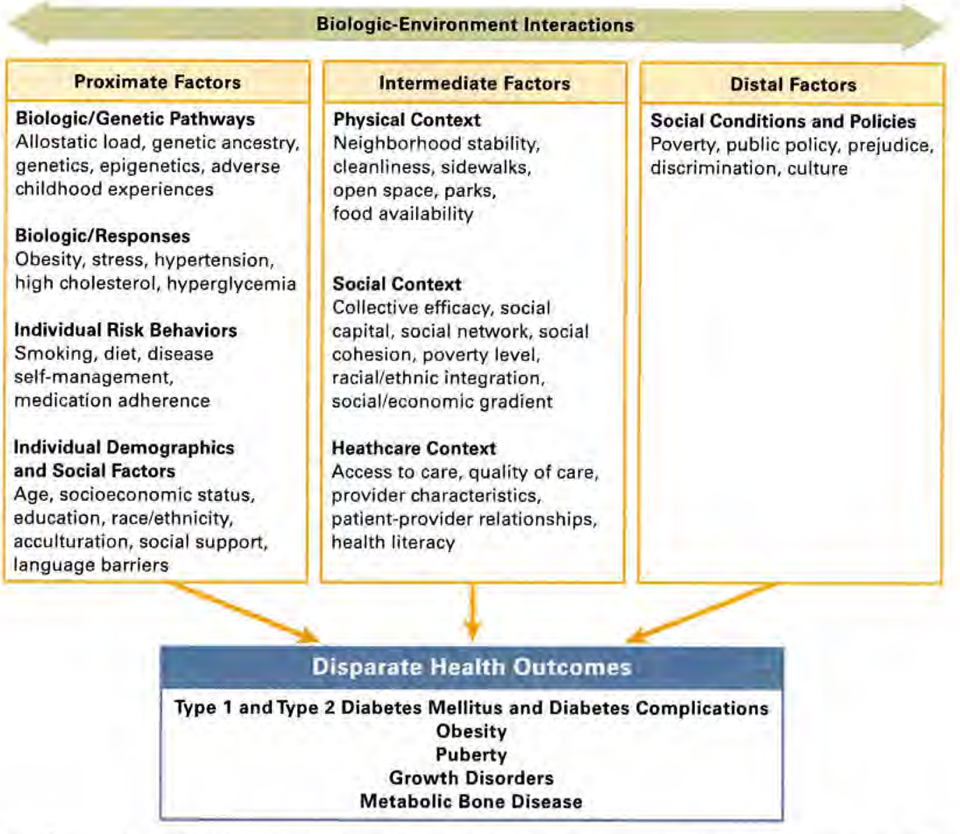


**Figure 1.** Conceptual framework model for disparities in endocrine disorders. Adapted with permission from the author from Warnecke RB et al. *Am J Public Health*, 2008;98(308):1608–1615. (19)

of pathology but is most often result of variation in normal growth patterns. For some children, treatment with recombinant human growth hormone (rhGH) may be considered. As stated by Halas and Grimberg, "Combining issues in defining "normal," the reliability of data and testing, discrepancies in diagnostic cutoffs, demographic skew, patient/parent/pediatrician interaction, societal and commercial pressures, treatment safety, treatment efficacy and expectations, impact on psychosocial function, and considerations of cost and coverage, a discussion of pediatric rhGH treatment is a prismatic study of the problems that affect medicine as a whole." (24)

Review of commercial insurance claims data showed that in the United States, treatment with rhGH nearly tripled from 2001 to 2016 among people under the age of 18, from 5.1 to 14.6 claims per 10 000 beneficiaries (25). The U.S. Food and Drug Administration (FDA) has approved rhGH treatment for 8 pediatric conditions (Table 5), of which idiopathic short stature (ISS, unexplained short stature sufficiently severe to cause height below −2.25 SD for age and sex—in other words, below the 1.2nd centile on the Centers for Disease Control and Prevention reference charts and not expected to result in an adult height in the normal range if left untreated) encompasses the potentially largest group (26). Not only did the ISS indication greatly increase the potential number of children for whom rhGH treatment may be prescribed, but it shifted the focus from treating underlying pathology to treating short stature per se; rhGH thus represents "expansive biotechnology," whereby a biomedical technology expanded from treating disease (in this case, growth hormone deficiency [GHD]) to treating conditions that blur the boundary between disease and variations of normal (35).

Although the desire for rhGH-mediated height enhancement prompts many referrals to pediatric endocrinologists, rhGH is indicated for only a small subset of children with growth disorders. Growth disorders result in 2 conditions—(1) short stature (height more than 2 SD below the mean for age and sex in the referent population or more than 2 SD below the specific child's gender-adjusted midparental height Z-score) and/or (2) growth failure (abnormally slow height velocity, which if left unaddressed for sufficient duration, presents as height dropping across major centile lines on the growth chart) (24). The differential diagnosis of growth disorders includes psychosocial, nutritional, genetic, disease, and iatrogenic processes, each with health ramifications beyond the question of height that are beyond the scope of this paper (36). Emphasizing height can lead to the overmedicalization of healthy children, particularly White boys, who want to be taller, while socially vulnerable children for whom increased height is deemed less important or unimportant, are more likely to experience delayed or missed diagnosis of underlying health issues that present with growth failure. For this paper, we focus on disparities in the path to rhGH treatment as the most readily quantifiable markers of the management of pediatric growth disorders, with commentary on general growth disorders as applicable.

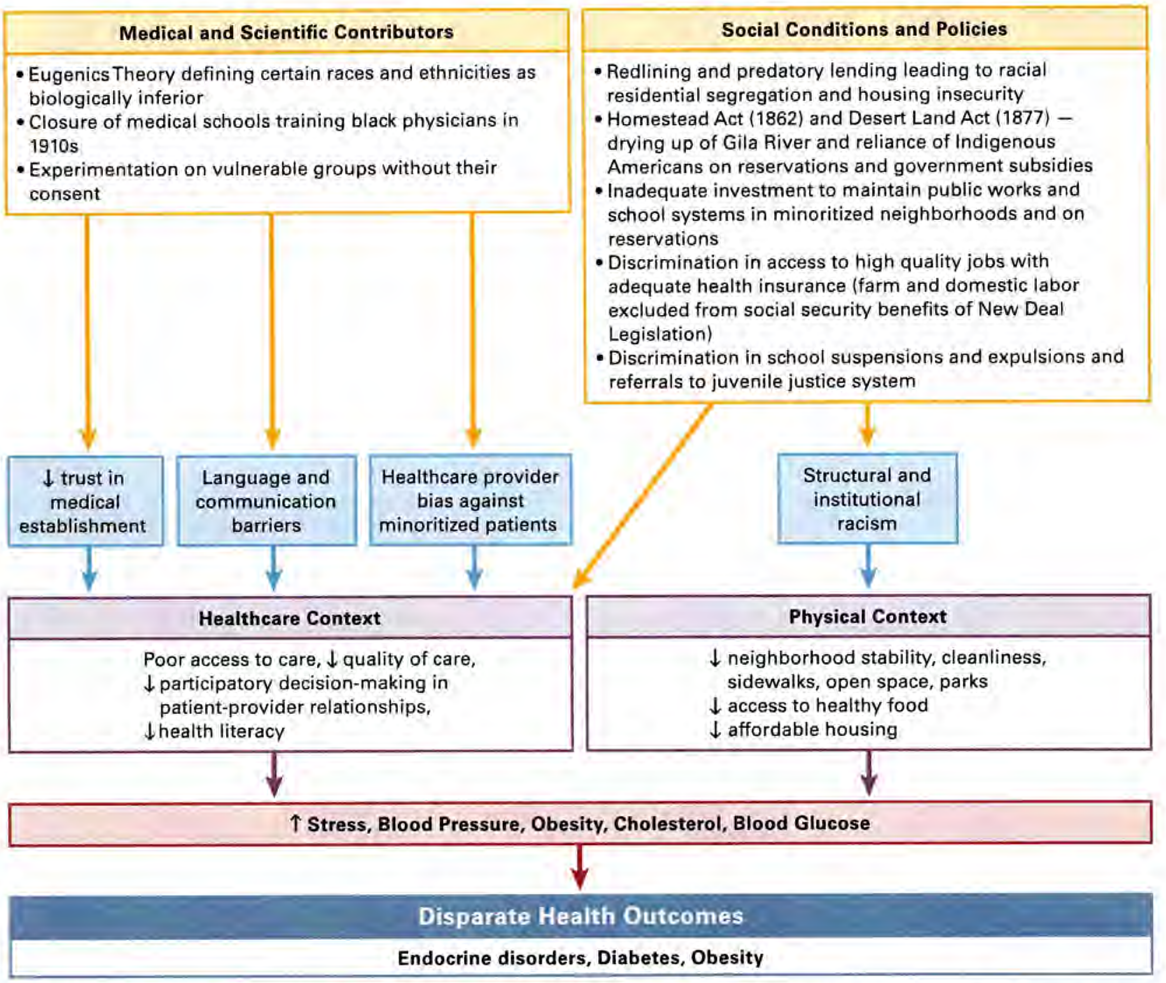


**Figure 2.** Medical, scientific, and social policy contributors to endocrine health and health care disparities in the United States. Reprinted from Golden SH, et al. *J Clin Endocrinol Metab.* 2021; 106(4):e1909-e1916. © Endocrine Society. (20)

## Disparities by Race/Ethnicity

### Epidemiology

NHW children are overrepresented in US rhGH registries (37, 38) and among US commercial insurance claims for rhGH medications (25). NHW children constituted 82% of subjects enrolled in 4 US pediatric rhGH registries (for all indications combined and for ISS specifically), whereas US census data indicate that NHW accounted for 67% of the pediatric population in 2005 and 63% in 2011 (37, 38). However, from 2001 to 2016, the share of commercial insurance claims for rhGH medications among US NHW youth dropped from 80% to 77%. During this period, the share of these claims increased among Black (3-4%) and Asian (1-4%) youth, but they were consistent among Hispanic youth at 9% to 10% (25).

Data from the US cohort in the Pfizer International Growth Study (KIGS) shows that the sex-based disparities summarized below cut across racial groups. For the entire cohort, the sex distribution depended on the specific indication, with greatest male predominance for "softer call" indications, such as familial short stature/constitutional delay of growth and puberty (CDGP)/ISS, idiopathic GHD, and neurosecretory GHD. These diagnoses allow more subjective influences on the decision to treat than do organic causes (37, 39). Male predominance did not differ by race for any of the combined indications (ISS, idiopathic GHD, congenital GHD, acquired GHD, and small-for-gestational age) such that the total number of Black subjects enrolled were underrepresented within the Black subgroup and girls were underrepresented as in the NHW subgroup (37).

### Race/ethnic differences in proximate biological factors

Racial differences in the tempo of growth and puberty have been described in data from the National Health and Nutrition Examination Survey (NHANES) of US-born, non-Hispanic children from birth cohorts of 1942-2002. Black children had a faster tempo of growth than White children starting at age 3 years, such that the average height difference between NHB and NHW children were +1 cm for boys and +1.2 cm for girls age 2-10 years, and +1.5 cm for boys and +1.8 cm for girls age 11-13 years (40, 41). However, average height differences between NHB and NHW teens age 14-19 years was <–1 cm for boys and –1.5 cm for girls

**Table 5. FDA-approved indications for pediatric growth hormone treatment**

| Year of FDA approval | Indication | Definition | Epidemiology | References/ Guidelines |
|---|---|---|---|---|
| 1985 | Growth hormone deficiency (GHD) | Inadequate GH secretory capacity that can be congenital or acquired | 1:3500 children | Grimberg et al 2016 (26) |
| 1993 | Chronic renal insufficiency | Reduced creatinine clearance (glomerular filtration rate) for at least 3 months | Prevalence ranges from 15 to 74.7 cases per 1 million children<br>Male/female ratio ranging from 1.3 to 2.0 (higher incidence in males of congenital anomalies of the kidney and urinary tract) | Drube et al 2019 (27)<br>Harambat et al 2012 (28) |
| 1996 | Turner syndrome | Partial or complete absence of the second X chromosome in girls (45,X genotype); may be mosaic | Females only<br>1:2000 live newborn females | • (Gravholt et al 2016 (29) |
| 2000 | Prader–Willi syndrome | Loss of paternally inherited imprinted genes on chromosome 15q11-13 | ~1:15 000-25 000 children<br>Females = males. | Heksch et al 2017 (30)<br>McCandless 2011 (31) |
| 2001 | Small-for-gestational age (SGA) without catch-up growth | SGA = birth length below −2 SD for gestational age, or birth weight below 10th centile for population. Must allow at least 2 years for endogenous catch-up growth before consider GH | Variable prevalence globally (4.6-15.3% across Europe to 27% in low- to middle-income countries)<br>~85% of infants born SGA experience catch-up growth in the first 2 years of life and would be ineligible for GH | Clayton et al 2007 (32) |
| 2003 | Idiopathic short stature | Height below −2.25 SD, growth velocity not expected to reach a normal adult height, and causes of growth failure that should be observed or treated by other means have been excluded | −2.25 SD = 1.2nd centile<br>Females = males | Grimberg et al 2016 (26) |
| 2007 | *SHOX* gene haploinsufficiency | Deletion or mutation in a copy of the *SHOX* gene on the short arm pseudoautosomal region 1 (PAR 1) of both the X and Y chromosomes | 2-15% of individuals with formerly idiopathic short stature<br>Females and males | • (Binder 2011 (33) |
| 2008 | Noonan syndrome | Germ-line mutation in a gene of the RAS/mitogen-activated protein kinase (MAPK) pathway (*PTPN11*, *SOS1*, *RAF1*, and *KRAS*) | 1:1100-2500 live births; may be closer to 1:100 for milder phenotypes<br>Short stature present in up to 70% of people with Noonan syndrome | Romano et al 2010 (34) |

(40, 41). This stemmed from earlier puberty in NHB adolescents, measured by both median age of entry and mean age at each Tanner stage (42). Similarly, on multivariate modeling of height <−2.25 SD, the threshold for the FDA-approved indication for rhGH treatment of ISS, among 145 710 pediatric primary care patients in a regional population, NHB patients had a 0.66 (95% CI 0.57-0.78) partial odds ratio compared with NHW patients. However, odds for height <−2.25 SD were significantly higher for Asian and Hispanic youth compared with their NHW counterparts (38). These findings were consistent with prior studies (43-46). Since heights of all US children are assessed clinically against the same growth charts (47), faster growth in NHB children may mask underlying growth problems. Thus, the relative odds ratios of height <−2.25 SD from the former study were used to adjust census-based proportions in determining the expected frequency of short stature by race/ethnicity. Yet, NHB children were still significantly underrepresented in the KIGS database of US pediatric rhGH recipients (37).

Variability in human height is a heritable polygenic trait, and group differences in background frequencies of height-related alleles are pertinent when considering superimposed growth problems. For instance, adult height in women with Turner syndrome, caused by partial or complete absence of the second X chromosome, is highly correlated with adult heights of both the woman's parents and unaffected women in their country of origin (48). Thus, the major centile lines on the Turner syndrome–specific growth chart constructed from data of patients in Germany, Finland, and France (44) demarcate shorter heights than the corresponding lines on charts from patients of Northern Europe (Netherlands, Sweden, and Denmark) (45), similar to the growth charts for the respective unaffected populations. Meta-analysis of genome-wide association studies (GWASs) using data from ~700 000 people of European ancestry identified 3290 near-independent single nucleotide polymorphisms (SNPs) associated with height that explained about one-quarter of the variance in adult height (49). Some of the SNPs identified in GWAS studies overlapped with Mendelian forms of abnormal skeletal growth syndromes (50), suggesting that mild alterations in potentially disease-causing genes may contribute to some of the variability in human height.

### Race/ethnic differences in nonbiological proximate/individual factors

The data above underscore the importance of assessing a child's growth against a growth chart constructed from a

pertinent reference population. US Centers for Disease Control and Prevention growth charts are constructed from cross-sectional data of mostly formula-fed NHW children from 4 data sources that have been combined (51). Because growth charts are used clinically as a guide to how children *should* grow, the WHO aimed to create growth standard charts based on a study population with no known health or environmental constraints to growth (eg, favorable socioeconomic conditions, exclusive or predominant breastfeeding for at least 4 months, no maternal smoking, not at high altitude). The WHO multicenter growth reference study further aimed to capture data representing racial, ethnic and geographic diversity, collecting longitudinal measurements from birth to 24 months of 882 infants growing in predefined ideal conditions in Brazil, Ghana, India, Norway, Oman, and the United States (52-55). Despite the infants' racial and ethnic diversity, they grew remarkably similarly across the 6 countries, highlighting the importance for human growth of being raised in healthy environments and following recommended feeding practices (52) (Fig. 1).

Although lower socioeconomic conditions, poor nutrition, and poor health care lead to impaired growth, children receiving height-related care at subspecialty centers tend to come from NHW families of higher socioeconomic status (SES) and higher parental educational background (56). As is the case for sex-based disparities (see below), differences in parental attitudes and concerns likely contribute to these race/ethnicity disparities. In a survey of 1820 parents of pediatric primary care patients, the median height offered by respondents as "too short" for both an adult male and adult female was 2 inches taller for NHW parents than for parents of other racial/ethnic groups (57). Further, in a model of the heights offered by the respondents as too short, significant predictors included not only sex of the adult considered and sex of the respondent, but also the parent's race, height, income, and the location of their primary care practice (urban vs nonurban), and whether the parent had concerns about their own child's height (57). The fact that race was an independent factor in a model that included markers of SES suggests racial differences in body ideals and tolerance for short stature may contribute to the over-representation of NHW families seeking medical care and treatment short stature.

### Race–ethnic differences in nonbiological intermediate factors

Child growth is very sensitive to SDoH—anything that adversely impacts a child's overall health, nutrition, and well-being can impair statural growth. Psychosocial deprivation itself (emotional deprivation and/or a pathological environment that disrupts normal parent–child attachment) has long been recognized as a cause of growth failure in children of all ages and socioeconomic strata (58). Although growth failure in the setting of emotional deprivation is commonly associated with malnutrition, it can also occur even despite adequate dietary intake (59). The hallmark of growth failure due to emotional deprivation is reversibility of the growth stunting and GH secretory abnormalities (when found) upon removal from the hostile environment and placement into a nurturing one (60-62), with catch-up in height serving as a positive predictor of cognitive recovery (63). Patient characteristics that are associated on regression modeling of height <–2.25 SD among 145 710 pediatric primary care patients in a regional US population included history of premature birth, race/ethnicity, age, and Medicaid insurance (relative to private insurance). This model also showed an inverse association with body mass index (BMI) Z-score (38) (Fig. 1).

Although growth may be more likely to be impaired among children living in conditions characterized by adverse SDoH, because short stature is not a disease, it may receive lower priority among socially vulnerable families and their clinical providers. As 1 parent explained during a focus group in a study of height-related concerns among parents of pediatric primary care patients, "There's so many other issues to be concerned about in the African-American community that I don't think that... height and trying to address that through medicine would come at the top of the tier here... on the other side, a family that may be more affluent, uh, particular a Caucasian family, maybe that would be something that they would consider" (64).

The health care system itself can introduce additional disparities on the path to pediatric rhGH treatment. Because regular surveillance of growth (both height and weight) is the responsibility of primary care clinicians (65), children with reduced access to primary care or those whose parents forego routine well-care visits for sick or urgent visits are more likely to have delayed or missed detection of a growth problem. Likewise, reduced access to endocrinology clinics may limit evaluation, diagnosis, and management of an underlying growth problem. However, access is only 1 dimension of this problem. Among 7425 children (5905 NHW, 800 NHB, and 720 Hispanic) seen at an endocrine clinic for growth evaluation, NHW children were 1.4 (95% CI, 1.04-1.8) times more likely than NHB children and 1.7 (95% CI, 1.2-2.2) times more likely than Hispanic children to undergo provocative GH testing, adjusted for sex, medical insurance type, height Z-score, and height differential from their midparental height Z-score (66). Although the proportions of tested children who were subsequently prescribed rhGH did not differ among NHW, NHB and Hispanic patients, fewer NHB (53%) than NHW (77%) patients were treated with rhGH after a stimulated peak GH concentration of 7 to 10 ng/mL, a "gray-zone" response range that is susceptible to subjective influences on treatment decisions. The proportion of rhGH-treated Hispanic patients with such GH peaks (73%) was intermediate between NHB and NHW patients (66). Further, in this study, of all patients prescribed rhGH, NHB children were more severely affected than NHW, with greater height deficits relative to both the general population and their midparental height Z-scores, and lower median peak GH concentrations on provocative testing (4.7, 95% CI 1.2-8.3 ng/mL vs 7.2, 95% CI, 4.9-9.7 ng/mL, respectively) (66). This observation suggests that NHB children were less likely to have their growth problems detected and had more severe disease at the time of diagnosis.

### Race/ethnic differences in nonbiological distal factors

Child growth is so sensitive to overall health and well-being that secular trends in height and timing of puberty have been followed—particularly in Europe since the early 19th century–as markers of societal and subgroup-level health, nutrition, and socioeconomic conditions (67). Mean adult height increased around 1 to 3 cm per decade in most European countries and age of menarche dropped over the last (20th) century (68). Despite the height increases and earlier menarche being most marked in the more nutritionally deprived subgroups

(68) and those of lower socioeconomic strata (69), there were diminishing but persistent height deficits over time relative to adults in higher socioeconomic strata of the same country (67, 69). For instance, upward trends in height among German military conscripts occurred during democratization and periods of political turmoil that facilitated upward mobility of people from lower social strata (69). Similarly, upward trends in height of children and adolescents in China were observed, particularly around puberty, together with socioeconomic development and they were associated with increases in gross national income and life expectancy (70). Pooled data on height, weight, and BMI from 2181 population-based studies (50 million children aged 5-19 years and 15 million adults aged 20-30 years from 200 countries and territories) showed highly variable trends in height, weight, and BMI from 1985 to 2019 across countries (71).

## Disparities by Sex

### Epidemiology

In the 4 US pediatric rhGH registries, boys outnumber girls 2:1 for all indications combined and 3:1 for ISS (37, 38). Consistent with these observations, US commercial insurance claims data showed a drop in the proportion of female pediatric rhGH recipients from 34% in 2001 to 28% in 2016 (25), potentially reflecting increased treatment of ISS among boys during this period. In contrast, no sex differences in prevalence of height below –2.25 SD or in distribution of height Z-scores were observed in 189 280 pediatric primary care patients from 28 practices (72).

The KIGS database, the world's largest postmarketing surveillance database of pediatric rhGH, also reveals sex differences in rhGH treatment globally (39). The United States had the second greatest male predominance (64% overall), second only to Asia (mostly Japan; 65%) but greater than Europe/Australia/New Zealand (55%). All 3 of these regions significantly exceeded 50% males treated with rhGH, whereas rhGH recipients in South and Central America, Egypt, and South Africa were 47% male. The latter regions had fewer rhGH recipients than each of the 3 other regions by more than an order of magnitude. The top 10 countries with over 1000 patients enrolled in KIGS ranged from 65% male (Japan) to 53% male (United Kingdom). In these countries, the proportion of male recipients did not correlate with mean adult height for either sex, markers of population health (life expectancy or infant death rate), health care (physician density or total health expenditure as percent of gross domestic product), or financial heterogeneity (Gini index, a measure of income or wealth inequality within a nation) (39).

### Sex differences in proximate biological factors

Because normal growth follows a predictable pattern it allows construction of growth charts. Growth is fastest in utero, gradually slowing during infancy to the steady and slower childhood growth from age 2 years until puberty. This is followed by a period of acceleration ("the growth spurt"), eventual growth plate fusion and cessation of statural growth (36). Not only do girls start puberty on average 1 year earlier than boys, but girls achieve their peak growth spurts earlier than boys in puberty sequence (73, 74). Among males, the combination of a longer period of growth and slightly higher peak height velocity during puberty makes the average adult height about 5 inches greater for men than women (73, 74).

CDGP (ie, late blooming) is a common cause of healthy variant growth retardation and occurs in children of both sexes (75). However, because boys with CDGP lag behind all their peers in both height acceleration and sexual maturation, these physical differences can drive much concern among patient families, often leading to greater seeking of medical attention for growth evaluation and treatment.

The effects of puberty can be seen in US pediatric rhGH registries. Focusing on age at initiation of rhGH treatment for ISS, the median (interquartile range) age is 11 (8-14) years for females and 12 (9-15) years for males. For both sexes, the peripubertal period has the largest numbers of patients initiating rhGH, as well as the maximal difference in numbers between the sexes (38). However, although puberty seems to amplify the sex-based disparity in rhGH treatment, it is not the sole period in which these disparities are observed. Males significantly outnumber females in initiating rhGH treatment for ISS at every year of age starting age 1 year (38).

### Sex differences in nonbiological proximate factors

Because short stature is not a disease, parents and clinicians share in medical decision-making. The degree of parental concern influences rates of both referral by primary care pediatricians and prescription of rhGH by endocrinologists, independent of objective measures of the child's growth (56, 76-79). In a mixed-methods study of parents of pediatric primary care patients, the child's sex was 1 of 22 concerns raised by parents that would impact whether they would decide to intervene medically for a child's short height (64). Multiple parents commented that intervening would be "worth it" for boys more so than for girls. One parent explained, "I think culturally, if we tell the truth, it's okay for girls to be small... but it's not as okay for boys ...I think that's an American thing." (64) Similarly, in a survey of parents of children receiving height-related subspecialist care in a mid-sized ethnically diverse US city, parents believed that short men, but not short women, suffer in terms of self-esteem and that these men face more hurdles than tall men (56) (Fig. 1).

Sex also plays a role in acceptable height thresholds. When 1820 parents of pediatric primary care patients were asked to provide the height they perceived as "too short" for an adult, the median intrarespondent difference between male and female heights offered was 5 inches (57). This finding may reflect respondents' experience with adult heights in society or their beliefs about the importance of height in men. In addition to the sex of the adult considered by the respondent, the respondent's sex was also a significant factor, with women respondents accepting a height about 2 inches taller than male respondents (57).

### Sex differences in nonbiological intermediate (health system) factors

Disparities by sex are evident in multiple steps on the path to pediatric rhGH treatment. Among children with growth faltering from 4 urban pediatric primary care practices, pediatricians obtained lab work screening the GH/insulin-like growth factor axis twice as often among boys compared with girls (80). Boys outnumber girls among children referred to pediatric endocrine clinics for growth evaluations (56, 81, 82). Not only do boys outnumber girls by about 2:1, but the referred girls had a greater height deficit relative to both the general population and their midparental height Z-scores, and they

were also 2.7 times more likely (95% CI 1.8-4.2) than boys to have an underlying organic disease (81). These findings suggest that not only fewer girls than boys receive subspecialist care for growth problems, but the ones who do see a subspecialist are shorter and more likely to require medical treatment (Fig. 1).

Disparities by sex continue during subspecialist care. In a national survey, pediatric endocrinologists were 1.3 times more likely to recommend prescribing rhGH for otherwise identical hypothetical case scenarios that described boys than cases describing girls (83). Among over 10 000 children referred for growth evaluation at a tertiary referral center between 2012 and 2019 (also about a 2:1 male:female ratio), girls were 33% less likely (95% CI 0.59-0.77) than boys to undergo provocative GH testing, even when controlling for height Z-score, pubertal status, insurance type, clinic location, and race–ethnicity grouping (82). However, after GH testing, there were no sex differences in stimulated peak GH levels nor in the proportion of tested children who received either pituitary magnetic resonance imaging or rhGH prescription (82). These findings indicate that the sex-based differences in rates of rhGH treatment are driven mainly by who sees a subspecialist and who gets tested for possible GH deficiency.

### Sex differences in nonbiological distal factors

As suggested by the parents' comments above, parental concerns—as well those of patients themselves, their primary care clinicians, pediatric endocrinologists, and the extended family, social circle or health care team who advises the patient or family regarding the child's height—are often shaped by prevailing societal attitudes. Heightism refers to the pervasive prejudice against shorter individuals and seems to particularly affect males (84, 85). It has been discussed in the lay press (86-88), and is embedded in our language with implied judgments in phrases such as "looking up to" or "looking down upon" someone. Multiple studies have found associations between tallness and markers of financial, social, and occupational success (89-92). These findings extend to achievement as an academic (93, 94), perceptions of presidential candidates (95), and perceived performance and leadership in military service (96). With few exceptions, the association between tallness and power is ingrained early in childhood (heroes are always big and strong) and is exploited in Hollywood and politics (85). Taller males also are assumed to have an advantage in mating and dating preferences (97). An interesting study of the "tall-man stereotype" suggested it is a learned association. When 77 adults were read the same story about a fictional man whose height Z-score was either +2 or −2, the 43 sighted adults but not the 34 adults with congenital blindness rated the tall man higher than the short man in terms of intelligence, wealth, leadership, and social status (98). It is perhaps not surprising that parents of both primary care patients (64) and patients receiving height-related subspecialty care (99) reported concerns about psychosocial functioning—both current and projected into adulthood—as major motivators in the decision to seek medical care for a child's short height (Fig. 1).

## Summary, Implications, and Future Research Needs

Disparities by sex, race/ethnicity and SES have been consistently evident from postmarketing surveillance studies since the first description of US children receiving rhGH. Of 2331 children from 112 centers started on rhGH treatment for GHD and other causes of short stature between October 1985 and October 1987, 70.5% were male, 88% were NHW, and 6% were Black (100). These data highlight disparities in treatment, and indicate that action is needed. Actions to address these disparities should not be to increase rates of rhGH prescriptions for girls and children of racial/ethnic minorities so they match those of NHW males. Rather, the goal must be to promote equity in the detection, evaluation, and treatment of underlying growth problems that need intervention of any kind, with an eye to increase value of growth-related care for all children.

The appropriateness of rhGH treatment to augment height in healthy children for psychosocial benefits has been debated since the advent of rhGH in 1985 (101) and it continues today (102, 103). In a survey of parents whose children were treated for ISS at a subspecialty endocrine center, 88% indicated that average height increases from rhGH still fell below the threshold to improve quality of life (QOL) (99). This indicates that treatment rates in NHW males may be seen as excessive. In addition, the high cost of rhGH treatment—estimated in 2006 at $52 634 per inch for 5 years of rhGH therapy for a cohort of 10-year old prepubertal boys with ISS (104)—raises further questions about access to treatment and equitable allocation of these growth-related health care resources.

Growth failure is often the first or only sign of underlying health issues that require intervention. Thus, sex, race/ethnicity, and SES-based disparities in the diagnosis of short stature or growth failure can also lead to missed or delayed diagnosis of other underlying health problems in socially vulnerable youth. These missed opportunities may carry consequences not only for height, but also for other aspects of the child's health. For example, celiac disease may occur in children whose only symptom is decreased growth (105-107). Growth faltering was present in most children prior to diagnosis of celiac disease such that auxological screening could have resulted in earlier diagnosis (108). Longstanding, untreated celiac disease, that can be reversed with a gluten-free diet, increases risk of other autoimmune conditions like thyroiditis (109), as well as gastrointestinal lymphoma (110, 111) and osteoporosis (112, 113).

Timely detection of growth problems in youth requires access to regular primary care well visits, where height/length and weight are measured accurately and carefully tracked on appropriate growth charts. Future studies should evaluate whether interventions, such as electronic health system-based alerts, can help improve or systematically identify children with worrisome growth patterns, including children who have been historically underdiagnosed. Both primary care and subspecialist physicians should be mindful of the role that social determinants of health play in promoting disparities, and the impact of these inequities on delivery of height-related health care. Parental education is also important in setting realistic expectations of healthy growth variations and potential interventions. Frank and thorough discussion with parents of the potential benefits and risks of rhGH treatment is very impactful, as treatment characteristics (proven efficacy and safety) were the most commonly cited concerns among parents. These concerns have a substantial impact on parents' height-related medical decisions in the pediatric primary care setting (64) as well as among parents of patients receiving growth-related care in a subspecialty clinic (99).

## Puberty

Puberty is among the most transformative processes humans experience in postnatal life. Normal pubertal timing varies across a broad range of chronological ages and this range is further increased by both physiological variation (early or delayed) and pathological conditions (central precocious puberty or hyper/hypogonadotrophic hypogonadism; see Table 6 for normal and abnormal states). Although a discussion of these states is beyond the scope of this Statement, we focus on health disparities in pediatric pubertal developmental states by race/ethnicity and sex, their effects, opportunities for intervention, and areas of needed research. Pubertal development of gender diverse youth, specifically transgender youth, is covered in the Statement under "A Conceptual Framework for Race/Ethnic and Sex Disparities in Pediatric Endocrine Disorders."

Beginning from at least 1830, age of puberty has diminished dramatically and uniformly across diverse populations (115) with some geographic variation. Concurrently, there has also been a worldwide increase in hormonally sensitive cancers and cardiometabolic diseases. It is important to understand changes in secular trends in pubertal development not only to determine who requires evaluation for abnormal pubertal development, but also as a potential signal of environmental influences on long term human health. Changes in pubertal timing have long been associated with increased risk of developing certain adult conditions and diseases. Chan et al reviewed Mendelian randomization studies examining the possibility of causal associations of variations in pubertal development with later disease states (116). This work found later onset of puberty was associated with lower bone mineral dentistry (BMD) despite faster rate of bone gain once puberty was initiated (117), decreased BMD at the lumbar spine (118, 119), and persistently lower BMD into adulthood (120-122). Later puberty is also associated with lower BMI in adulthood. Hormone-related cancers such as breast, endometrial, and prostate cancers (123, 124), increased fasting blood glucose and blood pressure (122, 125, 126), decreased forced vital capacity, and increased asthma risk (127, 128) are all associated with early pubertal development. Finally, psychosocial characteristics including reproductive behaviors, educational attainment, and depressive symptoms are also affected by age at puberty (129-132). Taken together, these data suggest that puberty is a critical window that affects health throughout the life course, and it is likely that genetic, environmental, hormonal, and psychosocial factors all exert some degree of influence on this trait. It is in this context that disparities in pubertal timing or factors affecting pubertal timing may contribute to ongoing disparities in cardiometabolic, neoplastic, or psychiatric conditions/diseases in adulthood.

### Disparities by Race/Ethnicity

#### Epidemiology

Global changes in pubertal trends are generally reported by country rather than race. In a meta-analysis by Eckert-Lind et al, the most common race groups reported were "Black" or "White," leading to missing data for other racial groups and/or simplification/miscategorization of participants (133). Of 38 included studies that were examined by region (Europe, Middle East, Asia, North America, South America, Africa, and Oceania) only 5 US, 1 South African, and 1 Oceanian study reported data by race. In that meta-analysis, median age at thelarche ranged from 9.8 to 10.8 years in Europe, 9.7 to 10.3 years in the Middle East, 8.9 to 11.5 years in Asia, 8.8 to 10.3 years in the United States, and 10.1 to 13.2 years in Africa (133). Although the studies varied in whether they used visual inspection, palpation or both techniques to assess thelarche, a significant decrease in age at onset of thelarche was observed over the time period they covered (1977-2013) with an average decrease of almost 3 months/decade.

Decreases in mean age of menarche among industrialized nations appear to be related to similar increases in height, observations that suggest a nutritional component (134). Decreases in average age of menarche have been observed in developing regions as well, where the causes are often difficult to ascertain (135). Significant variation in mean age of menarche are also observed across nations and socioeconomic conditions, suggesting the potential for genetic and/or environmental causes. Chinese, Japanese and Indian girls had menarchal ages similar to girls in the Mediterranean region, while girls in Cameroon and South Africa had older ages, 12 years and 13.2 years, respectively. One study of Senegalese girls noted that those of lower SES had average menarchal ages as high as 16.1 years (136), an observation that the authors attributed to malnutrition. Later age of menarche was also reported in Nigerian, Guatemalan, and Columbian girls compared with Chilean and Venezuelan girls (137-140). In the United States, evaluation of female pubertal trends by Parent et al imply that although age at menarche stabilized from 1973 to 2001, age at thelarche continued to decrease over the same period, thereby extending the overall time course for pubertal development in females (134). In Europe, thelarche did not show significant differences between countries but age at menarche varied geographically, with France and Mediterranean countries having lower age at menarche than other European countries. There may also be differences in pubertal development in children residing in rural or urban environments within a particular country, but these have been studied less often.

Overall, data on puberty in males is less robust than that of females. There are only a handful of studies that have characterized entry to male genital stage 2, and most have depended on visual inspection, not testicular volume measurement. In the United States and European countries, mean age at entry to male genital stage 2 remained relatively stable from 1970 to 2001 (141) at 11.5 years. However, differences were noted in NHANES 1988-1994 with males average age at genital stage 2 of approximately 10 years. In the United States, NHB males tended to be classified as visual male genital stage 2 at an earlier age (9.5 years) than Mexican (10.4 years) or White (10.1 years) males (134).

Racial differences in pubertal timing between NHB and NHW children in the United States were not assessed until the 1970s (142, 143). Race was found to have an independent effect on age at menarche after controlling for BMI z-score and age in NHANES III with NHB children having an earlier initiation of pubertal development than NHW children (144). Pubertal timing in Hispanic females in the United States was not assessed until the 1980s in the Hispanic Health and Nutrition Examination Survey, making trends in this population difficult to establish (145). Asian groups are often not represented in significant numbers and there is no study that accounts for the heterogeneity of Hispanic and Asian

**Table 6. Characteristics of normal and abnormal pubertal development**

| | Physical features | Physiological underpinnings | Timing characteristics | Other |
|---|---|---|---|---|
| Typical female puberty | Tanner (SMR) 2 breast development or thelarche is appreciated as a palpable subareolar breast bud before it can be observed visually<br>Age 8-12 year | Timely activation of the hypothalamic–pituitary–gonadal axis | Progression through pubertal stages to completion of growth and hypothalamic–pituitary–growth axis maturation | Thelarche = initiation of breast development<br>Menarche = initiation of menses<br>Thelarche (early marker) and/or age at menarche (late marker) are typically used for female pubertal development |
| Typical male puberty | Tanner (SMR) 2 genital stage is characterized by increase of testicular volume to ≥ 4 mL, enlargement of the phallus, thinning of the scrotum<br>Age 9-14 years | Timely activation of the hypothalamic–pituitary–gonadal axis | Progression through pubertal stages to completion of growth and HPG maturation | Gonadarche = increase in testicular volume to >4 mL<br>Appearance of pubic hair or change in genital appearance (early marker) and age at voice breaking (late marker), commonly used for male pubertal development. Testicular enlargement is less often used. |
| Isosexual central precocious puberty | Female: breast development Tanner (SMR 2) age <8 years<br>Male: testicular volume ≥4 mL age <9 | Premature activation of the hypothalamic–pituitary–gonadal axis leading | Progression through pubertal stages to completion of growth and HPG maturation | Global incidence rate 5.66 cases per million person years at risk (114)<br>Annual incidence 0.02-1.07 cases/100 000 |
| Delayed puberty | Female: lack of breast development tanner (SMR 2) by age 13 years; male: lack of testicular volume ≥4 mL by age >14; failure to progress through puberty in 4 years | Heterogeneous causes including lack of activation of the hypothalamic–pituitary–gonadal axis, primary gonadal failure, or functional hypogonadism | Nonprogressive or slowly progressive | |
| Premature thelarche | Breast development <8 years in female | Exposure to endogenous estrogen or estrogen analogs | Non progressive or slowly progressive | |
| Premature adrenarche | Pubic hair development prior to thelarche or gonadarche<br>Age <9 years for boys and <8 years for girls | Activation of the hypothalamic–pituitary–adrenal axis (1 proposed mechanism) | Slowly progressive | |

American populations. Review of available data indicates that NHB females in the United States enter puberty earlier than their NHW and Hispanic counterparts (146). It is also important to understand that implicit in any discussion of racial differences in pubertal timing in American girls is the confounding of race with SES. SES affects known predictors of pubertal timing such as nutrition, environmental stress, and family composition.

There is debate regarding the magnitude of racial differences in sexual precocity (defined as thelarche before age 8 years in females and attainment of genital stage 2 in males before the age of 9 years) in the United States Performed in the United States, the Pediatric Research in Office Setting (PROS) study noted significant differences in age of appearance of thelarche between NHW and NHB girls and proposed using different cutoffs for sexual precocity for each population (7 years for NHW females and 6 years for NHB females). Adoption of these lower thresholds would significantly decrease the number of children undergoing evaluation and possible treatment for abnormal pubertal development. Notably, the PROS study used mainly visual evaluation of breast development in the larger cohort and undersampled NHB girls, who constituted only 10% of the study population (147). The Bogalusa Heart Study and NHLBI Growth and Health study had greater representation of non-White participants and did not find this degree of difference. However, in these studies the general pattern of NHB girls having earlier pubertal development than NHW girls persisted (148, 149).

Premature adrenarche is also noted to demonstrate significant racial variation (150-152). Premature adrenarche is associated with early pubertal development, insulin resistance, and subsequent development of metabolic syndrome and polycystic ovary syndrome (153, 154). In a review of NHANES III data, the emergence of pubic hair occurred earlier in NHB females than in NHW females and often occurred prior to thelarche.

## Race/Ethnic Differences in Proximate Biological Factors

### Obesity

As noted earlier, in the United States, obesity prevalence varies by race/ethnicity with higher rates among NHB and Hispanic groups. Given that BMI is linked with pubertal development, racial differences in obesity have clear implications for adult health disparities. Putative mechanisms linking BMI to pubertal development include leptin as a permissive factor, expression of aromatase in adipose tissue, insulin resistance, and decreased sex hormone binding globulin (155). Recently, evidence linking puberty and nutritional status highlighted the

melanocortin pathway with an important role for the melanocortin 3 receptor (MC3R) in regulating the timing of sexual maturation, the rate of linear growth, and accrual of lean mass (156) (Fig. 1).

Although obesity (measured by BMI) is significantly associated with early puberty in both White and NHB girls, its association in NHB girls may be weaker (157). These differences may be mediated by changes in BMI during critical windows or by environmental factors. Kaplowitz et al reanalyzed the PROS data and found a relationship between age-corrected BMI, earlier onset of puberty, and faster pubertal timing in White girls but not NHB girls. There were fewer NHB girls in the cohort in the younger age groups and that may have some influence on these findings (157). Recently, Chen et al, using peak height velocity as a surrogate marker for pubertal attainment, found that overweight/obesity at age 2-7 years was associated with earlier onset of puberty in a mostly NHB cohort in Boston. The authors noted that interventions to normalize weight could be helpful in delaying peak height velocity in this group (158). Other work showed that higher prepubertal BMI was associated with early puberty in Chinese boys and girls (159).

### Insulin resistance

Puberty itself is associated with a marked decrease in insulin sensitivity (160). For children born small for gestational age (SGA, also known as low birthweight), this association may be strengthened because SGA is associated with increased insulin resistance in childhood (161). Furthermore, children born SGA tend to have earlier pubertal development, particularly those who experience rapid catch up growth (162). Information from US birth certificates from 2005 showed that a greater percentage of NHB women gave birth to an SGA infant (17%), followed by Asian/Pacific Islander women (14%). Hispanic, American Indian/Alaska Native, and NHW women were less likely to have given birth to a SGA infant (9-10%) (163).

Insulin resistance varies by race with NHB girls having higher rates of insulin resistance during puberty than NHW girls. Increases in insulin resistance were associated with higher estradiol levels (164). Insulin resistance in pubertal NHB adolescents is not accompanied by increased insulin secretion, a contrast to NHW pubertal adolescents (165). While causality has not been determined, the association between insulin resistance and earlier pubertal development belie the underpinnings of a less favorable cardiometabolic profile in the future (166).

### Genetics and epigenetics

Although pubertal timing is thought to be closely tied to genetic regulation, with genetic factors accounting for 50% to 75% of all variations in pubertal timing (167), GWAS studies can only explain <5%, by generous estimate, of the variance in pubertal timing (168). Understanding the genetic regulation of pubertal timing has come largely from studies of rare diseases and population-based studies in mostly NHW women.

In the last 2 decades, GWAS studies have been used to identify loci that may be associated with variations in normal pubertal development. The largest cohort studied NHW women's age at menarche, yielding 389 loci that may account for variations in pubertal timing and cancer risk (123). Some SNPs in the estrogen receptor alpha (ESR1) seemed to signal differential genetic influences on breast cancer risk in European American women compared with African American women and in Han Chinese women (169, 170). The effects of these SNPs seemed to be modified by tumor subtype and estrogen exposures, especially in African American women. Studies of ESR1 polymorphisms have been inconsistently associated with changes in pubertal tempo in females (171, 172).

Previously identified loci have been investigated in cohorts of other ethnicities, but small sample sizes limit statistical power (368 888 NHW women vs 1800-3500 women of NHB, Hispanic, Korean, Chinese, Japanese origin). As expected, no new loci for variations in pubertal development were identified due to low numbers of subjects in the non-White cohorts (167). The Population Architecture using Genomics and Epidemiology (PAGE) study replicated GWAS reproductive trait SNPs of European American women and found that many were associated with age at menarche and age at natural menopause in a diverse population (42 251 women including Native American, African American, Asian, Hispanic, Native Hawaiian, and European American) (173). A meta-analysis of 15 studies of NHB females (n = 18 000) examining age at menarche and previously identified menarche loci in NHW women, provided the first cross-ethnic validation of *RORA* as important loci (174). *RORA* encodes 1 of the ROR nuclear receptors that regulate the transcription of numerous other genes and has recently been implicated in regulation of aromatase activity (175). Pathways involved in insulin signaling and interactions with growth factors may be important factors in menarche timing in NHB females (175). These studies generally support the cross-ethnic generalizability of menarche loci but also point to novel biological links in different populations.

Epigenetics may also play a role in pubertal timing and can offer links between reproductive health disparities and the impact of the environment on genetic architecture. Allostatic overload may influence pubertal timing though epigenetic changes. Changes in methylation may influence age at menarche in NHW women (123, 176, 177). This has not yet been studied in non-European descended groups. Environmental exposures may also exert their influence through epigenetic changes. Further research is needed in this area.

## Race/Ethnic Differences in Proximate Nonbiological Factors

Since puberty is a fundamental developmental and psychosocial milestone that signifies not only reproductive maturity but also, transition into the world of "adults," a life course view to factors that shape pubertal development is appropriate. Life course perspectives demonstrate that our current health is shaped by earlier exposures (even decades before) to physical, environmental, and psychosocial factors (178). When used in context of health disparities, this approach allows researchers to understand the origins, persistence, and transmission of these inequities across generations. Life course approaches typically use developmental and structural perspectives. As explained by Jones et al, "Developmental perspectives emphasize how socially patterned exposures to risk factors during sensitive life stages shift health trajectories, whereas structural perspectives emphasize how social identity and position within socially patterned environments

disproportionately allocate risk factors and resources, resulting in altered health trajectories" (179) (Fig. 1).

### Nutritional status

Nutritional status plays a significant role in pubertal timing when comparing children living in disparate socioeconomic strata. Food and energy availability influence sexual maturation and are unequally distributed throughout the world. Animal protein intake has been associated with earlier pubertal development and vegetable proteins with later development (180). Phytoestrogens, present in high vegetable protein diets, are hypothesized to have direct effects in delaying puberty (181). In an extensive review of age at menarche and menopause in diverse countries, vegetable protein intake and adult illiteracy were strongly associated with later menarche. In the latter study, lack of animal protein intake was considered to be a marker of socioeconomic strata and adult illiteracy was considered a marker of the need for girls to work rather than attend school. The authors posited that a frank calorie deficit and extrinsic environmental factors, rather than body composition, have effects on pubertal timing (181). Differences in timing of pubertal development exist between well-resourced countries compared with those often characterized as developing (134).

### Family structure, early life environment, and abuse and neglect

Associations of pubertal development with adverse early life experiences have been studied in psychological and social science settings. In a meta-analysis of 54 studies examining the association of early life adversity with pubertal timing and cellular aging (measured by telomere length and DNA methylation age), early life adversity characterized by threat rather than deprivation was associated with accelerated pubertal timing and cellular aging (182). Threat was defined as exposure to violence and deprivation was defined by psychosocial neglect. Analysis of the Black Women's Health Study demonstrated increased risk of early menarche among NHB women who experienced childhood sexual abuse (183). Similarly, in a study of Peruvian women, any abuse, but particularly the combination of physical and sexual abuse, was associated with early puberty (184). The findings of these 2 studies suggest that girls in racial/ethnic groups that undergo earlier pubertal development may be at higher risk for certain types of abuse because of their apparent sexual maturity or that prior abuse may trigger earlier puberty.

### Psychosocial

Pubertal timing has also been studied in relation to development of internalizing and externalizing behaviors in children and adolescents. Among Americans children who identify as NHB, Native American, Hispanic/Latinx, or Asian, presence of these psychological conditions at an earlier or even later than expected age can complicate the social milieu. Early pubertal timing was associated with greater depression in NHB males when compared with NHB females. The authors theorize that this may be "perhaps in part due to the specific stigmas, biases, and concerns that come with visibly resembling an adult African American male—including concerns of physical safety, fairness in the legal system, or potentially being perceived as a threat by others" (185).

## Race/Ethnic Differences in Intermediate Environmental and Health Care System Factors

### Endocrine disruptors

Endocrine disrupting chemicals (EDCs) are environmental pollutants or chemicals that interfere with hormonal function and result in adverse health outcomes (186). These chemicals can change normal endocrine processes through several mechanisms—(1) binding to hormone receptors, (2) direct action on cell signaling pathways or neuroendocrine systems, (3) suppression of hormone synthesis, or (4) toxic effects on endocrine organs (187). Examining effects of EDCs on reproductive function has shown these chemicals can have estrogenic and/or anti-androgenic effects and can both accelerate and delay pubertal development. An inherent challenge in studying EDCs is that human populations are exposed to multiple toxins at various developmental stages and at different levels of exposure (188-190). The Environmental Protection Agency has specific guidelines when determining reproductive toxicity risk and these indicate that evidence of precocious or delayed pubertal timing should be considered when performing risk assessments (191, 192) (Fig. 1).

In 2015, the Endocrine Society reviewed available information on the effects of EDCs on puberty (186). There is a very large and strong body of evidence that male and female reproductive development can be readily disrupted, though evidence directly assessing pubertal changes as an outcome is more equivocal. Although limited information was available at that time, bisphenol A (BPA) and phthalates were found to have equivocal effects on pubertal timing in both humans and in animal models. Pesticides were not found to have significant effects on human pubertal timing but did have effects in animal models. Environmental contaminants, such as polychlorinated biphenyls, appeared to have some effects on pubertal development in animal models and perfluorooctanoic acid seemed to delay puberty in humans in 2 studies (193, 194) but not in all animal models. Research into endocrine effects of phthalates and BPA, which are commonly found in many consumer and cosmetic products specifically marketed toward racial/ethnic minorities, is ongoing.

Racial and ethnic disparities exist with regard to EDCs impact, in large part resulting from differences in opportunities for exposure (195, 196). Lead exposure not only has direct central nervous system toxicity but it also delays pubertal development. Lead levels have generally been linked to delayed menarche and pubic hair appearance in females. These delays are found more frequently in NHB females than in Hispanic females, although infrequently in NHW females (197, 198). Akwesane Mohawk Nation females were found to have later menarche by 1 year when their blood lead levels were >1.2 μg/dL compared with girls with lower levels (188). The Akwesane Mohawk Nation is located near several superfund sites that contain contaminants such as polychlorinated biphenyls. One study showed that the presence of multiple polychlorinated biphenyls in the blood was associated with significantly earlier menarche in females, even after adjusting for age, SES, and the presence of other environmental toxins (188).

### Location and migration

For reasons that are not entirely clear, geographic location, SES, and population movement can drive changes in pubertal timing. These changes may differ between and among

different racial and ethnic groups. Girls who live in urban areas have generally been noted to have earlier menarche than their rural counterparts. In a cross-sectional retrospective study of 2087 Ghanaian girls, menarchal age correlated with social class, parental ethnic origin, and educational institution. Girls who lived in urban areas also had earlier menarche (199). A cross sectional survey in Tianjin, China, showed earlier age at menarche for urban females by more than 1 year (200). Similar urban vs rural trends were observed in populations in Cameroon (201). These disparities have not been well studied in the United States

Adoption and migration have also been associated with earlier pubertal development. Children adopted from developing countries to Western Europe were noted to have earlier pubertal development than peers in their home country (134). The frequency of sexual precocity varied from 13% to 30% of children adopted into Sweden, The Netherlands, France, and the United States (134, 202). In a Belgian study, the incidence of central precocious puberty in all children was <0.01% but in adopted children it reached approximately 0.8% (203), and Indian girls adopted to Sweden had higher than average rates of sexual precocity (202). In a Spanish study, the relative risk (RR) of adopted children having central precocious puberty compared with native Spanish children was 27.8 and the risk among immigrant children was 1.55 (114). Some investigators have proposed that the impact of nutritional deprivation and restoration after migration may be crucial in some children who develop sexual precocity (134). However, there are also studies of children who migrated with their parents and did not encounter nutritional or psychosocial deprivation who also developed sexual precocity. A Belgian study noted that nonadopted children who moved to Belgium with their families from another country also had higher rates of sexual precocity than the general population (203). Taken together, these findings suggest a possible role of factors related to migration and changes in environment (environmental stress) on pubertal development.

#### Physical and social environment

Inequalities in built environments may influence pubertal timing beyond their impact on BMI. In a longitudinal cohort of Northern California females, the availability of recreational outlets was associated with timing of thelarche and pubic hair development for NHB girls. Even when strong predictors of puberty such as income and BMI were considered, more recreational outlets were associated with later thelarche (204). Notably, a study of the distribution of recreational facilities found that presence of recreational facilities in a neighborhood varied based on SES and race (205).

Climate change may impact pubertal age though increased exposure to EDCs released during cataclysmic weather events, changes in nutritional status due to the effects of climate on crops, and through climate-driven human migration (135). Migration has been posited to exert some of its effects though changes in exposure to "ambient" EDCs with change in location. Krstevska-Konstantinova and coworkers have hypothesized that moving could result in a change in exposure to EDCs when a child moves from the home country to a new country, thus causing sexual precocity to occur. They propose these changes in exposure can result in activation of the hypogonadotropic–pituitary–gonadal axis via cessation of exposure to estrogenic or antiandrogenic compounds (203). Conservative estimates of climate change "expect that with every degree of temperature increase, roughly a billion people will be pushed outside the zone in which humans have lived for thousands of years." (206). Populations that have less means and higher instability are likely to be more severely affected by these changes—these tend to be developing nations with predominantly non-White populations.

#### Health system factors

Pattern of pubertal development have socio-behavioral implications for children on both individual and system levels. Children with early puberty are often perceived as older than they are and conversely, children with pubertal delay are often infantilized. These perceptions can drive differences in care delivery with some discrepancies based on perceptions of race/ethnicity. A systematic review of females' pubertal experiences in the northeastern United States, highlighted that when discussing pubertal transitions, sexual behavior was emphasized in counseling NHB and Hispanic females whereas in NHW females, the physical changes of pubertal development were emphasized (207).

### Distal Factors—Social Conditions and Policies

Differences in pubertal tempo may have implications for adults who make judgements about children's ability to reason and make adult decisions. Children who have earlier development are taller and appear more mature than their chronological age. They are more likely to be perceived as adults rather than as children: "young Back male" rather than "Black teenager." This may come into play among racial and ethnic minority youth—especially NHB youth—who have interactions with the justice system in educational and criminal matters. In these settings, differences in pubertal tempo can cause significant disadvantages that are layered on the existing systemic racism that is embedded in these systems (208) (Fig. 1).

## Disparities by Sex

### Epidemiology

Puberty is a sexually dimorphic process but sex differences in pubertal development and timing are not entirely explained by differences in sex hormones. Sex differences in gene dosages due to incomplete X inactivation in females (resulting in higher transcript levels for some genes in females), some transcription factors themselves being sex specific (eg, SRY on the Y chromosome), and sex differences in epigenetic markers all contribute to differences in timing (168). Females have higher rates of sexual precocity (approximately 3:1 to 4:1 compared with males) and idiopathic causes are more common than organic causes at least 2:1 (female:male). Idiopathic precocious puberty, especially in female children close to and in the 6- to 8-year age group, presumably reflects normal pubertal physiology occurring at an earlier age. The origin of the remainder of patients with sexual precocity is explained by organic causes that must be identified and treated appropriately (191). Females with early menarche—not necessarily precocious puberty—are at a higher risk for early menopause, leading to loss of fertility at a younger age and possibly associated early menopausal conditions (209).

Premature adrenarche is also more common in females, with a rate of 5:1 compared with males (210), and this

condition is identified more often in females who have clinical signs of androgen action. However, in a study of nearly 600 Finnish prepubertal males and females, males with biochemical signs of premature adrenarche in the absence of clinical signs were more common than females (211). Females with premature adrenarche are at higher risk of polycystic ovary syndrome. Among males with premature adrenarche, findings concerning the risk of subsequent metabolic syndrome/cardiometabolic risk factors are equivocal (212, 213). In a systematic review using the UK Biobank, the association between early pubertal development and T2D/cardiovascular disease was stronger in females than in males (126).

There is less information on male puberty in part because pubertal development in boys is more difficult to ascertain in large studies. Pubertal delay is more commonly identified in males than in females—most otherwise healthy children with pubertal delay have self-limited constitutional delay with a male predominance of almost 2:1 (214). Although available data do not show conclusive evidence (215-217), pubertal development in obese boys seems to be delayed more often than it is advanced (218-220).

## Sex Differences in Proximate Biological Factors

### Birthweight

Variation in age at menarche has been associated with birthweight. Studies from the United States, Israel, and Spain showed trends toward earlier menarche among girls with lower birthweight, but this was not observed in French studies (134). Low birthweight has also been associated with premature adrenarche in females and subfertility in males (221).

### Obesity and body mass index

The relationship between weight and puberty appears to exhibit a sexually dimorphic pattern—lean girls have later menarche as opposed to lean boys who have earlier puberty, although not necessarily precocious (134). In females, higher BMI correlates with earlier age at menarche, and it also correlates with earlier breast gland development (222). The latter study noted that premature adrenarche was more common in boys than girls, and it also suggested that percentage of body fat measured by dual-energy x-ray absorptiometry (DXA) was also associated with clinical signs of adrenarche. The authors hypothesized that these findings may be mediated by the effects of body adiposity on secretion of adrenal androgens, the peripheral conversion of androgen precursors to active androgens, and the bioavailability of androgens though differences in sex hormone binding globulin (211).

Genome-wide associated loci for higher BMI, both in combination and individually, are associated with earlier puberty in females (223-225). Conversely, earlier puberty associated with the LIN28B rs314276 C-allele leads to faster adolescent weight gain and higher postpubertal BMI in women, without effects on prepubertal BMI (226). In a Mendelian randomization study of 3611 White-European female and male offspring from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort, age at puberty onset did not influence adiposity or cardiometabolic traits independent of childhood adiposity (122).

Other studies suggest that childhood weight or weight patterns influence the onset of pubertal development. Puberty was noted to have a dramatic effect on sex-specific fat distribution in males but not in females in a multi-ethnic study. Mechanisms driving these differences are not well understood, but differences in fat depot have been associated with differences in metabolic health (227). It is not known whether this indicates that both pubertal development and weight are working through a similar genetic pathway.

### Genetics

There are very few GWAS studies with large numbers of male subjects. In Zhu et al, analysis of 16 large GWAS studies for pubertal loci included only 2 male studies, and females outnumbered males by about 12:1 in that report (708 511 vs 59 640) (167). Some identified loci were similar for males and females and provided consistent phenotypes, whereas others differed in their associations between early or late variation in timing. For example, the major allele of the SNP rs314276 (located in intron 2 of LIN28B) was associated with earlier voice breaking and more advanced pubic hair development in boys and earlier age at menarche in girls (228). Other studies used loci previously identified in female cohorts to examine effects in males. For example, in the 1000 Genomes Project (consisting of genomes of 370 000 European women), 389 independent SNPs for age at menarche were identified. These were examined in other smaller cohorts of male puberty to study self-reported age at voice change as well as in registries of ovarian, breast, and prostate cancers. Results suggested that the "age at menarche" variants had differential effects mediated by sex, conferring earlier pubertal timing on female subjects and late pubertal timing on male subjects (123). Other studies examined links between genetic markers of pubertal development and sex steroid–responsive cancers (124, 229, 230). Here, too, there is a paucity of research on male subjects.

## Sex Differences in Proximate Nonbiological Factors (*Fig. 1*)

### Family structure, early-life experiences, and abuse/neglect

Although studies examining the complex interplay of family factors and SES with pubertal development are difficult to conduct, some have tried to understand links between childhood events and pubertal development (231). Psychological anxiety due to absence of a biological father was associated with earlier puberty in US boys and girls, independent of SES (232). Early pubertal development has been noted among children exposed to divorce and in stressful family situations (233, 234). In a prospective study of a racially and ethnically diverse sample of girls from northern California, exposure to a nonintact household early in life may increase the risk of early puberty in girls (235). Sharing a room with male persons and having more siblings increased age of menarche (135). Higher childhood SES and secure (vs insecure) mother–child attachment predicted later pubertal timing, suggesting these factors may protect girls from earlier pubertal development (236). Females are overrepresented in these studies, perhaps because age at menarche is a typically more reliable self-reported marker of pubertal development or because of increased focus on female compared with male reproductive capacity.

The presence of early life stressors has been linked with early pubertal development in females and later development in males. In a Puerto Rican cohort, childhood adversity had a differential effect on pubertal timing and tempo among girls and boys after adjusting for SES and age (237). In a cross-sectional study NHB children exposed to trauma, sex-specific

trauma was associated with earlier menarche in females. The study also suggested that trauma exposure in males may be associated with later pubertal development with overall faster tempo of puberty (238).

#### Psychosocial

Pubertal development can confer psychosocial risks that may differ between males and females. There is substantial evidence that early or precocious pubertal development is associated with externalizing behavior in youth (239), especially among boys (240). Early maturing girls have been consistently found to be at higher risk of depression and eating disorders (internalizing disorders) as well as substance use and conduct disorders (externalizing disorders) (191, 238, 241-243). They are more likely to exhibit poor academic performance in high school than on-time or later maturing peers (240). Adolescents of both sexes with earlier pubertal timing engaged in earlier and riskier sexual behaviors, with stronger associations in females (244). In the Great Smoky Mountain Study females aged 9-16 years with the highest levels of testosterone and estradiol during pubertal development had higher rates of depression later in life. Generally speaking, rates of depression in females outpace males after age 13 years (245). Trends related to sexual initiation, eating disorders, and depression among females are also noted in international populations (240).

### Sex Differences in Intermediate Health System Factors

Like treatment with growth hormone for short stature, gonadotropin releasing hormone agonist (GnRHa) therapy for central precocious puberty can be expensive. Goals of therapy include normalization of growth and development, attainment of appropriate genetic adult height, and minimizing psychosocial stress related to early development. However, it is unclear which patients would benefit from treatment because endpoints such as final adult height and psychosocial/behavioral stress are difficult to define. Variables for treatment evaluation (age of appropriate puberty, definition of significant bone age advancement, definition of decreased predicted height, and definition of a pubertal response to gonadotropin testing) are also not well defined and approached differently in the literature, all challenges that have led to heterogeneous recommendations (246, 247). Although there is little information on disparities in GnRHa treatment based on sex, there is some sex difference in treatment frequency of constitutional pubertal delay with males often receiving sex steroid therapy (248). Clinicians tend to wait longer to treat girls than boys with pubertal delay (214), and it is unclear if this reflects referral bias or differences in physician management practices. A better understanding of the heterogeneity found in the diagnosis/treatment of abnormal pubertal development and of which populations are offered treatment or close follow up is lacking (Fig. 1).

### Summary, Implications, and Future Research Needs

To broaden the lens of our understanding of puberty, it is necessary to describe the full range of pubertal experience across diverse youth and to better understand variability in pubertal changes and experiences. There are many components of typical development. These include sexual intimacy, spermarche, and gender identity, and these are often ignored in pediatric research. Avoidance of these issues is magnified with respect to understanding experiences of sexually marginalized or gender minoritized youth. It is also critical to design and implement longitudinal studies that start at very early ages and collect robust, standardized data on pubertal development and its variations in non-White populations, both in the United States and abroad. These data will broaden normative descriptions of pubertal development beyond Marshall and Tanner's sample of 420 White British youth as the de facto reference group. These efforts should include biological and nonbiological variables associated with disparities in pubertal development. There is a large gender gap in puberty-related publications that has remained stable over time, with about 1.67 times more puberty-related publications with the term girls than with the term boys (249), an indication of the need for more studies focused on male youth.

Genetic methods like GWAS need to expand their focus on non-European racial and ethnic groups. In diverse populations, GWAS has poorer coverage with current existing gene panels and lower imputation quality. Populations with African ancestry have greater haplotype diversity than White or Asian populations, and this yields lower sensitivity for GWAS studies. There is a need to expand GWAS studies to larger African and African American cohorts (174). Increasing use of recently developed methods for trans-ethnic meta-analysis allows researchers to combine several populations while accounting for the heterogeneity between racial and ethnic groups in GWAS studies (250).

Because puberty is such a critical developmental window, future research should define morbidity and mortality among non-White adults with a history of early pubertal development. These data should incorporate careful attention to the role of nonbiological factors and their contribution to potential disparities in morbidity and mortality. Future studies should also evaluate the importance of intersectionality—specifically, the ways in which pubertal development and stereotypes/discrimination differ among youth of color and LGBTQIA youth, and the effects of interactions between sex and race/ethnicity on pubertal outcomes.

## Metabolic Bone Disease

Osteoporosis may be considered a disease that originates in childhood. Bone mass attained early in life is perhaps the most important determinant of lifelong skeletal health. Growth in bone size and strength occurs in childhood and is complete by the third decade of life, making the accrual of peak bone mass largely a pediatric and young adult phenomenon. A 10% increase in peak bone mass gain can have significant influence on risk of osteoporosis later in life, and in 1 analysis, it postponed onset of osteoporosis by 13 years (251, 252). Suboptimal peak bone mass may be related not only to osteoporosis in later life but also to fractures in childhood and adolescence (253). Acquisition of peak bone mass is a function not only of genetics, but also sex and environment and is thus subject to factors that drive racial, ethnic, and sex disparities.

Differences in BMD vary by race, ethnicity, and sex in adult studies, particularly when measured by DXA. In pediatrics, DXA is also used as a measurement of bone density and mass but it produces varied results concerning racial and ethnic differences in bone measures among children and adolescents (254, 255). Differences are also noted in quantitative

computed tomography measurements of trabecular bone (256, 257) and in bone "size" (254, 258). Bone development is a sexually dimorphic process with pubertal development leading to a larger skeleton with higher bone peak bone mass in males, compared with females. Size effects are attributable not only to genetics, but also to the action of sex steroids and growth hormone: insulin-like–growth hormone on the developing skeleton (259). Thus, changes in pubertal development described earlier in this statement have secondary effects on bone health and may contribute to differences in measurement by DXA. Tools to evaluate bone health in pediatrics need to account not only for size, but also differences in physical maturity.

Although nutrition and physical activity are of paramount importance to bone health throughout the lifespan, childhood and adolescence provide a critical window. There is consensus that adequate calcium and vitamin D intake is required for bone health and that the need for these nutrients changes throughout the lifespan. However, for myriad reasons that include SDoH (eg, access to healthy food, and the ability to identify appropriate sources of nutrition), many children and adolescents fall far short on these building blocks. Poor nutrition, and lack of calcium and 25-hydroxyvitamin D (25OHD) can contribute to development of rickets. Physical activity early in life contributes to higher peak bone mass, and exercise intervention trials show most effect during skeletal growth. Physical activity during puberty increases bone mass on the bone surface and enhances bone strength. The effects of physical activity on bone mass are driven mainly by mechanical load, direct stimulation of the bone, and from muscle contraction (260). Interestingly, sites of bone mass improvement resulting from similar interventions may differ between males and females (261).

## Attainment of Peak Bone Mass

### Disparities by Race/Ethnicity in Peak Bone Mass

#### Race/ethnic differences in biological and clinical (proximate) factors influencing peak bone mass

*Bone metabolism.* Differences in bone metabolism across racial and ethnic groups have been postulated. Bell et al conducted controlled metabolic studies showing differences in calcium excretion between Black and White children (262). Other studies showed differences in parathyroid hormone levels with Black children having higher parathyroid hormone levels and lower 25OHD levels than those of White children (263, 264). Adult studies reflect these observations. Data from NHANES waves 2003-2004 and 2005-2006 show that BMD significantly decreased as serum 25OHD levels and calcium intake declined among NHW and Mexican-Americans, but not among NHB. These findings were observed despite NHB having higher parathyroid hormone and lower 25OHD concentrations than NHW (265).

*Genetics.* Racial and ethnic disparities exist with respect to uncovering the genetic underpinnings of determinants of bone density, mass, and accrual. Family and twin studies suggesting that BMD has a high heritability (50% to 85%) have primarily focused on NHW females (266, 267). In a review of bone-related loci identified by GWASs in children and/or young populations, 7 studies included 22 805 White children (termed European or European American), 1177 "other," 337 African American, 232 Middle Eastern, and 126 Hispanic or Latin American children (268). Changes in genes associated with childhood and adolescent BMD were noted in NHW children: LRP5 (LDL-receptor related protein 5, British White children) (269), ESR1 (estrogen receptor alpha, White women and children in the UK) (270). SP7 (Sp7 transcription factor), RANK (nuclear factor kB receptor activating factor), and osteoporogeterin (OPG) are associated with BMD in NHW children from the ALSPAC study (271, 272). Findings have not been sufficiently investigated in diverse populations, but efforts are under way to characterize genetic contributions in these groups. A large meta-analysis of 30 GWAS studies of total body bone mineral density (TB-BMD), including 66 628 individuals (14 624 subjects from 5 studies were described as either African or multiethnic) was performed to understand the associations between gene variants and TB-BMD. The authors reported that genetic variants influence BMD from a young age, supporting the value of peak bone mass as an important determinant of bone health later in life (273). These studies should include larger and better-described racial and ethnic groups.

*Nutrition: calcium.* The preferred source of calcium intake for healthy bones is dietary. Most advertising and even the frequently used MyPlate (https://www.myplate.gov/) promote "dairy" as the primary source of dietary calcium. However, individuals with lactose intolerance will not be able to use dairy as a primary source of calcium. The prevalence of lactose intolerance differs geographically and by race/ethnicity. Lactose intolerance is above 50% in South America, Africa, and Asia, reaching almost 100% in some Asian countries. In the United States, the prevalence is 15% among NHW, 53% among Mexican-Americans and 80% in NHB. Among Hispanic and NHB populations, lactose intolerance tends to appear in early childhood (274). In the United States, nutrition guidelines recommend dairy foods as a primary source of calcium often without highlighting other nondairy sources (275). MyPlate has recently added lactose-free dairy and fortified soy versions to its definition of dairy.

*Nutrition: vitamin D.* Vitamin D status has been closely tied with pediatric and adult bone health. In a review of 7 studies examining the association of 25OHD levels with bone outcomes in older children, there was "fair evidence of an association between serum 25OHD levels and baseline BMD and change in BMD/bone mineral content (BMC) indices from the studies in older children and adolescents" (276). Vitamin D deficiency is common and has disparate distribution worldwide. An international overview of 25OHD concentrations reveals that about 7% of global populations live with serum 25OHD below 30 nmol/L or 12 ng/mL. Worldwide, almost 1 in 3 newborns have vitamin D deficiency (concentrations <25 nmol/L). In India, if vitamin D deficiency is characterized by 25OHD concentration <50 nmol/L, 95% of neonates are classified as deficient (277). Immigrant, refugee, and non-White populations tend to have lower 25OHD levels (278). Mean serum 25OHD concentrations in the Middle East, the Gulf states, North Africa, Northern India, Pakistan, and Bangladesh, as well and Northern China and Mongolia are so low that many children fall below 12 ng/mL (279). In the United States, NHW populations tend to have higher vitamin D status than NHB and Mexican

Americans (280). In both NHANES III (1988-1994) and the 1999-2000 NHANES surveys for children aged 1-8 years, adequate intake levels for vitamin D from food were met or exceeded by 69% of Mexican American, 59% of NHW, and 48% of NHB children (281, 282). There are some differences in supplement use in these surveys, with NHW children having a higher prevalence of use (31%) than NHB (16%) and Mexican American children (19%). NHW also had higher levels of circulating 25OHD than NHB and Mexican Americans across all age groups (280).

Variation in serum 25OHD observed in different geographic areas and populations is mainly due to environmental and lifestyle factors, not racial differences. In a South African study, serum 25OHD levels of a highly pigmented population were compared with those of an albino Black population. Albino children had higher 25OHD levels than pigmented children, despite similar dietary intake and sunlight exposure. Nevertheless, parathyroid hormone and plasma calcium levels were similar in both groups (283). Among children, the association of obesity with low 25OHD levels is consistent across race, sex, and ethnicity (284-287). And although common variants in 25OHD pathway genes have been associated with serum 25OHD levels in adult NHB populations, the 3 identified SNPs only accounted for 4.6% of the variation in serum 25OHD levels in NHB, indicating the importance of nongenetic factors (288). Twin studies have shown that genetics influence up to 50% of the variation in 25OHD levels, but, thus far, studies have only elucidated polymorphisms that account for approximately 5% of this variation. One genetic variant of vitamin D binding protein, GC2, is associated with a modest (~10%) decrease in serum vitamin D binding protein and 25OHD concentrations, but the reason for this finding is unclear. Polymorphisms of CYPR1 have been found in many populations, but they contribute less than <2% of all variation in 25OHD levels (289).

*Growth and obesity.* Premature and low birth weight infants have lower than expected bone mass in the first few months of life, and it is unclear if these differences persists through the lifespan (253). This is important because rates of premature infant birth are higher in NHB than NHW women (290). Given racial differences in obesity rates in children and the differential effects of obesity on bone health and fracture risk in pediatrics, there may be racial/ethnic disparities in obesity-driven bone health among children that have not yet been studied. Furthermore, there is evidence that obesity's effects on bone health may depend on specific fat depots such that racial/ethnic differences in fat distribution may underlie specific bone health risks in these populations. For example, visceral fat can release inflammatory cytokines that have adverse effects on the bone mineral unit, and increased leptin levels have been associated with cortical porosity and decreased trabecular thickness (291, 292).

### Race/ethnic differences in proximate nonbiological factors influencing peak bone mass

*Physical activity.* The beneficial effects of physical activity on bone health may be optimized when dietary calcium is sufficient. In a South African study of Black and White children, at baseline Black children had lower baseline BMD, and calcium intake in White children was approximately twice that of Black children. After the physical activity intervention, no synergistic effects of physical activity at the lumbar spine were noted in the Black children (293) (Fig. 1).

*Immigrant status.* Immigrant families tend to experience higher levels of food insecurity than nonmigrant families because of lack of access to familiar foods and lack of knowledge about foods in the new country (294). Immigrant families differ from refugee families in that refugee families tend to arrive in worse physical health and are at higher risk of nutritional deficiencies including 25OHD deficiency. In a Canadian study by Vatanparast et al, mean serum 25OHD concentration was significantly higher in nonimmigrant children than in immigrant or refugee children, with 25OHD deficiency/inadequacy in 63% of migrants and 80% of refugees. Risk factors for 25OHD deficiency included female sex, darker skin pigmentation, and lack of food and/or supplements (295). TB-BMC was also lower in immigrant children (294).

*Socioeconomic status.* In a study of the association of childhood socioeconomic factors and adult bone strength, being raised in a single-parent household for most of one's childhood was associated with lower femoral neck strength in adulthood, independent of childhood and adult SES. This study was underpowered to make inferences on these differences by sex or race/ethnicity (296). Socioeconomic advantage in childhood, but not current financial advantage, and higher adult education level were associated with higher adult lumbar spine BMD in 729 midlife adults in the United States (297). Combing data from NHANES 2005-2010 and 2013-2014 to examine disparities in osteoporosis, Tsai noted that osteoporosis was more prevalent among US adults who were noncitizens, less educated, unemployed, and had lower income (298). There is a dearth of longitudinal data examining the effects of these parameters on peak bone mass in children and adolescents who also live with these SDoH.

### Race/ethnic differences in intermediate nonbiological factors influencing peak bone mass

The amount of sun exposure that is needed to generate sufficient UVB for conversion of 7-dehydrocholesterol varies on latitude, season, time of day, ozone amount, cloud amount, aerosol and reflectivity of the surface (276). Increases in ozone levels and particulate matter in the air can decrease availability of the UVB rays that are necessary for endogenous production of vitamin D (299, 300). Children living in areas of higher air pollution may therefore have lower contributions of endogenously produced vitamin D (301, 302). In a study in India, children living in 2 areas of the city with differing air quality not only had differences in 25OHD levels, but also in parathyroid hormone and alkaline phosphatase (300) (Fig. 1).

Increased air pollutants are associated with higher rates of asthma and other respiratory diseases. Among NHB and Puerto Rican children in the United States, there are higher rates of childhood asthma, and these cases are more severe (283), with African American children having much higher rates of hospitalization for their asthma than White children (283). Typically, children with severe asthma or asthma requiring hospitalization are prescribed oral glucocorticoids for exacerbations. Thus, to the extent that air pollution drives asthma severity in some populations, it can indirectly affect pediatric bone health by increasing risk of use of oral steroids.

## Disparities by Sex

### Epidemiology

#### Sex differences in biological and clinical (proximate) factors influencing peak bone mass

*Genetics.* In a GWAS study of 1399 children with abnormal clinical bone health (Bone Mineral Density in Childhood Study [BMDCS]; 720 girls and 679 boys; 53% Caucasian, 22% African American, 14% Hispanic), 2 loci connected to sex-specific bone accretion at the distal radius during growth were identified. These loci are rs7797976 within CPED1 (cadherin-like and PC-esterase domain containing 1) in girls and rs7035284 on 9p21.3 in boys (284). Rare variants near EN1, and common variants near SOX6 are associated with high bone mass in children, albeit with differences in relation to sex in another review of the BMDCS (285) (White children, 733 females and 635 males) (Fig. 1).

*Nutrition: vitamin D and calcium.* In developing countries, female sex and specific age groups (neonates, preschool children, and elderly people) are the most consistently reported risk categories for hypovitaminosis D (286). In general, males have higher vitamin D intakes and 25OHD concentrations than females. Children tend to have higher 25OHD levels than adults. Less is known about pubertal sex differences in calcium metabolism.

#### Sex differences in proximate nonbiological factors influencing peak bone mass

*Physical activity.* Disparities in physical activity can affect pediatric bone health in a sex disparate fashion. In some countries, females have lower participation in sports and vigorous activities or insufficient physical activity levels to create a demonstrable effect on bone mass. Females may also engage in physical activity that does not involve peak strain of the bone muscle unit and they may therefore not derive as much benefit from physical activity as males who are more frequently encouraged to be involved in peak strain activity (287, 288) (Fig. 1).

What was previously known as the female athlete triad (disordered eating, amenorrhea, and osteoporosis) presented a significant risk to peak bone mass accrual in young women. However, research has moved to a more general concept of relative energy deficit syndrome (RED-S), but there is a significant lack of research on RED-S in diverse racial and ethnic populations (303). Furthermore, there is concern that emphasis on RED-S may be an overgeneralized approach when considering the effects of sex, race, and level of athletic ability. There is also concern that RED-S may subvert specific features pertinent to female athletes–such as amenorrhea–that are significant risk factors for osteoporosis (304).

### Pediatric Skeletal Complications: Disparities by Race/Ethnicity and sex

#### Fracture

Fracture in children is a common event, with a reported prevalence of 30% to 50% (305). Children who fracture have a higher risk of recurrent fracture in adulthood, with distal forearm fractures in male children associated with a significantly increased risk of fragility fractures at older ages (306). Sex-related differences in growth rates and trajectories in childhood may also play a role in subsequent fracture risk (307). A race-based difference in fracture rates was observed in a South African longitudinal study of 359 children, with White children having higher rates than Black children. This finding was similar to studies in other populations (308, 309). Importantly, post fracture care is influenced by socioeconomic factors and may present significant health disparity in fracture outcomes for NHB children (310). Post fracture pain management may also differ by race/ethnicity as well as socioeconomic factors (311, 312), and neighborhood factors may contribute further to race/ethnic disparities in childhood fracture (313). Training community health workers or social workers as partners in postfracture care may help improve outcomes in NHB populations (314).

#### Slipped capital femoral epiphysis

Slipped capital femoral epiphysis is an adolescent hip disorder with displacement of the capital femoral epiphysis from the metaphysis through the physis. Prevalence varies by race, with frequencies relative to Whites of 5.6, 3.9, and 2.5 for Polynesians, Blacks, and Hispanics, respectively (315). This condition is also more common in males (316) and in obese children (317). Unstable slipped capital femoral epiphysis can cause significant morbidity including avascular necrosis. There are very few studies of slipped capital femoral epiphysis outcomes that account for racial/ethnic differences in identification, intervention, outcome, and health-related QOL.

#### Nutritional rickets

A disease of growing bone, rickets is caused by a failure of osteoid mineralization that leads to a characteristic appearance on radiograph described as "widening, cupping and or fraying of the growth plate." Rickets can have a varied etiology but is commonly nutritional in nature and most prevalent among infants and toddlers. The consequences of nutritional rickets include stunted growth, developmental delay, lifelong bone deformities, seizures, cardiomyopathy, and even death. Risk factors include exclusive breast feeding, maternal vitamin D deficiency, living in temperate climates, lack of sunlight exposure, darkly pigmented skin and social or religious customs that prevent sunlight exposure. Nutritional rickets is the tip of an iceberg that is linked to a series of less visible consequences of vitamin D (or calcium) deficiency (318). Development of rickets has often been viewed through the lens of race and environment, and its history mirrors the debate over and development of pediatric preventative health (319). The following sections review the contributors to race/ethnic differences in nutritional rickets.

*Epidemiology.* Nutritional rickets is commonly seen in children from the Middle East, Africa, and South Asia (320). It is endemic in Mongolia, Tibet, and northern China, as well as northern India, with a prevalence ranging from 5% to at least half of the population in these countries (279). Rickets is also found in Africa, North America, and Europe with surprising frequency. Migration patterns contribute to a country's rickets prevalence. In an Australian study using x-ray evidence of rickets, higher rates were found in migrants from the Indian subcontinent (37%), Africa (33%), and the Middle East (11%) (321). In the UK, incidence and prevalence of rickets is increasing, particularly among African and South Asian migrants (322). In a population-based study over 40

years in Olmsted County, Minnesota, the incidence of nutritional rickets in children younger than 3 years increased >200% between 1970 and 2000, with the highest increases coinciding with the arrival of large numbers of Somali refugees to the county (323). In a review of case reports of rickets from 1986 to 2003 in the United States, the vast majority of cases were in breastfed NHB children who had not received 25OHD supplementation (324).

*Race/ethnic differences in biological (proximate) factors: nutrition and genetics.* There may be differences in 25OHD levels at which rickets develops that are dependent on the calcium intake in the diet rather than pigmentation of the skin. In a study of Nigerian children, rickets was noted at higher than expected 25OHD levels (325). Calcium deficiency rickets was first recognized in African countries, but it has also been described in North America and Europe. Cultural food practices can influence nutritional rickets. The combination of low calcium and high phytate intake—which impairs calcium absorption—is probably the main cause of nutritional rickets in India (326) (Fig. 1).

Although numerous studies have reported polymorphism in the vitamin D receptor gene, the impact of these polymorphic alleles on vitamin D receptor protein function remains unknown. At this time, studies examining whether differences in vitamin D–associated alleles may be important contributors to the development of rickets have yielded only suggestive results.

### Health Care Interventions to Improve Metabolic Bone Disease Outcomes and Reduce Disparities

An interesting historical context to nutritional rickets led to early policy interventions to reduce the incidence of this disabling condition and its associated disparities. In 1916, Alfred Hess, a New York pediatrician, along with L.I. Unger, undertook a study in the Columbus Hill district of New York to study the efficacy of cod liver oil in preventing rickets. In their 1917 *JAMA* paper (327), they noted "our main reason (for undertaking this study) was the fact that, agreed to by all, that of all races the negro is most subject to rickets. This tendency is so marked that over 90% of colored babies have rickets and that even a majority of those that are breast fed show some signs of the disorder." At the time, the authors noted that the mortality of "negro" infants in the city was 202/1000 while that of White infants was 94/1000. Additionally, in the Columbus Hill district where the study was conducted, mortality among Black children was even higher at 314 deaths/1000, mostly related to pulmonary infections for which rickets was suspected to be a cause. He also noted that "the economic status of these people as of all the negro population in the larger cities, may be summed up as very bad." Hess's and Unger's efforts led to the establishment of a center in New York for maternal and child care with an emphasis on combating rickets (327).

Around this same time, many others were exploring rickets and its treatment. From the studies on pups by Findlay and Ferguson to the work of Huldchinsky and Chick et al with UV light, and the observations of Hutchinson and Shah in India, recognition of the environmental and nutritional underpinnings of rickets was discovered (328-331). Following these discoveries, policies were rapidly introduced in many countries that called for 1 teaspoon of cod liver oil, oral vitamin D supplements, or vitamin D–enriched foods to eradicate rickets (279). What started as an exploration of a condition that seemed to be "suffered" by a particular race became the fuel for implementation of social, economic, and environmental policies where preventive interventions at the societal level benefitted entire populations. Global consensus recommendations for treatment and prevention of nutritional rickets have been published (332).

### Summary, Implications, and Future Research Needs

To provide data that can assist in calculating fracture risk during childhood and puberty and into adulthood, prospective studies are needed that investigate genetic and nongenetic factors that drive peak bone mass accrual in diverse populations based on sex, age, race, and ethnicity. Environmental studies on the impact of endocrine disruptors on bone health in children are also needed. Results from these studies will support identification of multilevel intervention targets in racially, ethnically, and socioeconomically diverse pediatric populations that will allow the best opportunities for these children to achieve peak bone mass.

Calcium deficiency remains a significant problem. Special attention must be given to educating parents and caregivers about nutritional sources of calcium, especially when dairy foods are not part of the diet. Use of materials, such as MyPlate, needs to be expanded and adjusted to provide culturally appropriate food choices. Adding counseling about the importance of bone mass accrual in childhood and adolescence during routine pediatric care with specific infographics may prevent some later osteoporosis risks.

Despite our knowledge of nutritional rickets and its determinants, a recent Cochrane review examining the effects of vitamin D, calcium, or a combination of vitamin D and calcium for treatment of nutritional rickets in children found only 4 randomized controlled trials out of 4562 studies on the topic. Two studies were conducted in Nigeria and the other 2 in India. The authors were unable to draw conclusions about best treatment regimens, and there was insufficient evidence to comment on morbidity (fracture) and none of the studies assessed all-cause mortality, health-related QOL, or socioeconomic effects (333). For a condition with such a global impact, the lack of well-designed treatment trials is remarkable. Adequately designed trials are needed to establish the optimum dose, duration, and effect of vitamin D supplementation on key health outcomes in global populations.

In addition, a global initiative spearheaded by the WHO is needed to eradicate rickets in much the same fashion as has been done for iodine deficiency (279). Fortification of foods should account for culturally appropriate ready to eat foods that have longer shelf life, require minimal preparation, and have economic and technological feasibility (334). As shown by the Optimal Vitamin D Nutrition and Health Through the Life Cycle (ODIN) study group, a large variety of foods should be considered for supplementation including "food to fork" supplementation, supplementing animal feed with vitamin D (335).

## Type 1 Diabetes Mellitus

In the United States, T1D affects approximately 187 000 children and adolescents (336). The incidence, prevalence, and clinical presentation differ by race and ethnicity, and, to

some extent, by age and sex. Globally, these figures are more difficult to ascertain as only 97 countries have their own incidence data, and much of the published data are not current (337). In addition, there are disparities in disease management and processes of care that likely drive disparities in T1D-related morbidity and mortality (338).

### Disparities by Race/Ethnicity

#### Epidemiology

In the United States, the prevalence of T1D is highest among NHW youth (339). Worldwide, people who self-identify as White tend to be at greatest risk for T1D compared with other race/ethnic groups (340). Among US youth, NHW are about 1.5 times more likely to develop T1D as NHB or Hispanics, 4 times more likely than Asians and Pacific Islanders (API), and almost 9 times more likely than American Indians and Alaskan Natives (AIAN) (339). Using surveillance data of ~69.5 million youth <20 years in the United States, the SEARCH for Diabetes in Youth study reported that between 2002 and 2015, the incidence of T1D was higher among NHW youth (27.3 per 100 000 persons per year) than among NHB, Hispanic, and API youth (20.8, 16.3, and 9.4 per 100 000 persons per year, respectively) (341). However, the annual percent change in T1D incidence was disproportionately higher among minorities. Between 2002 and 2015, T1D incidence increased more among NHB, Hispanic, and API youth (2.7%, 4.0%, and 4.4%/year respectively) than among NHW youth (0.7%/year) (341). The annual percent change in T1D prevalence between 2009 and 2017 reflects similar trends, with higher percent changes among NHB, Hispanic, and API youth (3.7%, 2.4%, and 2.9%/year respectively) compared with NHW youth (1.1%/year) (342). The reasons for these differences in temporal trends are unknown. However, these trends, together with the shift in the landscape of the demographic distribution of the United States toward a more racially and ethnically diverse population, have yielded data projecting that, by 2050, T1D will increase 6.6-fold in Hispanics, 5.4-fold in API, 4.4-fold in AIAN, 3.0-fold in NHB, and only 2.5-fold in NHW. However, NHW are still projected to have the highest prevalence of T1D (343). It is estimated that 600 000 people <20 years will have T1D by 2050—a prevalence of 5.2 cases per 1000 (343).

#### Race/ethnic differences in proximate biological factors

The reasons for race/ethnic differences in of T1D prevalence and incidence in youth remain elusive. Different frequencies of high-risk genes likely contribute, but environmental triggers may also play a part (344). At present there is limited understanding of which environmental triggers may be involved and whether exposure differs by race/ethnicity (Fig. 1).

## Type 2 Diabetes Mellitus and Prediabetes

### Disparities by Race/Ethnicity and sex

#### Epidemiology—type 2 diabetes

Marked increases in pediatric obesity have led to corresponding increases in youth-onset T2D, a disease previously almost exclusively seen in adults. The SEARCH for Diabetes in Youth Study demonstrated significantly increased prevalence in youth-onset T2D among 10- to 19-year-olds, from 0.34 per 1000 in 2001 to 0.67 per 1000 in 2017 (342). However, NHB youth (0.85 per 1000) and Hispanic youth (0.57 per 1000) had the greatest absolute increase in prevalence. Moreover, adjusted incidence data from the SEARCH study showed an overall annual increase in incidence between 2002 and 2012 of 4.8%, with disproportionate increases in girls (6.2% annual increase) compared with boys (3.7% annual increase). Racial and ethnic disparities in incidence were even more extreme, with annual increases in T2D incidence in NHW of 0.6%, NHB of 6.3%, Hispanics of 3.1%, API of 8.5%, and AI of 8.9% (345). In contrast to US adults with T2D, youth-onset T2D has a significant female preponderance, with 2017 data demonstrating a prevalence of 0.82 per 1000 females compared with 0.51 per 1000 males (342).

Youth-onset T2D has also been increasing worldwide, particularly in minority and immigrant populations (346). In a recent review of country-specific incidence and prevalence rates of youth-onset T2D, Lynch et al found that economically developed countries such as the United States and China had higher rates of pediatric T2D, but the review was limited by a scarcity of data from some countries, as well as a lack of consistent application of diagnostic guidelines (347). In general, however, increases in pediatric T2D have followed increases in pediatric obesity, with most cases of youth-onset T2D occurring among obese individuals. However, although youth-onset T2D in the United States and Europe is usually associated with obesity, in countries such as Japan, India, and Thailand, 30% to 50% of youth with T2D have normal weight. Furthermore, some southern European countries such as Italy and Spain have very high rates of pediatric obesity, but relatively low prevalence of pediatric T2D (347). Lynch et al also report the highest incidence and prevalence of youth-onset T2D in African American, Aboriginal, Hispanic, and API, in contrast to youth from White and European ethnic groups. In Europe, prevalence of T2D is higher among immigrants from Asia, North Africa, and the Middle East than in native born people (346, 348).

Although US studies of T2D in Asian immigrant youth are limited, adult data suggest increased risk among South Asians at lower BMI compared with other groups. Regardless of BMI classification, South Asian adults in the United States have the highest BMI-specific prevalence of T2D among all ethnic groups (349). Furthermore, US adult data demonstrate age-adjusted T2D prevalence of 23% in South Asians, vs 6% in Whites, 18% in African Americans, 17% in Latinos, and 13% in Chinese Americans (350).

#### Epidemiology—prediabetes

Prediabetes is the intermediate state between normoglycemia and diabetes. It is defined by HbA1c (5.7-6.4%), impaired fasting glucose (100-125 mg/dL), and/or impaired glucose tolerance (2-hour glucose on oral glucose tolerance test of 140-199 mg/dL) (351). Youth with prediabetes are at increased risk for developing T2D, an argument in favor of screening at-risk individuals. Prediabetes in youth has increased, with 2020 NHANES data demonstrating a prevalence of 18% among US adolescents (352). Prediabetes prevalence is significantly higher in males than females, driven in part by higher levels of impaired fasting glucose among males. Prediabetes prevalence is higher among NHB (22.7%) and Hispanic (22.5%) youth than White (15.8%), and NHB youth are more likely to have elevated HbA1c

than others. However, NHB tend to have higher HbA1c for a given glucose level than Whites, which may be due to racial differences in hemoglobin glycosylation (353). These differences may have implications for the likelihood of diagnosing prediabetes and T2D among youth in various race/ethnicity groups as a function of which diagnostic tool is used.

### Race/Ethnic and Sex Differences in Biological (Proximate) Factors

#### Obesity and body fat distribution

Differential adipose tissue distribution contributes to racial and ethnic differences in metabolic risk. Increased abdominal or visceral fat is associated with adipocyte hypertrophy and impaired fat storage capacity. This leads to ectopic fat deposition in the liver, skeletal muscle, and heart. Increased visceral fat is also associated with proinflammatory and prothrombotic states, increased insulin resistance, hypertriglyceridemia, and higher cardiometabolic risk. However, subcutaneous fat is associated with adipocyte hyperplasia, and has been associated with a more insulin sensitive and favorable metabolic profile (354). Liska et al compared White, Black, and Hispanic youth in New Haven, CT, and demonstrated significant differences in adipose distribution. Hispanic youth had increased intramyocellular fat compared with White and Black adolescents, while White and Hispanic youth had more visceral fat than Black youth, who had increased superficial subcutaneous fat compared with Whites. In addition, Black adolescents had almost a total absence of hepatic fat. The authors found inverse relationships between insulin sensitivity and intramyocellular fat, hepatic fat, and visceral fat (355). Thus, the increase in intramyocellular, visceral, and hepatic fat in Hispanic youth may contribute to their increased T2D risk. However, these observations do not explain the increased risk of T2D seen in Black youth, which warrants further investigation. Obesity alone also does not explain the high T2D risk seen in South Asian youth. The "thin–fat Indian baby" paradox describes the 2003 finding by Yajnik et al that newborn infants in India had lower birthweight but preserved skinfold thickness (higher % body fat) compared with White newborns from the United Kingdom, while the Indian mothers also had lower BMI than White mothers (356). These findings have been replicated in South Asian immigrants (357). This differential body composition could contribute to increased T2D risk at lower BMI (Fig. 1).

#### Glucose metabolism

Recent data from a large registry of youth with T2D demonstrated significant racial and ethnic disparities in clinical disease course. NHB and Hispanic youth presented with higher HbA1c and had worse HbA1c trajectory over time than NHW youth. Moreover, NHB had 3-fold higher rates of diabetic ketoacidosis (DKA) and had lower C-peptide levels at presentation than the other groups, suggesting more severe disease at presentation (358).

### Race–Ethnic and Sex Differences in Proximate Nonbiological Factors

Other research has examined health behaviors in minority youth at risk for youth-onset T2D. In a study of Hispanic and African American seventh graders (359), Hispanic youth reported less physical activity, lower diet self-efficacy, and higher total fat intake. In addition, male youth reported more physical activity and more healthy food choices than females. In a study of health-related QOL in adolescents at risk for or with T2D (360), Black adolescents had the lower BMI-adjusted health-related QOL summary score than White, Hispanic, and other racial groups (Fig. 1).

## Complications of Diabetes Mellitus

### Acute Complications of T1D

#### Epidemiology

Acute presentation in DKA due to profound insulin-deficiency is often the presenting symptom of new-onset T1D, and it can be life-threatening (361). In addition to increased mortality and longer hospitalization, DKA at onset of T1D is also associated with long-term consequences, including higher insulin requirements, a shorter remission period (362), and less favorable glycemic trajectories over time (363). In the United States, the SEARCH study noted that a high prevalence of DKA at T1D diagnosis, at approximately 30%, but this was relatively stable between 2002 and 2010 (364). However, after that point, DKA at T1D diagnosis increased rapidly—at about 2% annually—from 35.3% in 2010 to 40.6% in 2016. The reason for this increase is unclear (365).

#### Nonbiological proximate/individual factors

The SEARCH (364) and other US studies (366, 367) showed that higher prevalence of DKA is associated with younger age at T1D diagnosis, non-White race/ethnicity, lower income, and lack of private health insurance. These findings were replicated by the T1D Exchange study group, which also found that the risk of DKA was higher in ethnic minorities, youth with public or no insurance, and youth from homes with lower household income (368). The Pediatric Diabetes Consortium (367) found that NHB youth were more likely to experience DKA compared with NHW youth (53% vs 36%, respectively), and both NHB and Hispanic youth were more likely to experience severe hypoglycemia than their NHW peers (11%, 7%, and 4%, respectively). Another study found that females were 2.3 times more likely to have 4 or more readmissions for DKA than males (369) (Fig. 1).

Like US data, a review of 46 studies involving >24 000 children in 31 countries demonstrated that younger age, being an ethnic minority, and lack of health insurance were risk factors for DKA at T1D onset (370). Younger age was consistently associated with increased risk of DKA at onset in numerous studies, an observation that is likely driven by multiple factors (371). Studies from developed countries have reported a broad range of prevalence estimates for DKA at T1D diagnosis (371). Countries with national insurance coverage experienced the lowest prevalence of DKA at diagnosis (372). The higher prevalence of DKA among US non-White youth with T1D, youth without private insurance, and those with lower family income indicate a persistent need for improved health care access.

Youth with T1D who identified as ethnic minorities are more likely to visit the emergency department and to be hospitalized (373). A recent study from the Children's Hospital of Philadelphia (373) analyzed hospitalizations and emergency department visits over ~14 months for diabetes-related events or any other causes among youth with T1D. NHB

youth with T1D were more likely to be hospitalized compared with Hispanic or NHW youth (18%, 10%, and 3%, respectively). Additionally, NHB and Hispanic youth were 7-fold and 4-fold, respectively, more likely to visit the emergency department compared with NHW youth. Importantly, a culturally sensitive medical and education program in Colorado reduced diabetes-related emergency department visits and hospitalizations among Latino youth with T1D and may serve as a model for similar efforts in the future (374).

### Nonbiological intermediate factors

A study from Maryland (369) found similar reasons for DKA hospital readmissions between 2012 and 2017. Compared with youth who lived in areas with the least deprivation, youth who lived in areas with at least moderate deprivation were more than 7.7 times more likely to have 4 or more readmissions for DKA. Compared with youth with private insurance, youth who had Medicaid were 1.85 times more likely to experience 1 to 3 readmissions and 2.81 times more likely to experience 4 or more readmissions for DKA (Fig. 1).

## Chronic Microvascular Complications of T1D and T2D

Individuals with poor glycemic and cardiovascular risk factor control are more likely to experience diabetes-related vascular complications as duration of diabetes increases (375). The SEARCH study found lower age-adjusted prevalence of early microvascular complications, especially diabetic kidney disease, among NHW participants with T1D compared with their non-White counterparts (375). The Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) was the first randomized controlled trial of youth-onset T2D (376). In recently published data from the TODAY study follow-up, among 500 participants with T2D who were analyzed at a mean age of 26 years, the cumulative incidence of any microvascular disease was 80.1% (377), and minority race or ethnic group was associated with increased risk. The risk of microvascular complication was 1.5 times higher in Hispanics and 1.46 times higher in NHB, compared with NHW. These findings are consistent with earlier data suggesting more severe disease and glycemic deterioration trajectories in minority youth with T1D.

### Biological proximate factors

*Glycemic control.* Glycemic control is the cornerstone of T1D management, yet several studies show disparities in the proportion of youth with T1D with optimal glycemic control measured by HbA1c. Non-White youth with T1D are consistently less well controlled than NHW youth (373, 378-383) and these disparities persist across T1D duration. The SEARCH study (383) found that 52% of AIAN youth, 36% of NHB youth, 27% of Hispanic youth, and 26% of API youth had HbA1c ≥9.5% within 5 years following T1D diagnosis, compared with 12% of NHW youth. Similar disparities have been observed in other cohorts with varying disease durations (384, 385) (373, 378, 386). The reasons for disparities in glycemic control are likely multifactorial but poorly understood. Even when youth are matched by age and insulin regimen, disparities in HbA1c remain between NHW and NHB youth (386, 387) (Fig. 1).

Disparities in glycemic control are not limited to T1D. Data from the TODAY (376) and SEARCH (388) studies show worse glycemic control among Black and Hispanic youth with T2D. Youth who were followed in the TODAY study had significant deterioration of glycemic control over time, with the prevalence of HbA1c ≥10% increasing from 0% at baseline to 34% at 15 years (377). Differences are also observed in response to pharmacological treatment of T2D among youth. Although studies of adults with T2D show a 21% failure rate for metformin monotherapy (389), studies in youth show a higher failure rate of 51.7% (376). Moreover, the metformin monotherapy failure rate among NHW and Hispanic youth was 44% to 45%, the rate in NHB youth was 66.2% (376). The reason for the increased metformin monotherapy failure rate among NHB youth has yet to be determined but possibilities include earlier beta cell failure in the setting of greater insulin resistance.

*Cardiovascular risk factors and comorbidities.* Youth with T1D or T2D who identify as ethnic minorities have worse cardiovascular risk factors than NHW youth. The SEARCH study found that non-White youth with T1D were 1.56 times more likely to have hypertension than NHW youth, with the highest prevalence of hypertension among AIAN (13.1%), followed by NHB ((7.8%), Hispanic (7.6%), and NHW (5.0%) (390). The Pediatric Diabetes Consortium (367) found that, compared with NHW youth, NHB youth with T1D were more likely to have hypertension (15% vs 7%), and Hispanic youth were more likely to have dyslipidemia (22% vs 12%). Among youth with T1D, obesity was most prevalent in girls, youth who identify as Hispanic or NHB, and those of lower SES (391). Since presence of cardiovascular risk factors during childhood and adolescence likely increases risk of cardiovascular disease in adulthood (392, 393), it is important to develop, test, and implement targeted interventions before development of end-organ complications.

### Nonbiological proximate/individual factors

*Socioeconomic status.* In the SEARCH study, participant characteristics associated with multiple microvascular complications in T1D included non-White race, lack of health insurance, and household annual incomes ≤$50 000 (394). Among 503 youth with T2D in the Pediatric Diabetes Consortium, 43% had family incomes below $25 000, and 70% had parents whose highest education level was high school or less (395). Similarly, in the TODAY study, 41.5% of the cohort had household incomes less than $25 000 and 26% had parents who had not finished high school (396) (Fig. 1).

In youth with T1D, several studies have shown disparities in HbA1c by health insurance status. A study from Baylor College (384) showed that youth with T1D with public insurance or no insurance had significantly higher HbA1c values than youth with private insurance (8.9% vs 8.1%). This difference may be explained, in part, by differences in the access to diabetes technology and continuity of care. In a cohort of youth from the Texas Children's Hospital diabetes clinic, youth with public insurance were about twice as likely to not use an insulin pump compared with youth with private health insurance (397).

*Social stressors.* Youth with T2D often experience significant social stressors. Among 497 youth in the final year of participation in the TODAY study, 67% reported having 1 or more major stressful life events and 33% reported having 3 or more

(398). The odds of medication nonadherence, depressive symptoms, and impaired QOL increased with the number of major stressful life events. Females reported more stressful events than males ($P < .0001$), but associations between the number of stressful events and clinical markers did not vary by sex. Data on differences in number of stressful events by race/ethnicity were not reported and warrant future attention.

*Health behaviors.* Family and behavioral factors have been linked to glycemic control. In a study of Hispanic caregivers of youth with T1D, barriers to optimal glycemic control included culturally driven dietary preferences and lack of family support (399). Caregivers reported that cultural recipes often included macronutrients that are not recommended for patients with T1D, and that patients' families had difficulty transitioning to the American diet. A report from the Type 1 Diabetes Exchange showed that distress about diabetes and self-care helped explained differences in glycemic control between NHB and NHW youth (378). The SEARCH study showed that youth with poor glycemic control had the highest weight, worst diet, least physical activity, and most screen time (400).

*Blood glucose monitoring.* Among youth without continuous glucose monitoring (CGM), NHW youth tested their blood glucose more frequently. In a cohort of youth with T1D recruited from the Children's Hospital of New Orleans, NHW youth were estimated to conduct 70% more blood glucose tests than their NHB peers (386). A large T1D trial that recruited participants from 3 university-affiliated hospitals in the United States found that Hispanic youth tested their blood glucose less frequently than NHW youth (4.4 times vs 5.2 times daily, respectively) (379). However, this difference did not persist after accounting for insulin management and SES. Barriers to blood glucose testing may include forgetfulness, the time required to test, pain, and embarrassment when testing around peers (380). Disparities in testing may also be related to differences in insurance coverage (401).

*Quality of life.* QOL among youth with T1D differs by sex, access to care, and household income. The SEARCH study found that QOL was higher among male youth, those with better glycemic control, private health insurance, and patients who used insulin pumps (402, 403). Data from the Teen COPE study (404) showed that youth with T1D from families with household income ≥$80 000 had better QOL than youth from moderate- or low-income families. Youth from high-income families had better self-management skills, less depression, and less perceived stress.

Non-White youth with T1D often have lower QOL. Baseline data from the Impact of Family Centered Tailoring of Pediatric Diabetes Self-Management Resources study (405), showed that NHW adolescents had better health-related QOL than their non-White peers. A study from 3 academic-affiliated hospitals (406) found that non-White adolescents internalized more stress than NHW adolescents. Non-White participants experienced more worry and distress about having diabetes and were more stressed about the perception of their disease among peers. It follows that youth who internalize more stress about diabetes adherence in front of peers may be at higher risk for poor glycemic control due to lack of glucose testing in social situations (407).

Interviews from an ethnically diverse cohort from the GRIT study offered themes concerning how T1D programs could improve QOL (408). Patients reported that T1D programs should provide better psychological and general support, put more effort into health literacy, improve T1D autonomy, and assist patients with coping both at the point of diagnosis and beyond.

### Race-ethnic differences in nonbiological intermediate factors

*General access to care.* Consistent access to quality health care is important for successful management of T1D. However, there are race/ethnic and socioeconomic disparities in access to care. The SEARCH study (409) found that compared with NHW youth, NHB youth were 2.6 times more likely to lack access to a regular healthcare provider. Hispanic caregivers reported significantly more issues communicating with health care providers, and receipt of contextual care (an understanding of a child's psychosocial needs and the impact of the child's diagnosis on everyday life). Youth from low- and middle-income families reported that the cost of health care services was a barrier to care and as expected, cost barriers are more prevalent among youth with public health insurance. One study showed a significant positive relationship between glycemic control and contextual care (409) (Fig. 1).

*Access to glucose management technology—insulin pumps and continuous glucose monitoring.* Although youth with T1D who use insulin pumps have lower HbA1c (410, 411), many barriers hinder uptake of and adherence to this technology. Youth who use insulin pumps are more likely to be NHW (343, 397), from families with high household incomes, and English-speaking (397, 411). They are also more likely to have private health insurance (343, 397). In a cohort from the Children's Hospital of Philadelphia, NHW youth were twice as likely to use insulin pumps compared with NHB youth, and 1.3 times more likely to use an insulin pump than Hispanic youth (373). These ethnic and racial disparities diminished among youth who had private insurance. Similar disparities in pump use have been reported by other groups (378, 411). In a survey of parents who did not initiate insulin pump use for their children, 43% felt that the financial burden was too high and 25% did not have coverage for this technology under their insurance policies (412).

Part of the disparity in insulin pump uptake may stem from physician prescribing patterns. A survey of Pediatric Endocrine Society members highlighted factors that providers may consider before prescribing insulin pump therapy (413). These included frequency of daily blood glucose testing; number of outpatient visits; whether the patient met a minimum HbA1c threshold; the patient's risk for hypoglycemia, and time since diagnosis. Some providers may also consider family motivation, patient lifestyle, financial stability, the family's ability to communicate with the provider's team, and SES.

CGM is associated with better glycemic control (410, 414, 415) and fewer episodes of severe hypoglycemia (415). However, CGM use varies by race. NHW youth are more likely to use CGM when than NHB and Hispanic youth (373, 397). In a cohort study of youth with T1D from the Children's Hospital of Philadelphia, NHW children were more likely to initiate use of CGM than NHB and Hispanic youth (416, 417). Once initiated, around 85% of NHW and Hispanic youth continued use of CGM; however, NHW

youth were 3.9 times more likely to continue use than NHB youth (416). In a population of Colorado youth with T1D and Medicaid, Hispanic youth were 66.5% less likely to use CGM successfully than NHW youth (410).

Several social barriers to insulin pump and CGM uptake have been proposed. A comparison of pump use between children aged 5-9 years and adolescents aged 10-14 years indicated that adolescents were less likely to use insulin pumps (411). In addition, females are more likely to use pumps than males (397, 411). A qualitative study explored reasons for poor uptake among Hispanic youth with T1D through caregiver interviews. These caregivers reported that their children were too embarrassed to wear the devices or that the children felt the technology was too restrictive with respect to play and sports. Importantly, many caregivers did not have a clear understanding about how the technology worked or when it should be initiated (399). In a study of experiences with diabetes technology, English-speaking Latinx T1D patients had more negative opinions, cited more barriers, and were less likely to initiate CGM (418). However, when a bilingual program was tailored to Latino patients with T1D in Colorado, the uptake of pumps and CGM improved (374).

*Access to metabolic surgery.* For adolescents with T2D, metabolic surgery is more effective than medical management for improving glycemic control, decreasing weight, and improving comorbidities (419). Yet, male and minority youth with severe obesity have lower than expected rates of metabolic surgery relative to rates of severe obesity in these populations (420). However, the effect of SES on these relationships was not clear. A recent study confirmed that female adolescents with severe obesity were 5.8 times more likely to undergo metabolic surgery than males. Moreover, Black and Hispanic youth were approximately half as likely as White adolescents to have these procedures, even accounting for the effect of insurance coverage. Minority youth with Medicaid were less likely to undergo metabolic surgery than privately insured peers. However, among White youth, Medicaid insurance was associated with increased rates of metabolic surgery (421). Although this study was not limited to adolescents with T2D, its findings are concerning given the disproportionate number of minority youth affected by T2D and the effectiveness of metabolic surgery for its treatment.

*Physical and social environment.* SDoH are associated with glycemic control. Data from a cohort of NHB youth with T1D recruited from Detroit and Chicago (422) showed that higher levels of neighborhood adversity and greater level of diabetes-related family conflict were associated with higher average HbA1c. A report from the SEARCH study showed youth with T2D who lived in homes with food insecurity had 2.37 times higher risk of poor glycemic control (423). In a study of youth with T1D from New Mexico (424), participants with household incomes of <$40 000 had significantly higher average HbA1c (8.8%) than those with higher household incomes (8.0%).

### Race/ethnic differences in nonbiological distal factors

*Access to glucose-monitoring technology.* For some people, insurance coverage for CGM can be difficult to obtain, but the American Diabetes Association recommends that people on intensive insulin regiments monitor blood glucose with CGM (425). Despite these recommendations, many insurance plans have not incorporated these recommendations into their coverage. Before July 2021, the Centers for Medicare and Medicaid Services required that patients perform blood glucose testing 4 or more times per day in order to cover CGM. However, in some states, Medicare only paid for 3 blood glucose tests per day. Anthem and AETNA had similar requirements to Medicare for CGM approval (401). In 2017, 39.5% of survey respondents reported that their insurance would not cover CGM (426). Another survey showed that people discontinued CGM because their out-of-pocket costs were too high (427). Fortunately, as of July 2021, Medicare eliminated all blood glucose testing requirements for CGM coverage for beneficiaries (428). CGM supplies often fall under durable medical equipment benefits, and third-party paperwork is required (415). While public insurance may also create barriers, it does not necessarily explain the racial disparities in uptake. In the Philadelphia cohort of youth with T1D (373) a higher proportion of NHW youth on public insurance used insulin pumps and CGM than NHB youth with private insurance. In the presence of so many insurance-related barriers, it has been proposed that provider bias may also account for some the disparities in the uptake of diabetes technology, particularly with respect to NHB youth (415) (Fig. 1).

## Mortality

There are marked race and sex disparities in mortality among people with youth-onset T1D. Among youth with T1D or T2D in the SEARCH study, females had higher mortality rates than males, and both Hispanic and NHB youth had higher mortality rates than NHW youth (429). Compared to males in the Allegheny County Childhood-onset Type 1 Diabetes Cohort, 40-year all-cause mortality was 30% higher in females (430). Mortality was higher among females than males for cardiovascular disease, renal disease, and infection. Overall mortality for NHB participants was 2.2 times higher than NHW participants. NHB participants had significantly higher mortality due to diabetic complications than NHW (acute complications RR 4.8, renal disease RR 4.6, CVD RR 1.9, and infection RR 2.8).

## Potential Health Care Interventions to Reduce Disparities

As summarized in the 2012 Endocrine Society Scientific Statement on Endocrine Health Disparities, multilevel interventions in adults with diabetes reduce disparities in diabetes and its outcomes (9). Successful interventions target the patient, provider, microsystem/health care organization, community/health care system, and policy (431). The tenets of successful health equity interventions, summarized by the Robert Wood Johnson Foundation, include (1) targeting multiple barriers a patient faces rather than relying on a single solution; (2) culturally tailoring the intervention; (3) using multidisciplinary teams; (4) employing interactive, skills-based patient training rather than passive learning approaches; (5) using patient navigators to support patients in traversing the medical system; and (6) involving family and community (432). These principles apply to both youth and adults with diabetes.

Gold et al. developed and implemented a novel, culturally sensitive, shared medical appointment and education program

for pediatric Latino patients with T1D, many of whom were covered by Medicaid and had poor glycemic control and low technology use (374). The program included a pediatric endocrinologist, program assistant, registered nurse, registered dietician, nurse practitioner, and social worker. Over 1 year, patients had 2 clinic visits and 2 program visits, and these covered diabetes care, nutrition, and behavioral health. Compared with controls, program participants had fewer diabetes-related emergency room visits and hospitalizations (374).

To address the lack of effective community-based programs to prevent youth-onset T2D, Hingle et al (433) designed the EPIC Kids Study. This clinical trial drew from the YMCA-based Diabetes Prevention Program protocol and was adapted for families. The trial tested a behavior change program targeting 9- to 12-year-old children and their parents with the goal of creating a scalable and replicable program that could partner with YMCAs nationwide. Results published in 2019 demonstrated feasibility of the intervention, as well as modest improvements in BMI z-scores and weight-related lifestyle changes that warrant further study (434). However, participant retention was challenging, with attrition of 25% at 12 weeks. The investigators planned to examine effects at 6 months and 12 months as well. Developing effective community-based interventions which are accessible to large numbers of youth is critical to improving metabolic health in vulnerable youth.

### Summary, Future Directions

Racial and ethnic disparities impact the burden, clinical presentation, processes of care, morbidity, mortality and QOL for youth with both T1D and T2D. The etiology of these differences in the prevalence and incidence of T1D in youth remains unclear. Ongoing research that identifies differences in biological and environmental triggers can lead to the design, testing, and implementation of interventions to reduce these disparities. There is global variability in prevalence and incidence of T2D that is not consistently correlated with obesity prevalence. Youth-onset T2D corelates with obesity prevalence in the United States and Europe, but a significant proportion of T2D in some parts of Asia occurs in children without obesity. Basic and clinical research are needed to elucidate nonobesity-related factors that contribute to T2D onset in nonobese youth.

Non-White youth with T1D have a higher incidence of DKA, and this risk is also associated with lower SES and coverage by public vs private insurance. Additional studies are needed to determine whether biological differences in glucose metabolism contribute to these race/ethnic differences when controlling for social factors such as type of insurance coverage. It is also important to integrate evidence-based interventions to increase access to care to prevent inequities in DKA, emergency department utilization, and hospitalizations for minoritized youth with T1D.

Minoritized youth with T1D and T2D have more chronic diabetes complications related to poorer glycemic control than White youth with diabetes. Additional research is needed to elucidate the drivers of metformin monotherapy failure among Black youth because of its contribution to glycemic deterioration. Because race/ethnic disparities in glycemic control are partly due to disparities in access to therapies that improve glycemia—including insulin pumps, CGMs and metabolic surgery—it is critical to remove financial barriers and craft policies that encourage initiation and maintenance of pump and CGM therapy and access to metabolic surgery. Importantly, there is a clear need to develop and test strategies to identify and remove unrecognized provider bias in providing diabetes technology and improve delivery of care to all T1D pediatric patients (435). These efforts will undoubtedly require working with insurers to reduce out-of-pocket expenses. Finally, diabetes-related mortality rates are higher among Blacks than Whites, much of which can be explained by differences in SDoH. However, the reasons for the higher mortality in girls than boys is unclear and requires additional investigation.

## Metabolic Syndrome

The metabolic syndrome is a clustering of at least 3 of 5 cardiometabolic risk factors—hyperglycemia, hypertension, central adiposity, hypertriglyceridemia, and decreased high-density lipoprotein cholesterol—which increases the risk for T2D and cardiovascular disease (436, 437). Given the existence of multiple pediatric definitions of metabolic syndrome, and a lack of consensus of which is optimal, the American Academy of Pediatrics recommended screening for component abnormalities and identifying youth with a clustering of cardiometabolic risk factors (438).

Table 7 summarizes race/ethnic differences in metabolic syndrome components in youth. Although NHB and Hispanic youth have increased obesity compared with White youth (439), NHB youth have increased insulin resistance and hypertension, and decreased dyslipidemia (440) compared with NHW and Hispanic youth. Hispanic youth have increased dyslipidemia (increased non–high-density lipoprotein cholesterol and decreased high-density lipoprotein cholesterol) (441) compared with NHB and NHW children. Thus, NHB youth have increased obesity and hypertension, but have decreased prevalence of the metabolic syndrome, potentially leading to an underestimate of their cardiometabolic risk (442) given their higher rates of T2D. Even after adjusting for SES and environmental factors, NHB males still had lower odds of metabolic syndrome and multiple components compared with NHW and Hispanic youth (443). Thus, race and ethnic-specific percentiles and cut points for components of the metabolic syndrome are needed to make this a useful construct (444) for health care providers, as has also been recommended for adults (9). Some studies have reported increased metabolic syndrome in boys compared with girls whereas others have not (444). Even with sex and race-specific cut-points, the utility of the metabolic syndrome as a predictive construct in youth would need robust testing and validation (444).

## Obesity

### Epidemiology

in the United States, obesity is the most common disease among children and adolescents aged 2-19. According to National Center for Health Statistics (NCHS), 19.3% of the pediatric population is obese (445). Racial and ethnic minorities have disproportionately higher rates of obesity with a prevalence of 25.6% among Hispanic children, 24.2% among NHB children, and 16.1% among NHW children (446). Non-Hispanic Black girls and Hispanic boys have the highest

**Table 7. Race/ethnic differences in metabolic syndrome components in NHB and NHW compared with White youth**

| | Hypertension | Obesity | Dyslipidemia | Insulin resistance |
|---|---|---|---|---|
| NHB youth | ↑ | ↑ | ↓ (compared with NHW and Hispanic) | ↑ |
| Hispanic youth | | ↑ | ↑ (compared with NHW and NHB) | No difference compared with NHW |

Abbreviations: NHB, non-Hispanic Black; NHW, non-Hispanic White.

rates of obesity at 25.1% and 28%, respectively (447). The lowest prevalence of obesity is among non-Hispanic Asian children, with a prevalence of 8.7% (445). Although less well documented, AIAN children and adolescents also have higher rates of obesity than their NHW counterparts (448). The etiology of the disparate rates of obesity is multifactorial, but SDoH, racism/discrimination, and genetics are among contributory factors (449).

## Race/Ethnic and Sex Differences in Biological (Proximate) Factors

### Genetics

Studies of the genetic contributions to obesity among children and adolescents are sparse. Munthali and colleagues investigated whether 97 SNPs with a strong association with adult BMI in NHW were prevalent in urban Black South African children (450). In this study, a genetic risk score for BMI was developed based on 71 of these SNPs. A higher risk score was associated with increased risk of belonging to the early onset obesity cohort, suggesting that susceptibility to higher adult BMI can be traced in part from childhood. There has been ongoing interest in determining how genetic ancestral markers influences early onset obesity disparities. Hazrati and colleagues investigated the relationship between children's genetic ancestral markers and excess weight at age 12 months in 825 children (451). They determined weight for length percentile at 12 months of age, and they found that only African ancestry was associated with early excess weight after accounting for confounding variables, suggesting that this ancestral background may contribute to differences in early childhood obesity (Fig. 1).

### Maternal prepregnancy weight and metabolic factors

Maternal metabolic characteristics may influence early childhood growth trajectories and childhood obesity risk. Hu and colleagues evaluated 3 maternal metabolic factors: prepregnancy overweight/obesity, gestational weight gain, and gestational diabetes mellitus, on early childhood growth trajectories and obesity risk (452). All 3 maternal characteristics were associated with childhood obesity at age 4 years, but this risk did not differ by race. In contrast, Liu and colleagues demonstrated in a cohort of 7 141 630 singleton live births that maternal prepregnancy obesity was associated with risk of preterm birth in the general population, and that this risk differed according to maternal age, race, and ethnicity (453). In NHW and Hispanic women, maternal obesity was inversely associated with preterm birth among women younger than 20 years but it increased risk of preterm birth in those older than 20. In NHB women, maternal obesity was inversely associated with preterm birth among those younger than 30 years and positively associated with preterm birth in those older than 30 years (454). In addition, both maternal prepregnancy obesity and preterm birth in NHB women were associated with a higher likelihood of obesity in children (454).

### Infancy and early childhood weight trajectories

Data from Roy and colleagues suggest that there are racial differences in obesity risk from infancy into childhood. The authors characterized infant BMI trajectories in a diverse cohort and investigated the relationship between infancy BMI trajectory and childhood obesity. Compared with NHW children, NHB children had a higher peak BMI that occurred earlier (455). Pineros-Leano and colleagues identified BMI trajectories for Black, Latino/a, and White children from birth to age 9 (456) and found different growth trajectories by racial/ethnic group, with Latino/a children with the steepest growth trajectories. These findings demonstrate that ethnic/racial disparities in childhood overweight and obesity start at birth, indicating the need to allocate more and earlier attention to these disparities.

In one of longest prospective studies to date, participants from the Child Health and Development Studies had height and weight data collected at ages 5, 9-11, and 15-17 years, and were followed up and measured again at the age of 50 years (457). At age 5 years, BMI was independent of sex for both NHB and NHW children, but by the age of 9-11 years, BMI was sex dependent in NHB, with higher BMI observed among females. The sex dependence for BMI among NHB persisted at ages 15-17 years and, remarkably, through age 50.

## Race/Ethnic and Sex Differences in nonbiological (Proximate) Factors

### Socioeconomic status

SES has been posited to contribute to racial and ethnic disparities in obesity. Yet, there are conflicting data regarding whether SES is protective against higher BMI in youth based upon racial/ethnic background. Assari found that higher family income was associated with lower BMI, with a small effect in NHB compared with NHW families (458). In a subsequent study on the effects of parental education and household income, Assari found that parental education, but not household income, lost some of its protective effect on childhood BMI among Hispanic White compared with NHW families (459) (Fig. 1).

Kininmonth and colleagues postulated that low SES can be a marker of a more "obesogenic' food environment, potentially encouraging behavioral expression of appetite avidity (460). They tested the hypothesis that lower SES children demonstrate increased appetite avidity from toddlerhood to 5 years. Results showed that that lower SES was associated with higher food responsiveness, higher enjoyment of food, lower satiety responsiveness, and lower food fussiness at 16 months. However, at age 5, lower SES was associated with higher food responsiveness, higher desire to drink, and higher emotional overeating. These results suggest that appetite may be a behavioral mediator of well-established links between childhood deprivation and obesity risk.

In one of the largest US studies evaluating disparities in childhood overweight and obesity by income, Weaver and colleagues conducted a meta-analysis of a nationally representative sample (n = 73 891) of children and adolescents from 3 datasets covering the period 1971-2014 (461). The authors evaluated household income to poverty ratio and they found that, overall, children from middle- and high-income families had lower rates of obesity. However, this was not observed in NHB families, in which a similar prevalence of obesity was noted across all family income levels.

The effects of SES and parenting factors on ethnic disparities in childhood BMI trajectory were examined in a longitudinal study of 29 254 children from 2 US cohorts—the Early Childhood Longitudinal Study-Birth (ECLS-B, 2001) and Kindergarten (ECLS-K, 1998-99) (462). Hispanic boys and NHB girls had the highest prevalence of overweight and obesity and mean BMI after than their White counterparts. The racial/ethnic disparities in childhood BMI trajectories were associated with household SES and family bedtime rules.

#### Food environments, stress and sociodemographic factors

Neighborhoods with predominately racial and ethnic minority residents often have fewer healthful food options, potentially contributing to obesity disparities (463). (Using electronic health records (EHRs), a cohort of 3724 predominately low-income, Black, and Hispanic children aged 2-5 years was examined (464). In this cohort, access to Women, Infants, and Children stores was associated with lower obesity rates and favorable BMI. Zurita and colleagues sought to determine the association between dietary intake and stress (465). Using a randomized cross-over design, ad libitum food consumption under control/relaxation and social-evaluative stress conditions were assessed. The authors found that NHB consumed more energy following relaxation than following stress, but they did not observe these differences in NHW and Hispanic/Latino children. Isahi and colleagues reported that, in four US cities, more self-reported caregiver stress is associated with more prevalent obesity among the Hispanic/Latino youth in their care (466).

Guerrero and colleagues also found disparities in BMI trajectories in NHB and Hispanic children in the ECLS-B. In that report, child characteristics (ie, age, BMI, and BMI percentile), maternal attributes, home practices related to diet and social behaviors, and family sociodemographic factors predicted BMI growth trajectories (467). NHB and Hispanic children had higher BMI trajectories, and greater consumption of fast food and soda were associated with these increases.

### Race/Ethnic and sex Differences in Nonbiological (Intermediate) Factors

#### Parental stressors and childhood adversity

Parental stressors play a role in the incidence of obesity in NHB youth. In 1 study, parent stressors (financial, legal, career, relationships, home safety, community safety, medical, housing, authority, and prejudice) were evaluated in relation to their impact on BMI and waist circumference in children. Parental exposure to stressors related to safety in the community and parents' description of these stressors as "difficult to get through" were associated with less favorable adolescent BMI and waist circumference. These relationships persisted after accounting for behavioral and psychosocial factors (468). A study by Beach and colleagues of 412 NHB adolescents followed participants over a 20-year period. The authors reported that change in BMI across adolescence was a possible mechanism linking childhood adversity and adult health (469) (Fig. 1).

#### Obesity treatment and healthcare access

Considerable research has suggested that there is race/ethnic and SES variability in efficacy of and access to obesity treatment (470, 471). Davison and colleagues evaluated family-based behavioral treatment in a racially diverse cohort and found that NHB children had less weight loss than NHW children in the first 4 months, but this difference did not persist between 4 and 12 months (472). Another study showed conflicting results in an evaluation of family-based behavioral treatment and parent-based treatment in Hispanic and NHW children. The latter study did not find differences in weight loss between groups despite Hispanic families attending fewer sessions than NHW families (473).

Despite the higher prevalence of obesity—especially severe obesity—in racial and ethnic minority populations, these groups have less access to effective treatments such as anti-obesity pharmacotherapy and metabolic and bariatric surgery, as discussed previously. Similar to Perez et al (421)., Bouchard and colleagues found race-based disparities in their cross-sectional analysis of adolescents aged 10-19 years who underwent bariatric surgery from 2009 to 2017 (474). Utilizing data from the Healthcare Cost and Utilization Kids' Inpatient Database and NIS, the authors found that vulnerable populations—which have the highest rates of severe obesity–undergo bariatric surgery at disproportionately lower rates than well-resourced populations (474).

### Summary

Childhood obesity is pervasive, but there is a disproportionate burden of obesity in racial/ethnic minorities in the United States The etiology of the observed disparities in childhood obesity is multifactorial. Key factors include genetics, maternal prepregnancy obesity and metabolic factors, infancy and early childhood weight trajectories, SES, dietary patterns, and treatment variation. Regardless of the etiology, there is a dire need to address obesity and associated disparities because obesity can lead to stigma and poor health outcomes in childhood and adolescence (bone/joint conditions, T2D) and it predicts poor health outcomes in adulthood. Early intervention and novel strategies to address the disproportionate rise in obesity in minority children and adolescents are needed to improve health in these populations, including policies to increase access to affordable healthy food options and safe spaces to engage in physical activity, particularly in marginalized urban and rural areas.

## Overview of Sexual Orientation and Gender Identity Development

Sexual orientation and gender identity are human characteristics that are often first apparent in childhood and adolescence, and development of a sexual orientation and gender identity often begins in childhood or adolescence. Previous models of development highlighted a process of recognition and concern regarding stigma, gradual acceptance, and, finally, disclosure to others. However, these models may not be applicable in settings where sexual orientation is less stigmatized and access to information on the internet is widely available to young people (475). Previous data suggested

awareness of same-sex attraction at age 9-10, and self-identification as gay or lesbian at an average age of 16-17 (476); however, these averages may shift in response to evolving social acceptance. The Williams Institute's 2014 report suggests that by adulthood (age 18-44) the prevalence of a gay, lesbian, or bisexual identity was 2.8% to 4.2% in the United States (477).

Like sexual orientation, awareness of gender identity is a process that begins in childhood. Children as young as 2 years learn to label themselves as a boy or girl, and by 4 or 5 they can understand gender identity (478). Children referred for assessment and management of gender dysphoria/gender incongruence may demonstrate gender nonconforming behaviors as early as age 3 while others may self-identify as transgender in adolescence or adulthood (479). By age 13-17, 1.4% of adolescents identify as transgender, compared with 1.3% age 18-24, 0.45% age 25-64, and 0.32% age 65 and older (480). In 2017, the Endocrine Society published a clinical practice guideline for the endocrine treatment of gender-dysphoric/gender-incongruent persons. This guideline discusses management of gender dysphoria/gender incongruence in adolescence, including guidance on evaluation and treatment (481).

## A Conceptual Framework for Endocrine Health Disparities in Sexual and Gender Minorities

Several etiologies for health disparities in sexual and/or gender minorities have been proposed. First, the health care system treats some LGBTQIA people as suffering from mental health disorders with mental health solutions (15). Second, because sexual orientation and gender identity are not collected systematically in health care or health research, treatment frameworks do not typically include identified LGBTQIA people for development of best practices (482). Third, despite some increase in acceptance, societal bias against LGBTQIA people remains strong in many settings, contributing to stressful encounters with the health care system or avoidance of medical care. Fourth, there are insufficient providers with appropriate training to provide high-quality health care to LGBTQIA people. Finally, biases in policies, such as insurance company coverage policies for gender-affirming care, contribute to health and health care disparities for LGBTQIA people. We can utilize a similar framework to the race/ethnic disparities framework to describe historical and current contextual contributors to disparities in endocrine disorders in those who are part of sexual and gender minoritized communities and we will reference it throughout this section (Fig. 3).

### Sex Differences in Biological (Proximate) Factors

#### Obesity and disordered eating

Sexual minority individuals are at higher risk for overweight and obesity. Data from the Behavioral Risk Factor Surveillance System collected from 2014 to 2017 demonstrated that compared with straight adults, lesbian and bisexual women had significantly higher odds of overweight or obesity, whereas gay men have lower odds (483). Similar data in childhood are also emerging. Female sexual minority youth and bisexual boys have been shown to have higher odds of obesity than heterosexual peers (484, 485). Gay males at younger ages may have higher risk for obesity, but by late adolescence, they appear to have lower average BMI than heterosexual peers. Sexual minority status has been identified as a male-specific risk factor in adolescence and adulthood for the development of anorexia and other eating disorders (486).

Etiology of these disparities is likely multifactorial, but stress and its effect on weight-related behaviors has been suggested as a potential driver. For gay adolescents and men, striving for a "gay ideal body type" may contribute to risk for development of a restrictive eating disorder (487).

Transgender individuals are also at higher risk for abnormal BMI, more often with obesity *or* underweight compared with cisgender peers (488). While transgender individuals may share a potential stress-related etiology of obesity risk with sexual minorities, there is also concern that transgender individuals have very high risk for binge eating disorder and restrictive eating. A Canadian study demonstrated disordered eating behaviors in nearly half of transgender youth aged 14-18 (489), with the authors considering how pressures to conform one's body to societal gender expectations may contribute to these findings. Since transgender youth are often prescribed hormone interventions such as pubertal suppression and sex hormones, research has been conducted to determine whether these interventions are independent risk factors for obesity and dyslipidemia. A study evaluating patients treated with these interventions who were followed from age 15 to 22 years demonstrated more obesity but otherwise similar cardiovascular risk profiles in these patients compared with cisgender individuals (490).

#### Statural growth

Gender minority patients may have specific concerns about statural growth (481). The average adult height in the United States is 5 feet 4 inches (162.6 cm) for females and 5 feet 9 inches (175.3 cm) for males. Short stature in transgender boys and tall stature in transgender girls, when present, may contribute to psychological distress. Decisions regarding timing of hormonal interventions should be primarily driven by assessment of gender incongruence and patient and family readiness. Considerations such as prescribing a slower escalation in testosterone dosing to provide a longer period of growth in transgender boys to treat short stature or a more rapid escalation of estrogen dosing in transgender girls to treat tall stature have been discussed (491). In transgender populations, GnRHa treatment effects on final adult height and growth manipulation using adjunctive medications such as aromatase inhibitors and growth hormone require further study (492). Regardless, discussion of height prediction and patient goals and concerns should be included in gender-affirming care.

#### Pubertal development

Gender minority youth and young adults may experience increased stress, particularly during pubertal transitions, and this can be viewed through the lens of the "minority stress" model (493). This model proposes that members of minority communities experience specific and additional stressors when compared with the everyday stress experienced by majority populations over the lifespan (494). Over time, this can lead to activation of the hypothalamic–pituitary–adrenal axis. There is some evidence of an association of these markers (ambulatory blood pressure measurements, C-reactive protein, and awakening cortisol response) with perceived stress, the transition process, and cross-sex hormone therapy (495, 496).

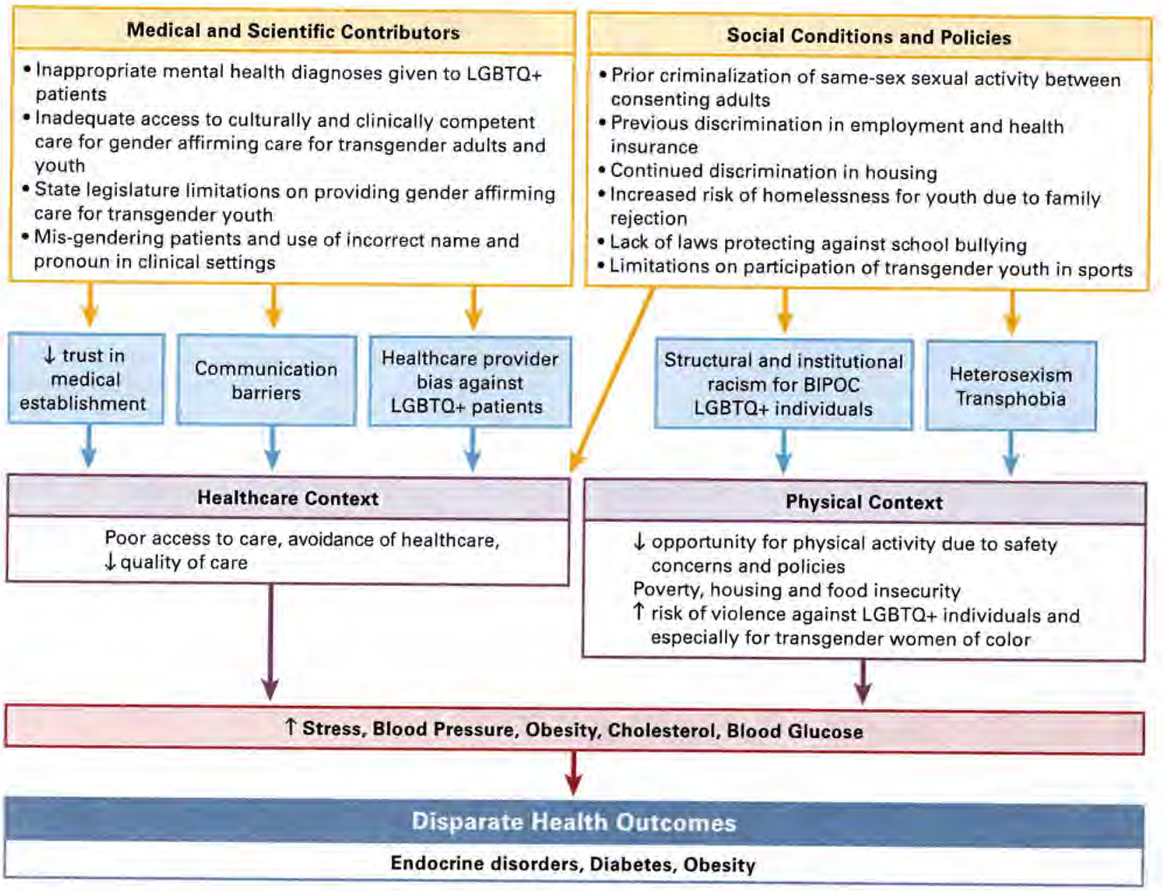


**Figure 3.** Medical, scientific, and social policy contributors to endocrine health and health care disparities in sexual and gender minorities in the United States.

During the pubertal transition, GnRHa therapy is used to delay development of secondary sexual characteristics. As in treatment for central precocious puberty, these agents seem to be well tolerated. Although rigorous long-term longitudinal studies of this therapy are not abundant in SGM populations, available literature points to improvements in affect and psychological functioning. However, this treatment is also linked to some concerns about changes in body composition, growth, cost, and lack of insurance coverage (497, 498).

### Reproductive health

SGM youth and adults are at risk for health disparities concerning sexual and reproductive health. Sexual education that is provided to youth in the school setting is reported to be overwhelmingly heteronormative, leaving SGM youth without important information (499). While there is a rich literature with respect to risks for HIV and sexually transmitted illnesses, less is known about contraception and sexual dysfunction counseling or screening for and rates of reproductive cancers (500-503). Transgender men may choose to use contraception, experience pregnancy, and have abortions, even while receiving gender affirming hormone treatment. Transgender men also remain at risk for gynecological malignancies but may not always receive needed screening (504). Health care providers must be prepared to discuss these issues and provide appropriate guidance. Further research is needed into optimal contraception and fertility preservation, if desired, among SGM (505).

### Bone mineral density and vitamin D

Gender-affirming hormone therapy (GAHT), including sex hormones in transgender men and women, adjunct testosterone-lowering therapy in transgender women and gonadotropin-releasing hormone agonists to delay puberty in youth, can impact bone health because both estrogen and testosterone regulate bone formation during puberty and bone turnover during adulthood (506). Research to understand long-term bone effects of hormone regimens is ongoing. A meta-analysis showed that there was no significant change in BMD in transgender masculine individuals receiving masculinizing GAHT whereas feminizing hormone therapy in transgender women was associated with increased lumbar spine BMD (507). Other work shows that transgender adults have 25OHD levels below the level of sufficiency (30 ng/mL) (506), potentially impacting bone health. Despite understanding the impact of sex hormones and testosterone-lowering therapy on BMD in adults, there is a paucity of data on prevalence of osteoporosis and osteopenia in transgender individuals. In a Belgian study of transgender women not treated with hormones, the prevalence of osteoporosis and osteopenia at

the lumbar spine was 16% and 32%, respectively, based on a male reference range (508). There are no data on the prevalence of osteoporosis and osteopenia in transgender individuals in the United States and very few data on fracture rates in the transgender population (506).

The literature on the impact of GAHT in transgender youth is limited. One small study showed no change in absolute BMD of the spine during GnRHa therapy and a slight increase in absolute BMD after initiating GAHT in transgender girls (509). In contrast, there was a significant decrease in spine absolute BMD during GnRHa therapy with stabilization after initiation of GAHT in transgender boys. In 1 of the largest studies of bone mass development, transgirls had low BMAD z scores at the initiation of the study and after 3 years of estrogen therapy (510). These findings raise concerns about prolonged GnRHa therapy without (and in some groups, "with") sex hormone therapy on bone health in transgender youth and adults (506).

### CVD and lipids

Previous work suggesting that GAHT in adults may have adverse effects on cardiometabolic health in Europe and the United States included individuals treated with ethinyl estradiol, not currently used in most GAHT regimens due to known adverse effects on cardiometabolic risk factors (511). Longitudinal studies using current hormone regimens are needed (512).

Information on glycemic status and elevated blood pressure readings in transgender populations is limited and available data vary. Transgender men do not appear to have clinically significant elevations in blood pressure; among transgender women, higher testosterone levels were associated with higher odds of hypertension, although in a small study, this seemed to be mitigated by use of a progestin (513). Review of EHRs of the Study of Transition Outcomes and Gender (STRONG) cohort noted increases in incidence and prevalence of T2D in transgender women when compared with cisgender women but not cisgender men, and no significant association with GAHT use (514). Studies on insulin resistance generally show differential effects with respect to GAHT, with testosterone supplementation inducing increased lean mass and decreased fat mass without change in insulin resistance whereas transgender women receiving GAHT may have experienced worsening insulin resistance and less favorable metabolic changes in body composition (514).

Other risk classical risk factors may not show significant differences between groups. Lipid profiles in transgender and gender diverse individuals do not appear to have significant differences from ranges in similar cisgender adolescent, young adult, and adult individuals and long-term effects of small differences are unknown (515). In a multicenter, cross-sectional database analysis, transgender youth tended to have more diagnoses of obesity, dyslipidemia, hypertension, liver dysfunction, and polycystic ovarian syndrome than controls; however, these differences, except for obesity, disappeared after adjusting for significant covariates (516).

There is a growing focus on disparities across a wide variety of cardiovascular risk factors in transgender and gender diverse individuals compared with cisgender peers. In 2021, the American Heart Association proposed that excess risk is not simply the result of differences in health behaviors or hormone therapies, but likely "driven in part by psychosocial stressors across the lifespan at multiple levels, including structural violence" (517). Psychosocial stressors across the lifespan may contribute to poor cardiovascular health outcomes for transgendered individuals in both direct and indirect fashion (518).

### Intersex conditions

Infants and children with intersex conditions should meet with multidisciplinary teams. These teams may include pediatric endocrinologists, geneticists, urologists, gynecologists, and mental health professionals. Needed services may not be available at all medical centers and it is rare to find them in a dedicated, interdisciplinary intersex service line (519). Moreover, decisions made regarding gender of rearing can be complicated and are often made prior to meeting with a multidisciplinary team. These decisions are made in infancy and do not include the individual. As the individual grows there is increased awareness of gender identity that can be expressed and shared with others. Thus, individuals with intersex conditions may have higher rates of dissatisfaction with their gender of rearing (520). There may also be increased prevalence of sexual minority status in intersex individuals, with the most robust literature in this area related to individuals with congenital adrenal hyperplasia who were reared female (521).

Intersex individuals have a higher risk for health disparities than nonintersex populations. Disorders of Sexual Development (DSD)-LIFE is a European longitudinal cohort of intersex adults. Recent findings show significantly higher rates of health problems (eg, dyslipidemia, obesity, autoimmune, and psychiatric conditions) and physical health limitations than controls. Rates of specific conditions varied by underlying diagnosis (eg, Klinefelter syndrome vs 46XX DSD) as well as by age at diagnosis, emphasizing importance of the underlying medical condition (522). A population sample of US intersex adults demonstrated a high prevalence of anxiety, depression, and post-traumatic stress disorder, and a higher percentage of respondents reporting fair or poor physical health than the general population (523). A recent analysis of the PEDSnet (an EHR-based database of 6 participating children's hospitals), noted a significantly increased rate of behavioral and neurodevelopmental diagnoses in DSD youth compared with matched non-DSD youth controls (524). The health care system may contribute to these disparities by perpetuating binary ideals and overpathologizing intersex variation (525).

### Asexual persons

There is a general lack of information about asexual persons, and they are generally included under the SGM umbrella term. Based on self-reported data from a small series of adults, asexual individuals may experience more stigma than other SGM populations (526). One study of adolescents who identified as asexual showed respondents felt they were minorities within the SGM umbrella (527).

## Sex Differences in Nonbiological (Proximate) Factors

### Socioeconomic status

SGM youth may experience family rejection including decreased financial and emotional support, increasing their risk for homelessness along with interactions with the child

welfare system, and the juvenile justice system (528-530). Once SGM youth enter the child welfare system, they face increased obstacles including reduced placement in permanent options (531) (Fig. 1 and 3).

### Race/ethnicity, psychological stress, and allostatic load

The intersection of race/ethnicity and SGM status increases allostatic load and can lead to increased stigma. In a telephone survey of 489 LGBTQ adults, more than 90% of respondents reported a high incidence of discrimination, including in health care. However, LGBTQ persons who identified as a racial or ethnic minority reported significantly increased rates of discrimination based on their identity when applying for jobs, engaging in legal matters, or in expression of their political rights compared with their White counterparts (532). In a study of 334 Midwestern youth with psychiatric hospitalization, LGBTQ persons had higher rates of lifetime suicide attempt than cisgender youth with the highest rates were found among minority LGBTQ youth (533).

### Physical activity

Transgender individuals engage in less physical activity than cisgender individuals (534), which can contribute to obesity and T2D risk as well as low vitamin D levels due to less sunlight exposure and weight-bearing activity. The latter also has implications for bone health. The lack of safe gender-neutral recreational facilities to engage in physical activity can contribute to obesity and metabolic disorders (535) in these populations.

## Sex Differences in Nonbiological (Intermediate) Factors

### Health care system

Health care systems in the United States have not implemented processes to identify sexual minorities through collection of EHR demographic data (482). Thus, disparities among LGBTQIA people are not measured systematically. These data shortfalls are notable because transgender people often depend on the health care system if they seek gender affirming medical and/or surgical interventions. In addition to the gaps in best practices for SGM in general, some systemic biases are also apparent. Genital reconstruction surgeries are considered medically necessary when done for cisgender people but facial reconstruction is considered cosmetic for cisgender people. The result is that insurance coverage for phalloplasty and vaginoplasty for transgender people is common, but even where gender affirming health care is offered, coverage for facial feminization surgeries is rare (536) (Fig. 1).

One consequence of the persistent mental health framing of being transgender is that access to gender-affirming care often requires diagnosis of gender dysphoria from the Diagnostic and Statistical Manual of Mental Disorders (DSM). The World Professional Association for Transgender Health Standards of Care notes that transgender individuals seeking gender-affirming surgeries may need to obtain a letter from a mental health professional documenting their persistent gender dysphoria. A survey of transgender people found that 12% of those seeking hormone therapy did not experience psychological distress (537). Of those who did report psychological distress, a majority attributed it to external social rejection because of being transgender. Still, some payers specifically limit support of medical and surgical interventions to those that ostensibly "relieve dysphoria" (538).

Transgender persons report that the largest barrier to effective care is lack of knowledgeable providers (539). Some gaps in provider knowledge are attributable to the fact that mainstream medical education is often limited to cultural sensitivity, and lacks formal instruction focused on delivery of gender affirming health care (540). SGM adults also experience more negative health outcomes, and race/ethnicity mediates some of these differences (541). Although HIV status and risk factors have been frequently studied in relation to the intersection of race and sex/gender minorities, research into other areas where intersection of these identities creates unique challenges and is limited.

Aspects of gender affirming care involving hormonal therapy may affect a person's future fertility, but fertility preservation options remain inaccessible to most SGM people and their families because of their high cost and limited insurance coverage. For pediatric patients to access current fertility preservation techniques, they may need to undergo pubertal maturation out of alignment with their gender identity. Many choose to forgo fertility preservation in order to receive gender affirming hormonal therapy earlier (542). There is emerging evidence that transgender men can regain ovulatory function following cessation of testosterone (543, 544) and that transgender women can resume spermatogenesis following cessation of estrogen (545).

### Socioenvironmental context

Transgender people are targeted for discrimination in locales where there are proposals to ban gender affirming care (546) and participation of transgender people in athletic categories that match their gender identities (547). In addition to inhibiting access to care, these efforts may contribute to stress-related morbidity among transgender people. Limits on athletic participation among transgender people would likely contribute to obesity and T2D as well as and bone health through lower vitamin D levels.

## Sex Differences in Nonbiological (Distal) Factors

### Societal bias

Societal bias regarding SGM is reflected in both stigmatization and hostile policies. Homosexual relations between 2 consenting adults remain a criminal offense in much of the world (548), and in the United States, some jurisdictions maintain legal discrimination against LGBTQIA people in access to health insurance, employment, housing, marriage, adoption, and retirement benefits (535). Social acceptance of SGM mitigates some of the adverse mental and physical health outcomes suffered by SGM youth (549) (Fig. 1 and 3).

### Policy bias

Historically, LGBTQIA people have been given mental health diagnoses when presenting for health care. Indeed, the American Psychiatric Association only removed the diagnosis of homosexuality from its DSM in 1973 (550), and the WHO only removed homosexuality from the International Classification of Diseases (ICD-10) in 1990 (550). The DSM continues to have a transgender section termed "gender dysphoria" and the WHO's ICD-10 references transgender

people as suffering from gender dysphoria in the chapter on mental health (542). For ICD-11, the WHO plans to remove the term gender dysphoria and to use "gender incongruence," the sexual health term, to refer to transgender people.

Many sexual and/or gender minority youth suffer because of a lack of legal protection against school bullying. Furthermore, several state legislatures have recently proposed varying bans on the prescribing of GnRHa or GAHT for SGM youth, some including prosecution of medical providers (551). Other states have proposed or passed laws restricting participation of SGM youth in school related sports activities in ways that can be stigmatizing. These include limiting sports participation to a team that represents their gender recorded at birth rather than their gender identity (552-558). States have also passed or proposed laws protecting individuals and institutions from discrimination legislation when refusing to provide services to SGM populations (559).

### Summary and Future Directions

People who are SGM are at elevated risk for disparities in endocrine-related health outcomes, particularly obesity. The most recent edition (8th) of the World Professional Association for Transgender Health (WPATH) Standards of Care (SOC) guidelines support a thorough assessment and risk/benefit discussion of any physical conditions that "could negatively impact the outcome of gender–affirming treatments." This should also occur regardless of GAHT use (560). While not the focus of this statement, SGM people are also at higher risk for being the victims of bullying and violence, along with increased rates of mental health illness, sexually transmitted infections, smoking and substance use (539). Indeed, studies of transgender people find disparities in multiple areas that can be connected to minority stress including HIV prevalence, tobacco use, alcohol use, and suicide (561). Further, available literature fails to adequately consider the contributions of ethnicity, SES, and other demographic factors to these health disparities (539). For example, Black, Indigenous, and Hispanic members of the LGBTQIA community experience more episodes of violence, particularly transgender women, due to lack of safe spaces. These shortfalls may mask areas of even greater morbidity.

For individual providers, asking about sexual and gender identity and allowing for confidential disclosure may be the first step toward developing a successful treatment plan. In the care of patients known to be LGBTQIA, special attention should be paid toward monitoring metabolic parameters and screening for disordered eating. In this context, growth manipulation using adjunctive medications such as aromatase inhibitors and growth hormone require further study (492). Regardless, discussion of height prediction and patient goals and concerns should be included in gender-affirming care. Further research is also needed to determine optimal timing and duration of gonadotropin hormone agonist therapy in transgender youth as it relates to bone health and to determine the prevalence of osteoporosis, osteopenia, and fractures among transgender youth and adults (506). In addition, options for fertility preservation in SGM should be included in patient-physician discussions. The WPATH SOC 8 explicitly calls for the discussion of possible effects of therapies on fertility and available fertility preservation options (560). Additional research is needed to provide best practices in fertility preservation options and reproductive care of SGM patients (562).

Reduction in health disparities for intersex populations will require careful attention to supporting the mental and emotional health of patients with these conditions and working with patients and families to navigate cultural and social preferences and to support patient autonomy.

More data are needed to explore how sexual and gender identity development may be impacted by chronic disease, and how chronic disease management may be affected by SGM status. This will require health care providers and systems to collect data on sexual orientation and gender identity in their health care records. Longitudinal studies are needed to understand CVD risks over the lifespan. Delivery of effective and equitable gender affirming care needs to be incorporated into undergraduate and postgraduate medical education to ensure that providers in all areas of medicine are prepared to care for patients with diverse sexual and gender identities. Finally, policy level changes are needed to ensure access to insurance coverage for SGM, to depathologize these conditions, and to facilitate access to care.

## Conclusions

This Scientific Statement summarizes important areas for future research in the areas of race/ethnic and sex disparities in pediatric endocrine disorders as well as disparities in endocrine disorders for SGM (Table 8). To advance the field it is critical to ensure adequate enrollment of non-White and gender-diverse participants into clinical trials and clinical research studies so that these studies are adequately powered to draw meaningful conclusions from subgroup analyses. Despite the recommendation from the 2012 scientific statement that future studies accurately identify racial and ethnic subgroups, most studies continue to group all Black, Hispanic, and Asian populations together, despite their heterogeneity. Because subgroups within these populations have different lived experiences and societal perceptions, health inequities may not impact all members of a race/ethnic group equally. In addition, our current race and ethnicity classifications do not account for admixture within groups, which can be better ascertained through the use of ancestry informed genetic markers, allowing for a precision medicine approach to addressing inequities. Consequently, a critical area for future research remains ascertaining which subgroups require focused interventions and resource allocation to achieve health equity.

Puberty, growth, and attainment of peak bone mass are interrelated aspects of pediatric and adolescent maturation. Because of societal preferences for taller males, NHW males with idiopathic short stature are often overtreated with growth hormone, whereas girls and minoritized children with short stature are not evaluated as aggressively. This results in failure to identify underlying health issues that may manifest as delayed growth. To address these disparities, EHR–based alerts and other interventions need to be developed and evaluated to determine if they support timely identification of children with worrisome growth patterns. The norms of pubertal development, including Tanner staging, were developed from a European population and likely do not reflect race/ethnic and global variation in normal puberty. Furthermore, most puberty research focuses on female and not male youth. Attainment of peak bone mass is intertwined with pubertal development and has implications for future fracture risk. To better understand normal variation in pubertal development and peak bone mass, longitudinal studies that enroll patients

**Table 8. Summary recommendations for future research and policy needs to address pediatric endocrine health and health care disparities**

| Race/ethnic disparities | Sex disparities |
|---|---|
| **Overall:** Ensure adequate enrollment of non-White and gender diverse participants into clinical trials and clinical research studies so that they are adequately powered for meaningful subgroup analyses | |
| **Pediatric growth disorders** | |
| • Educate pediatric care providers to recognize growth failure in minoritized children and girls as a potential sign of an underlying health issue requiring further evaluation<br>• Evaluate whether interventions, such as electronic health system-based alerts, may identify children with worrisome growth patterns in a demographic-blind manner | • Develop assessment and intervention strategies to prevent overtreatment of idiopathic short stature in NHW boys |
| **Puberty** | |
| • Launch longitudinal studies, starting at very early ages, to collect robust, standardized data on pubertal development and its variations in race/ethnic groups other than White in the United States and globally<br>• Identify biological and nonbiological variables associated with disparities in pubertal development<br>• Expand genetic methods, such as GWAS, to focus on non-European racial and ethnic groups, particularly those focused on African and African-American cohorts<br>• Establish data on morbidity and mortality for adults with a history of early pubertal development in race/ethnic groups other than US Whites (with attention to the role of nonbiological factors in these disparities) | • Expand research studies focused on puberty in male youth<br>• Launch studies to evaluate the importance of intersectionality in understanding how pubertal development and stereotypes/discrimination among youth of color and sexual and gender minority youth impact pubertal outcomes |
| **Metabolic bone disease** | |
| • Launch prospective studies to determine peak bone mass accrual in diverse populations based on race, ethnicity sex, and age to support calculation of fracture risk during childhood and puberty and into adulthood and to identify best opportunity/window for achieving peak bone mass by population<br>• Conduct environmental studies to examine the impact of endocrine disruptors on bone health in children<br>• Design randomized controlled trials to establish the optimal dose, duration and effect of vitamin D supplementation on multiple health outcomes (eg, bone mass, fracture risk) globally<br>• Develop a worldwide initiative to eradicate rickets through food fortification efforts | |
| **Diabetes mellitus** | |
| • Elucidate etiology for race/ethnic differences in prevalence and incidence of T1D in youth<br>• Elucidate the mechanisms of the differential contribution of obesity to youth-onset T2D in different world regions, with particular attention to normal weight T2D and the role of body fat distribution | • Determine the contributors to lower physical activity levels and sex difference in dietary choices contributing to higher T2D prevalence in female youth<br>• Understand why males and race/ethnic minority youth less likely to undergo bariatric surgery<br>• Etiology of higher diabetes-related mortality rate among women compared with men and Blacks |
| **Diabetes complications (acute)** | |
| • Elucidate the etiology for higher rates of DKA in racial and ethnic minority youth (difference in glucose metabolism)<br>• Development of interventions to ensure earlier and more consistent health care access for minority youth for earlier T1D detection (so they do not present with DKA so often and need to utilize ED and hospital so often) | |
| **Diabetes complications (chronic)** | |
| • Basic and clinical research studies are needed to elucidate the etiology for the increased metformin monotherapy failure among Black youth (which contributes to glycemic control deterioration)<br>• Design intervention studies to address hypertension and dyslipidemia in minority youth with an eye toward preventing microvascular and macrovascular complications in adulthood<br>• Remove financial and policy barriers contributing to race/ethnic disparities in initiation and ongoing use of pumps and CGM, which improve glycemic control (advocate for insurance plans to decrease out-of-pocket costs) | |
| **Metabolic syndrome** | |
| • Develop race/ethnic specific cut-offs and percentiles for metabolic syndrome in youth | • Develop sex specific cut-offs and percentiles for metabolic syndrome in youth |

(continued)

**Table 8.** Continued

| Race/ethnic disparities | Sex disparities |
|---|---|
| **Obesity** | |
| • Develop early multilevel interventions and novel strategies to address the disproportionate rise in obesity in racial and ethnic minority children and adolescents, including policies to increase availability of and access to healthy food options | • Develop strategies to reduce the gender disparities in obesity prevalence |
| **Sexual and gender minority health** | |
| • Design studies to quantify and elucidate endocrine health and health care disparities in non-White LGBTQIA youth | • Design health care demographic data collection systems to allow patients to report self-identified sexual orientation and gender identity data.<br>• Determine the optimal timing and duration of gonadotropin hormone agonist therapy in transgender youth related to bone health<br>• Design longitudinal studies to determine the prevalence of osteoporosis, osteopenia, and fractures among transgender youth and adults<br>• Generate the evidence base to determine the best practices in fertility preservation options and reproductive care of sexual and gender minority patients<br>• Design studies to examine how sexual and gender identity may be impacted by chronic disease and how chronic disease management may be impacted by sexual and/or gender identity minority status<br>• Develop policy changes to ensure broadening of insurance coverage for sexual and gender minorities and to depathologize sexual orientation and gender identity to remove further barriers to care |

Abbreviations: CGM, continuous glucose monitoring; DKA, diabetic ketoacidosis; ED, Emergency Department; GWAS, genome-wide association study; LGBTQIA, lesbian, gay, bisexual, transgender, queer, intersex, and asexual; NHW, non-White Hispanic; T1D, type 1 diabetes; T2D, type 2 diabetes.

starting at early ages, and that have racially and ethnically diverse participants are needed. These studies should collect robust, standardized data on markers of pubertal development and BMD measures and evaluate the importance of intersectionality (eg, race, ethnicity, sex, sexual and gender minority status) in determining these outcomes. By incorporating life course approaches with decades long follow-up into the study designs, there is also an opportunity to examine the impact of early puberty on morbidity and mortality in adulthood (eg, fracture risk, cardiometabolic diseases).

Nutritional rickets remains a significant public health problem for marginalized youth across the globe. Addressing this persistent challenge requires a worldwide initiative to fortify food with vitamin D and studies that determine the optimal dose, duration, and effect of vitamin D supplementation on peak bone mass, osteopenia/osteoporosis, and fracture risk.

Racially and ethnically minoritized children continue to be disproportionately affected by obesity, which contributes to their higher rates of T2D. Despite this elevated risk, these children are less likely to undergo metabolic surgery. Minoritized youth with T1D are also more likely to initially present with and continue to experience DKA. To address this inequity, it is important for clinicians to recognize that while T2D may be more common in minority youth and adolescents, a diagnosis of T1D must be considered in any child or adolescent presenting with hyperglycemia, regardless of race/ethnic background. In addition, there are persistent financial and policy barriers that hinder access to optimal diabetes care, and these contribute to race/ethnic disparities in the use of technologies (eg, insulin pumps, CGMs) that are known to have beneficial effects in young patients. Accordingly, we need to advocate for equal access to health care in general, and glucose management devices in particular, especially for minority children and adolescents. Finally, female youth have a higher prevalence of obesity and T2D, and these are exacerbated by lower levels of physical activity in girls and poorer dietary choices compared with male youth. Interventions to lower obesity rates in young women may be an important step in reducing the higher diabetes-related mortality among women.

Defining and quantifying endocrine health disparities in LGBTQIA youth and adults is a rapidly evolving area of research, particularly the interface of race and ethnicity with SGM status. Prospective studies are needed to determine the timing and duration of gonadotropin hormone agonist therapy in transgender youth that optimizes peak bone mass. Such studies will also enable determination of the prevalence and incidence of osteopenia, osteoporosis, and fractures among LGBTQIA youth and adults. Two major barriers that continue to impact our ability to address health disparities in SGM are health care system design and health care and educational policies. Because self-reported demographic data on sexual orientation and gender identity are not routinely ascertained during care delivery, it is challenging to use real world data to study disparities in these populations. As part of the clinical encounter, we advocate for routine collection of sexual orientation and gender identity data, in addition to race, ethnicity, and preferred language for health care. This information will also aid health systems in identifying which clinical areas see a high enough volume of LGBTQIA patients so that staff and clinicians can access appropriate training to deliver culturally competent care to this population. Finally, numerous policies limit insurance coverage for gender affirming care, pathologize sexual orientation and gender identity, limit participation of transgender youth in sports, and forbid discussion of SGM in schools. Crafting policies that meet the needs to SGM youth and adults will require targeted advocacy efforts aimed at removing barriers to care so all patients can achieve health equity.

Finally, a critical contributor to ongoing health inequities stems from a lack of diversity in the biomedical workforce. The Flexner Report, which was published in 1910, promoted use of the biomedical model as the gold standard for medical education in the United States and eliminated medical schools as proprietary entities (20). This resulted in closure of multiple medical schools, with an especially strong impact on the 7 historically Black medical schools that were training future Black physicians. Following publication of the Flexner Report, only Meharry Medical College and Howard Medical School remained open at a time when Blacks could not gain access to White medical schools (20). The long-term impact of these closures was quantified by Campbell et al, who estimated that had those 5 medical schools been provided resources to remain open and deliver the biomedical education model, they would have collectively trained ~35 000 Black physicians by 2019 (563). Because historically Black medical schools also train individuals of other non-White races, the racial and ethnic composition of our current day physician workforce would have been much more diverse. The Endocrine Society's Policy Perspective on eradicating racism outlined recommendations to diversify the endocrine work force, including implementing policies and practices that promote increased recruitment, equitable compensation structures, transparent and balanced promotion process, and active retention of clinical and nonclinical health professional of diverse backgrounds (4). These efforts also need to include individuals who are bilingual as well as members of the LGBTQ community. Ultimately, having endocrine health care professionals, a diverse research workforce, and leaders who reflect the populations impacted disproportionately by endocrine disorders will ultimately support greater diversity in clinical trials and more equitable health care delivery.

## Disclaimer Statement

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## Disclosures

S.H.G. served on the Health Disparities Advisory Committee for Abbott and the Health Equity Advisory Committee for Medtronic, Inc. A.G. received the 2020 Growth Hormone Research Competitive Grant Program Award from Pfizer, Inc. and served as consultant for a seminar on growth hormone deficiency for Pfizer medical staff. J.S. is a board member of the World Professional Association for Transgender Health, has consulted for the American Civil Liberties Union, and has received honoraria for talks in academic settings. F.C.S. served as an advisor/consultant for Novo Nordisk, Eli Lilly, Boehringer Ingelheim, Currax, Gelesis, Rhythm Pharmaceuticals, Calibrate, and Pfizer. The other authors declare no conflicts.

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Ex. 18

# Gender-affirming multidisciplinary care for transgender and non-binary children and adolescents

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# Gender-affirming multidisciplinary care for transgender and non-binary children and adolescents

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**ABSTRACT**

Modern transgender and non-binary (TGNB) pediatric health care originated in the 1990s. This patient population is adversely affected by minority stress, victimization, mental health disparities, and barriers to health care With improving social and cultural support for TGNB identities and favorable evidence for affirming social and medical interventions, the need for pediatric gender services clinics has grown. Gender-affirming care requires collaboration between social and medical entities, including school personnel, community services, medical providers, and mental health professionals, which is best served within a multidisciplinary treatment model of care. This article provides an overview of the components within multidisciplinary pediatric gender clinics.

## Introduction

Gender identity is the internal sense of oneself as a girl, boy, combination of both, somewhere along the spectrum of girl-ness or boy-ness, or neither (Forcier, Van Schalkwyk, & Turban, 2020). A complex interplay of biological, environmental, and cultural factors contributes to gender identity formation, which becomes evident after one reaches a certain level of psychological development and self-awareness (Rosenthal, 2014). In contrast, sex, also known as sex assigned at birth or natal sex, is the designation of being female, male, or intersex based on external genitalia, internal reproductive organs, and sex chromosomes or hormones (Forcier et al., 2020). While sex can be assigned after birth, gender identity is assumed since the majority of infants assigned male or female sex at birth, will have a gender identity of boy or girl, respectively, in childhood. Terminology that reflects different gender identities includes the following: cisgender reflects people whose gender identity aligns with the sex they were assigned at birth; transgender describes people whose gender identity does not align with the sex they were assigned at birth; nonbinary defines people whose gender identity does not align within either gender in the male/female gender binary.

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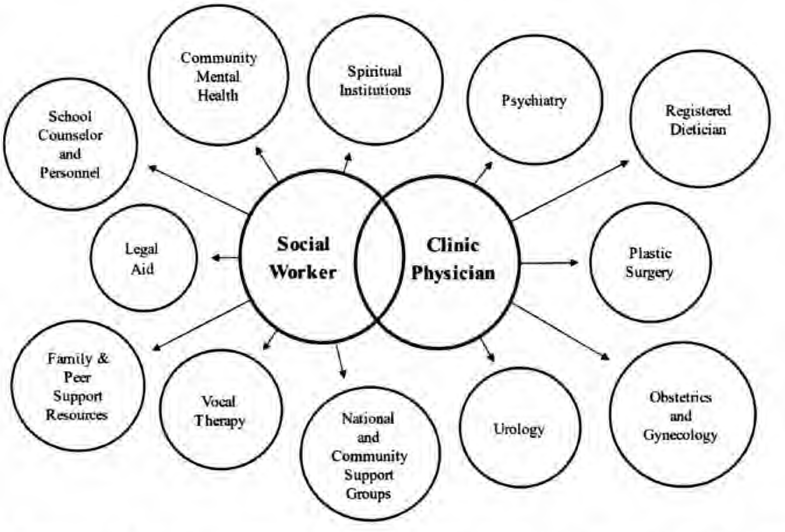


**Figure 1.** Diagram of the multidisciplinary care team within a pediatric gender-affirming services clinic. The two foundational members of the multidisciplinary team are the clinic social worker and physician, who may be a specialist in either pediatric endocrinology or adolescent medicine. From these two keystones, referrals and/or recommendations for services or resources are provided to the patient and/or family. The social worker provides contact information for community mental health, legal aid, vocal and communication therapy, family, peer, and community support groups or services, and religious or spiritual institutions. The social worker will also coordinate care and education with school counselors, other school staff, and personnel to support inclusive, safe school environments for TGNC youth and adolescents. The clinic physician provides referrals, as indicated, to other healthcare professionals including registered dieticians, psychiatry, plastic surgery, urology, and/or obstetrics and gynecology.

Subspecialty pediatric clinics providing care for transgender and non-binary (TGNB) children and adolescents have grown significantly in number over the last 20 years. Children and their families seek medical care and other services to help support and affirm TGNB children's gender identities. Of note, while many TGNB youth seek gender-affirming services, the goal for each child and family is varied: some seek mental health support or assessment, school, or family resources, and/or hormonal or surgical treatment. The surge in referrals to clinics across several continents has been attributed to de-stigmatization of gender variance and/or an increase in prevalence of TGNB identifying children (Zucker, 2017). TGNB children and adolescents benefit from a treatment model that is comprised of multidisciplinary experts and professionals with gender-related expertise as well as other collaborative social entities. Many clinical practice guidelines and consensus statements for the care of TGNB youth exist, of which the majority state comprehensive treatment is best delivered within a multidisciplinary team. However, only two contemporary summary articles review the multidisciplinary model of care at specific institutions: the gender services clinics at Ann & Robert H. Lurie Children's Hospital of Chicago and Seattle Children's Hospital (Chen et al., 2016; Salehi et al., 2018).

Despite the growing number of TGNB children and adolescents seeking care, national survey data on gender identity in the United States in this age group is lacking. Therefore, estimates of TGNB youth prevalence rely on state-based surveys (Forcier et al., 2020). In Boston, a survey found approximately 1.7% of 908 youth ages 13 to 19 years old identified as transgender (Almeida, Johnson, Corliss, Molnar, & Azrael, 2009). In San Francisco, the Youth Risk Behavior Surveillance System survey from 36 schools found 1.3% and 1.6% of middle- and high-school students, respectively, identified as transgender (Shields et al., 2013). A Minnesota survey of 80,929 students found 2.7% of high-school students identified as transgender (Rider, McMorris, Gower, Coleman, & Eisenberg, 2018). In Rhode Island, the Youth Risk Behavior Survey found that 2.3% of youth identified as transgender while 19% identified as gender expansive or "equally feminine and masculine," masculine if assigned female at birth, or feminine if assigned male at birth (Rhode Island Department of Health, 2018).

Gender identity diversity inconsistent with the gender binary paradigm within the field of medicine was first conceptualized in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) of the American Psychiatric Association (APA). The DSM also coined the terms "gender identity disorder of childhood" and "transsexualism" with respect to adolescents and adults (Zucker, 2017). This diagnostic classification as a mental disorder has been challenged with more recent efforts to favor gender identity as a wide spectrum of identification and a fundamental human experience that may or may not be accompanied by distress requiring clinical attention (Beek, Cohen-Kettenis, & Kreukels, 2015; Drescher, Cohen-Kettenis, & Winter, 2012). In the fifth edition of APA's DSM the experience of "gender dysphoria" was labeled as an incongruence between affirmed and assigned gender identity associated with clinically significant distress or impairment for at least 6 months (American Psychiatric Association, 2013). "Dysphoria" may stigmatize and pathologize gender identity variation or nonconformity less than "gender identity disorder," but contestation remains regarding its presence in the diagnostic manual on psychiatric disorders (Drescher et al., 2012). Of note, this term may soon be referred to as "gender incongruence" in the International Classification of Diseases and Health-Related Problems (ICD) of the World Health Organization (WHO) in an effort to reflect the diversity of gender identity (Beek et al., 2015). It is important to note that only some transgender or gender noncomforming people experience gender dysphoria. An effort to reframe gender as an affirmative experience, not solely defined by discomfort or dysphoria, is demonstrated by the term "gender euphoria" which reflects the positive emotions or the feeling of rightness related to one's gender (Beischel, Gauvin, & van Anders, 2021).

### Definitions and terminology

Adoption of consistent terminology regarding gender and sex is important as healthcare professionals are adapting and adhering to gender-affirming models of care for TGNB children and adolescents. Gender identification is something that can only be self-defined by each child or adolescent, and terminology describing the gender experience is always evolving. Diverse and varying terminology, including *bigender, agender, genderqueer*, and *gender-fluid*, imply an evolving understanding of gender that goes beyond a male/female binary. In this sense, some youth manifest their gender identity in a way that does not involve changing from one gender role to another (E. Coleman et al., 2012). While healthcare professionals should be literate and understand the general concepts of gender diversity, transgender, and nonbinary identities, only youth can label and describe what their gender identity means to them.

Additional related, but distinct, terminology warrants discussion. Gender expression is the reflection and/or interpretation of the outward manifestation of one's gender. It is based on traditional expectations of the gender binary with respect to appearance, physical characteristics, behaviors, and mannerisms. Sexual orientation is also distinct from gender identity as this term to describe the emotional, romantic, and/or physical attraction to a certain sex and/or gender.

### History of gender-affirming care

Contemporary gender-affirming care has its origins in the 1930s. Sex hormones, such as testosterone, estrogen, and progestin, were isolated and developed into compounds to be administered as medication in the 1930s (Shumer, Nokoff, & Spack, 2016). These would eventually come to serve as treatment in gender-affirming hormone therapy (GAHT). The first published orchiectomy was performed in 1930 for a Danish transgender woman who then received penectomy, implantation of ovarian tissue, and vaginoplasty (Elbe, 1933). Medical literature from 1940s to 1950s documents the surgical treatment of transgender patients in Germany and the Netherlands (Hamburger, Stürup, & Dahl-Iversen, 1953; Huelke, 1948). The first gender-affirming surgery (GAS) for a transgender male was performed in 1966 at the Johns Hopkins' Gender Identity Clinic (Siotos et al., 2019). In 1988, a gonadotropin-releasing hormone (GnRH) agonist was first utilized for puberty suppression in transgender adolescents in the Netherlands (Waal & Cohen-Kettenis, 2006).

Medical interventions to support adolescents with TGNB identities were first described in the 1990s with the use of puberty-blocking hormones (GnRH agonists) in the Netherlands (Forcier et al., 2020). Providers in this pioneering clinic described a medical-ethical conflict whereby transgender

youth, who would later persist in their transgender identity, could benefit from pubertal suppression, thereby delaying the development of secondary sex characteristics of their natal puberty. In later adolescence, should transgender identity persist, GAHT could be prescribed to allow for development of puberty in-keeping with their affirmed gender identity. By following this stepwise approach, the individual would be spared the unwanted and potentially devastating effect of natal puberty, a reversible intervention, while delaying decisions around the more permanent changes associated with GAHT until an age where more critical and abstract thinking about gender was possible. From this frame of thought, the first longitudinal studies of gender variance and/or dysphoria sought to determine characteristics of individuals who would persist in their gender variance and would therefore be candidates for gender-affirming medical treatment (Forcier et al., 2020). Investigators initially found most gender variant children did not continue on to become transgender adolescents or adults and consequently promoted efforts to encourage gender variant youth to accept their natal gender (Rosenthal, 2014). This perspective of encouraging desistance of gender variance has subsequently lost favor in most modern pediatric gender clinics due to the understanding that it may be damaging. It has largely been replaced by an affirming model of care with room for gender identity exploration over time (Forcier et al., 2020).

The first established pediatric gender clinics and their respective protocols for evaluation, treatment, and management contribute largely to the current guidelines utilized today. Protocols changed over time and reflect the nature of ever-evolving gender-affirming care in pediatrics in order to provide the best patient treatment and outcomes. We present the history of the Center for Transgender Health at Johns Hopkins Medicine, Baltimore, Maryland, an adult clinic, and compare this to the pediatric clinics at VU University Medical Center in Amsterdam, Netherlands, and Boston Children's Hospital in Boston, Massachusetts.

In 1972, Johns Hopkins Medicine established the Center for Transgender Health where gender-affirming surgical treatments were offered to adult patients who completed a four-stage application described in the *Annals of Plastic Surgery* (Siotos et al., 2019). The clinic consisted of a panel of multidisciplinary specialists who provided GAHT and GAS. In the same year, the gender clinic in Amsterdam, Netherlands was established, and in 1987 children and adolescents were evaluated and referred there for further treatment. At Boston Children's Hospital in 1998 youth with gender dysphoria were first evaluated and treated, and later in 2007 this clinic would become the first pediatric multidisciplinary gender services clinic in North America. Clinic specialists included those in pediatric endocrinology, urology, and psychology followed by the addition of psychiatry and social work given a perceived increase in patients with complex comorbid psychiatric conditions.

At Johns Hopkins, prerequisites for treatment included an established relationship with a competent community psychiatrist and family support. After initiating GAHT and living as their affirmed gender for six to twelve months, patients were eligible for GAS. Amsterdam's clinic had a similar protocol that is outlined in the *European Journal of Endocrinology* which included a three-stage approach with a standardized psychological assessment, a real life-experience with hormonal interventions, followed by surgery (Waal & Cohen-Kettenis, 2006). In addition, puberty suppression was offered to those older than 12 years of age with Tanner 2 or 3 sex characteristics and pubertal levels of sex hormones. Adolescents could start GAHT at 16 years of age, the legal adult age of consent in the Netherlands, if they had increased gender dysphoria around puberty and could receive GAS at 18 years of age. Boston Children's Hospital utilized a protocol for initial evaluation and assessment that was adapted from the protocol used in the Netherlands (Spack et al., 2012). Eligible youth had a gender-identity focused, comprehensive clinical interview and testing with the clinic psychologist. In contrast, Boston Children's Hospital offered puberty suppression with no age restriction to those with gender dysphoria and Tanner stage 2 or 3 physical characteristics and GAHT to 14 to 16 year old adolescents on puberty suppressants or with Tanner 4 or 5 sex characteristics.

The Johns Hopkins Clinic closed in the late 1970s due to lack of funding, reimbursement for physicians and administrative staff, and patient ability to pay for GAS, which was largely not covered by insurance. The clinic's closing was also influenced by the publication of a highly criticized psychiatric article on the quality of life of patients receiving GAS and transphobic and discriminatory statements made by the Chair of Psychiatry (Siotos et al., 2019). In contrast, the Amsterdam Gender Clinic cared for more than 95% of the country's transgender population and would go on to provide a great resource of longitudinal data for studies about this population (Wiepjes et al., 2018). After the negative effects of natal puberty on psychological functioning and well-being were observed, their protocol changed to allow adolescents in later phases of puberty to receive puberty suppression. This allowed for easier transition to their affirmed gender by stopping further development of secondary sex characteristics. Similarly, the age requirement for GAHT was previously older, but due to psychologic and socioemotional problems and possible unfavorable postoperative results this age was decreased to 16.

### *Guidelines for gender-affirming care*

The development of gender service clinics, like those mentioned above, aided and contributed to several clinical practice guidelines that exist regarding the evaluation and management of TGNB patients. These clinical practice guidelines were written for subspecialty providers such as endocrinologists or other

hormone providers, social workers, psychologists, and psychiatrists. Later articles for primary care physicians, pediatricians, and obstetrician-gynecologists have been published by American Family Physician, Pediatrics in Review, and ACOG in order to expand the reach of gender-affirming care and minimize barriers for TGNB youth accessing health care (American College of Obstetricians and Gynecologists, 2021; Klein, Paradise, & Goodwin, 2018; Rafferty, Donaldson, & Forcier, 2020).

More contemporary philosophy of gender-affirming care seeks to dispel the notion that all youth with gender variance must be treated with a protocolized, one-size-fits-all, approach. Treatment of distress related to gender dysphoria varies from person to person and may include medical treatment options such as GAHT and/or GAS (Coleman et al., 2012). Hormone therapy and surgery have been shown to alleviate gender dysphoria in many patients, but some individuals may need only one of these options, or neither (Coleman et al., 2012). Current standards of care and guidelines, which are described below, summarize the available treatment options for TGNB youth. All guidelines encourage affirmative models of care that emphasize supporting youth and treating them as "the strongest authority on their own gender identity" (Forcier et al., 2020).

In 1979, the World Professional Association for Transgender Health (WPATH) established its Standards of Care (SOC) to assist health professionals in providing evidence-based health care to transgender and gender nonconforming people (Coleman et al., 2012). The SOC are published in the *International Journal of Transgenderism* and describe how to support gender affirmation and/or alleviate gender dysphoria. This includes, but is not limited to, competency requirements for mental health professionals, how to support changes in gender expression or social transition, psychological and social interventions, preventive and primary care, gynecologic and urologic care, reproductive health, and voice and communication therapy. Medical treatments, fully reversible, partially reversible, and irreversible, for gender dysphoria are described along with how to obtain informed consent and the criteria for treatment, specific regimens, side effects, and associated risks. With respect to children and adolescents, the 7$^{th}$ edition of the SOC recommend initiating puberty suppression at Tanner Stage 2, starting GAHT with parental consent or at the age of legal majority or consent, and offering GAS at the legal age of majority after 12 months of living as the affirmed gender. Of note, chest surgery for transgender men may be carried out earlier after living as the affirmed gender and after one year of testosterone treatment. WPATH SOC reflect findings from research in North America and Western Europe, so standards may differ in other parts of the world.

In 2009, the Endocrine Society published a clinical practice guideline for treatment of gender dysphoric/gender incongruent people, which was most recently updated in 2017 and published in *The Journal of Clinical*

*Endocrinology and Metabolism* (Hembree et al., 2017). For adolescents with gender dysphoria, this guideline recommends suppression of puberty with the use of reversible GnRH agonist (GnRHa) at Tanner stage 2, which mirrors the recommendation from the 7th edition WPATH SOC. Mental health provider assessment is recommended for children and adolescents to diagnose gender dysphoria. GAHT with gradually increasing dosing is recommended for adolescents who have sufficient mental capacity to give informed consent, which occurs usually by 16 years of age according to this guideline. It also appreciates that there may be compelling reasons to start GAHT earlier, but reflects on the limited published studies of GAHT in youth younger than 13.5 to 14 years of age. Monitoring of pubertal development every 3 to 6 months and laboratory testing every 6 to 12 months is recommended.

The University of California San Francisco's Center of Excellence for Transgender Health has published guidelines on primary and gender-affirming care for TGNB people, the second edition of which was published in 2016 (UCSF Transgender Care, 2016). This complements previous clinical practice guidelines and is designed not only for specialists but also for use in everyday primary care settings by physicians in adolescent medicine, family medicine, pediatrics as well as nurse practitioners and physician assistants. It provides recommendations on creating affirming spaces, puberty suppression, and GAHT with respect to monitoring, induction of amenorrhea, and surgical interventions. It advocates for a supportive model in which youth are aided in articulating their gender experiences, identifying their needs, and/or hopes for GAHT with less reliance on medical and mental health providers controlling access to care. With respect to age of GAHT initiation, these guidelines recommend an individualized decision based on the patient's development as opposed to chronological age. Additional factors to consider include length of time on GnRHa, which may adversely impact peak bone mineral density, the emotional and social challenges of physically appearing as a sexually immature person in high school, and the risks of experiencing puberty in the last years of high school or early college. For GAS, a similar decision-making process is recommended given that TGNB youth are transitioning at earlier ages. Surgery can address the negative impact on social development, intimacy, and risk for assault and possibly death with gender identity disclosure.

The Pediatric Endocrine Society published a statement in 2017 agreeing with the multidisciplinary, gender-affirming approach to care of TGNB youth and adolescents with respect to mental health evaluation and medical intervention readiness assessment (Lopez, Marinkovic, Eimicke, Rosenthal, & Olshan, 2017). It is important to note some transgender health programs or services are following informed consent models of care that allow certain TGNB adolescents to start GAHT without a mental health evaluation and diagnosis of gender dysphoria. For example, Fenway Health allows adolescents

who are 18 years old and have completed pubertal development to start GAHT as long as they are competent, able to understand risks, benefits, and make an informed decision (Cavanaugh, Hopwood, Gonzalez, & Thompson, 2015).

### *Gender identity development*

As a normal part of human development, gender identity development is influenced by genetic, neuroanatomical, hormonal, and environmental factors. Sex hormones affect sex-specific changes during fetal development and infancy and are thought to contribute to different behaviors in birth-assigned males and females later in life (Shumer et al., 2016). The hormonal impact of prenatal and postnatal sex hormones on gender identity has been applied to patients with disorders of sex development and can be helpful in postulating the effects of hormones on gender identity in transgender people. For example, 5–11% of individuals with 46, XX and 21-hydroxylase deficiency in virilizing congenital adrenal hyperplasia, a disorder of the adrenal glands in natal-sex females that produces excess levels of androgens with subsequent masculinizing physical changes, report gender dysphoria, atypical gender identity, or transgender identification. This percentage of identification is more common than expected in comparison to the prevalence of transgender men in the general population (Berenbaum & Bailey, 2003; Dessens, Slijper, & Drop, 2005; Meyer-Bahlburg, Dolezal, Baker, Ehrhardt, & New, 2006). This may imply some impact of prenatal or postnatal androgens on gender identity development. For an in depth discussion of gender identity development in the setting of hormonal or non-hormonal disorders of sex development refer to the article by Rosenthal (Rosenthal, 2014).

With regard to the genetic influences on gender identity, studies on twins where at least one twin met criteria for gender identity disorder (GID) found that 39.1% of twin pairs both met criteria for GID (Heylens et al., 2012). From an anatomic standpoint, several brain structures appear sexually dimorphic or have shared differences in characteristics between cisgender men and women. One study found that the volume of the bed nucleus of the stria terminalis in transgender women was equivalent to that in cisgender women (Zhou, Hofman, Gooren, & Swaab, 1995). Another study found that the volume of the right putamen in transgender women was larger than in cisgender men and was within the average range for cisgender women, but this has not been confirmed in subsequent studies (Luders et al., 2009). MRI studies have found that transgender people have patterns in the superior longitudinal fasciculus that are more similar to people of same gender identity rather than sex (Rametti et al., 2011).

Environmental factors on gender identity development include social relationships between parent and infant or child as well as societal norms (Shumer et al., 2016). Children with autism spectrum disorder (ASD) may feel less

pressure from societal norms to conform to birth-assigned sex. Studies of people with ASD found that approximately 22% of women and 8% of men reported gender nonconforming feelings in comparison to 4% of women and 5.7% of men in a Dutch study (Dewinter, De Graaf, & Begeer, 2017). Other factors that may influence the timing of gender identity development include stigma, lack of support or knowledge, tempo of general development, and family support (Forcier et al., 2020).

Gender identity development is impacted by the above factors but is generally accepted as a natural part of childhood development. Youth can express feelings of gender variance and transgender identity as early as toddlerhood, as an adolescent when puberty begins, or as an adult. At about 18 to 24 months of age children begin to categorize people by gender and at 3 to 4 years of age they begin to develop a more stable gender identity (Forcier et al., 2020; Shumer et al., 2016). School-age children start to recognize gender bias and become more open to gender diversity and non-conformity (Forcier et al., 2020).

In the United Kingdom referrals to the Gender Identity Development Service were analyzed and found that referrals for children were skewed in the direction of birth-assigned males, and skewed in the other direction, toward birth-assigned females, for referrals in adolescents (de Graaf, Giovanardi, Zitz, & Carmichael, 2018). This may be secondary to decreased cultural tolerance for cross-gender behavior in birth-assigned boys (Forcier et al., 2020). A similar skew toward childhood referrals for birth-assigned males has been seen in North America: it is postulated that gender diverse behavior is more obvious and less tolerated in birth-assigned boys compared to birth-assigned girls on this continent as well (Aitken et al., 2015; Wood et al., 2013).

Adolescence is also an important period in development with regard to gender identity formation. This period can be marked as temporary fluctuation in experienced gender or persistent clear gender variance and/or incongruence with sex assigned at birth. This gender variance may or may not be associated with feelings of distress that require clinical intervention. Onset of puberty and development of secondary sex characteristics in TGNB adolescents can be accompanied by increasing distress as physical attributes not-in-line with one's affirmed gender develop. The emergence of, or worsening of, gender dysphoria with puberty increases the likelihood of becoming an adult with transgender identity (Rosenthal, 2014). Recent studies support that the birth-assigned sex ratio favors birth-assigned females in adolescence (Aitken et al., 2015; de Graaf et al., 2018). This could support the idea that the development of physical sex characteristics and menarche may intensify gender variant identification for birth-assigned females.

Longitudinal studies of pre-pubertal youth with gender variant identity have historically noted that most no longer meet criteria for "gender dysphoria" once they enter puberty and do not persist in a transgender gender

identity (Rosenthal, 2014). However, youth with persistence of transgender identity and increased dysphoria in adolescence were more likely to have a stable transgender identity as adults (Shumer et al., 2016). A follow-up study of 70 adolescents diagnosed with gender dysphoria who received puberty suppressants all started GAHT (de Vries, Steensma, Doreleijers, & Cohen-Kettenis, 2011).

### *Theory and rationale for gender-affirming care*

Transgender youth are disproportionately affected by mental health disparities. They have a two to threefold increased risk of depression, anxiety disorder, suicidal ideation, suicide attempt, self-harm behaviors, and utilization of both inpatient and outpatient mental health services compared to cisgender youth (Reisner et al., 2015). Nearly 50% of transgender youth report a history of suicidal ideation and 25% report prior suicide attempts (Forcier et al., 2020). Transgender youth with gender dysphoria also have higher rates of substance use including alcohol, tobacco, cannabis, and other drug use (J. Olson, Schrager, Belzer, Simons, & Clark, 2015).

Transgender youth participate in behaviors that increase their risk for sexually transmitted infections and HIV. A study of transgender youth seen at an urban community health center found that 87.3% were sexually active and nearly half engaged in unprotected anal or vaginal sex (Reisner et al., 2015). Overall, literature cites that transgender youth engage in more frequent sexual experiences, less barrier protection, and more referrals for STI and HIV testing in comparison to cisgender counterparts (Andrzejewski et al., 2020; Bungener, de Vries, Popma, & Steensma, 2020). Transgender adolescent females have higher rates of sex work and HIV: approximately 19% of transgender girls and women 15 to 24 years of age from Los Angeles and Chicago were HIV positive (Wilson et al., 2009).

Minority stress from stigma, prejudice, and discrimination contributes to the elevated risk of mental health comorbidities in TGNB youth (Testa, Habarth, Peta, Balsam, & Bockting, 2015). TGNB youth are also negatively affected by societal constructs that do not affirm their gender identities. Research shows that stigma and perceived discrimination are correlated with depression, poor overall mental health, suicide attempts, and non-suicidal self-injury (Bockting, Miner, Swinburne Romine, Hamilton, & Coleman, 2013; Veale, Peter, Travers, & Saewyc, 2017). Cultural and societal stigma associated with gender nonconformity increases the risk of abuse and neglect (E. Coleman et al., 2012). TGNB youth who experience verbal and physical abuse are also more likely to attempt suicide (Grossman & D'Augelli, 2007). Gender-related victimization, such as bullying and harassment, predicts increased risk of substance use as well as binge eating and fasting or vomiting to lose weight (Reisner, Greytak, Parsons, & Ybarra, 2015; Watson, Veale, &

Saewyc, 2017). Hypervigilance associated with discrimination and victimization is an additional source of stress that impacts well-being (Forcier et al., 2020). Finally, concealment of gender identity also predicts more psychological distress (Forcier et al., 2020).

Mental health comorbidities in gender dysphoric youth, however, are not inevitable. These comorbidities significantly diminish or resolve when youth receive gender-affirming care (Rosenthal, 2014). Prepubertal transgender youth who are supported, affirmed in their gender identities, and allowed to socially transition have comparable depression and self-worth to cisgender controls (K. R. Olson, Durwood, DeMeules, & McLaughlin, 2016). Similarly, youth who have supportive parents report significantly greater satisfaction with life and self-esteem as well as decreased suicide attempts in comparison to those whose parents were not (Rosenthal, 2014). Family and school connectedness, caring friends, and social support are all positive predictors with respect to mental health disparities and are also linked to lower odds of disordered eating (Veale et al., 2017; Watson et al., 2017). In contrast, transgender youth who are not allowed to socially transition demonstrate significantly higher rates of depression and anxiety than their cisgender peers (Forcier et al., 2020). Research demonstrates that social transitioning and gender-affirming care be fundamental for the healthy development of transgender children and improved mental health functioning and decreased rates of psychopathology (Chen, Edwards-Leeper, Stancin, & Tishelman, 2018). Failure to provide timely intervention for TGNB youth and adolescents can prolong gender dysphoria and contribute to the development of natal-sex physical characteristics that increase the risk for discrimination, stigmatization, and abuse (E. Coleman et al., 2012).

### *Medical management*

TGNB youth may present for care at varying ages depending on their gender identity development, parental concern, or dysphoria. Prior to onset of puberty, medical interventions are not indicated for gender dysphoria. Prepubertal TGNB youth and their families who seek medical care are provided resources on gender literacy, family, or individual therapy, parent–child support groups, as well as gender affirmative social groups (Forcier et al., 2020). Multidisciplinary care can also assist youth with social transition to their affirmed gender, if desired, which can include changing their clothing, attire, and socially changing their name and pronouns.

For TGNB adolescents who experience gender dysphoria there are nonmedical options to affirm their gender such as chest binding, padding of breasts, hips, or buttocks, genital tucking or penile prosthesis, and hair removal. TGNB adolescents may also change their name and/or gender markers on identity documents. Voice and communication therapy may help individuals develop

vocal characteristics, like pitch, intonation, and resonance, and nonverbal communication patterns, such as gestures, posture, and facial expressions, which facilitate comfort with their gender identity (Coleman et al., 2012).

TGNB adolescents' who desire primary or secondary sexual characteristics can receive treatment with masculinizing or feminizing interventions including medications and/or surgery (Rosenthal, 2014). Standards of care and clinical guidelines discussed above delineate reversible, partially reversible, and irreversible types of interventions for the treatment of gender dysphoria. Puberty suppression with GnRHa is considered a reversible treatment. It suppresses natal estrogen or testosterone production and delays the development of secondary sex characteristics. Not all clinics offer puberty suppression and the pubertal stage at which an individual can start it varies (Coleman et al., 2012). Additional reversible treatments include continuous oral contraceptives or progestin-only long-acting reversible contraceptives to suppress menses in individuals with uteri or anti-androgens like spironolactone to decrease the effect of androgens in individuals with testes (Coleman et al., 2012). Puberty suppression can be continued for a few years until a decision is made to either start GAHT or stop treatment and proceed through natal-puberty. GnRHa can also be used for adolescents in later stages of puberty to stop ongoing development of secondary sexual characteristics and as concurrent treatment with estrogen to help adequately suppress natal testosterone production (UCSF Transgender Care, 2016).

GAHT is considered a partially reversible treatment that consists of testosterone or estrogen for individuals who desire masculinization or feminization of their physical appearance, respectively. The goal of GAHT is to suppress endogenous natal-sex hormone secretion and maintain sex hormone levels within the normal range for the person's affirmed gender. Hormone regimens for TGNB adolescents differ from adults and are adapted with respect to somatic, emotional, and mental development that occurs during adolescence (Coleman et al., 2012). GAHT results in physical characteristics of the affirmed gender that may be reversible, partially reversible, or irreversible. The most irreversible effect of estrogen is breast development, which could require reconstructive surgery to reverse. Changes to muscles and fat distribution and skin changes are more reversible. Testosterone can result in vocal cord changes and deepening of the voice, which are irreversible. Changes to hair may be partially reversible, while muscle and fat distribution changes are more reversible. While receiving GAHT, providers monitor the effect of the intervention closely, with guidelines in place to monitor growth, emotional response to treatment, and laboratory parameters, such as cholesterol, hemoglobin A1c, liver and kidney function, and hematologic measurements. Pediatrics specialists involved in this care may include pediatric endocrinologists, adolescent medicine providers, and general practitioners (pediatricians and/or family medicine providers).

GAS changes primary and/or secondary natal-sex characteristics and is considered an irreversible treatment option. This consists of many surgical options with the overall objective of decreasing phenotypical and functional characteristics of natal sex and creating those of the opposite sex that is consistent with the patient's affirmed gender identity (Siotos et al., 2019). Surgical preferences can vary and are patient specific depending on their goals and desires for gender-affirmation. GAS includes but is not limited to facial feminization or masculinization, vocal cord surgery, laryngeal chondroplasty, breast augmentation or mastectomy, vaginoplasty, orchiectomy, phalloplasty, vaginectomy/hysterectomy/salpino-oophorectomy, metoidioplasty, and/or scrotal reconstruction. Surgeons who provide this care include urologists, plastic surgeons, and gynecologists.

### *Multidisciplinary teams in gender-affirming care*

A multidisciplinary model of care is widely agreed upon as the best way to provide gender-affirming care to the pediatric population and should include medical, mental health, and other social service professionals with gender-related expertise. This type of comprehensive approach promotes high-quality medical and mental health care in addition to socioemotional well-being within family units, school or peer groups, and communities (Chen et al., 2016). We first present information on the structure of our program at C.S. Mott Children's Hospital at the University of Michigan, challenges and lessons learned, followed by pertinent literature regarding important facets of multidisciplinary gender-affirming care for this population.

At our institution, the Child and Adolescent Gender Services Clinic provides multidisciplinary care, which centers on a collaborative effort between social work services and medical physicians. Initial intake and mental health assessment is conducted by the clinic social worker. This intake is conducted over the telephone with the patient and parent(s) to obtain information related to patient and family goals for the referral. This intake is followed by a comprehensive psychosocial and gender assessment performed by the clinic social worker. This assessment is conducted in four discrete segments – first with the family together, then with the child alone, then with the parent(s)/guardian(s) alone, and finally together again for a summation. Information regarding the patient's medical, psychiatric, social, and gender history from both the patient and their family is collected. Gender-specific measures that are collected include the Utrecht Gender Dysphoria Scale. The primary goal of this assessment is to provide a detailed summary of the patient's gender development, their current understanding of their gender, body satisfaction, emotional, and behavioral functioning. This assessment lasts approximately 60 to 90 minutes. The assessment and plan that is documented by the social worker identifies

patient and family treatment goals, psychosocial functioning, and the psychosocial education delivered on gender development, diversity, and gender-affirmation. Collateral information is also collected from the patient's therapist or other mental health professional(s) if applicable. If indicated based on patient and family goals, a follow-up appointment with a pediatric endocrinologist or adolescent medicine physician is coordinated to further discuss medical interventions for gender-affirmation. Referrals to longitudinal therapy or counseling, education and training of school staff or personnel, arranging connections to school counselors, legal aid, and other community, peer, or family support resources are provided as well at the initial intake and at follow-up appointments as needed.

If desired and appropriate, the first medical appointment occurs on a separate date, and includes a detailed medical history, physical examination, and often baseline laboratory testing if pubertal suppression or GAHT is being considered. An in-depth education on risks and benefits of medical intervention is performed prior to the initiation of GAHT. If a patient meets criteria for gender dysphoria and is eligible for a medical intervention, after this discussion of risks and benefits a verbal consent is obtained from the patient's parent(s) or guardian(s) or informed consent is obtained from the adolescent if they are older than the age of consent. Consent is obtained from all parents or guardians with medical-decision making rights, and in rare scenarios legal aid is consulted for assistance in navigating complex family and parental dynamics with respect to custody and medical-decision making. Referrals to indicated health professionals such as psychiatry, dieticians, and surgeons are placed during treatment if indicated.

Lessons learned from our program's development center around optimizing clinical care quality and delivery. On a monthly and annual basis, clinic staff reassess our impact, patients' needs, and how to adjust our approach in order to provide better care. Also, our program utilizes a patient survey database to examine facets of and barriers to care that are unique to our patient population, such as disordered eating, the impact of social media, perceived stress, and social support. Published research based on this data comments on how social media platforms provide emotional and informational support that transgender youth may not access otherwise (Selkie, Adkins, Masters, Bajpai, & Shumer, 2020).

In response to an increase in new referrals, changes were made to accommodate these patients and streamline care for established patients. Additional clinic staff are joining our team to complete pre-clinic phone consultations. Mid-level providers are being added to the team of medical doctors to evaluate and care for new patients. Affiliated providers in family medicine, internal medicine and pediatrics, and obstetrics-gynecology departments are taking on gender-affirming care for young adult patients who transition to adult medical services.

In order to provide seamless transfer of care between social work to medical providers, staff meets at weekly case conferences to discuss new patient evaluations, incoming referrals, and care continuation for established patients. In response to the limited availability of community mental health providers, social workers from our and affiliated clinics provide individual and/or family-based therapy for a select number of patients. Our social workers also provide case management expertise with coordinating access to community resources. During the COVID-19 pandemic both new and return patient visits were accommodated through virtual care. As well, patient education on medication (injection) administration was adapted to take place over phone and video. Virtual care has continued to be utilized to improve access to care for patients and families who live distant from the clinic.

### *Additional disciplines involved in gender-affirming care for TGNB children and adolescents*

Multidisciplinary care addresses and treats gender dysphoria, if present, and supports TGNB youths' social transition, familial, and community belonging. Social workers, psychologists, and psychiatrists are aptly situated to support TGNB youths' gender identity development before, at the onset of puberty, and afterward (Chen et al., 2018). Theoretical approaches to supporting these children and adolescents and meeting their needs provide a framework for this model of care (Edwards-Leeper, Leibowitz, & Sangganjanavanich, 2016). The American Psychological Association has also published guidelines for practice with TGNB individuals to optimize effectiveness of services offered and to prevent harm (American Psychological Association, 2015). Prior models placed too much emphasis on "gatekeeper" practices and the assessment of medical intervention readiness which compromised TGNB youth and adolescents' relationship with the health team and increased barriers to care (Olson-Kennedy, 2016).

TGNB adolescents may experience a complex interplay between gender identity, body image, and dissatisfaction that places them at risk for disordered eating behaviors (Linsenmeyer, Reed, Giedinghagen, Lewis, & Garwood, 2020; Romito et al., 2021; Sequeira, Miller, McCauley, Eckstrand, & Rofey, 2016). There is ongoing need for eating disorder screening and treatment prior to and throughout gender-affirmation for TGNB adolescents (Hartman-Munick et al., 2021). Clinical articles and dissertations provide key strategies to integrate into TGNB nutritional practices that include establishing healthy weight and lifestyle goals without use of energy intake targets and the problematic use of gendered energy requirement estimations (Fergusson, Greenspan, Maitland, & Huberdeau, 2018; Joy & Numer, 2018; M. Wilson, 2019). TGNB youth with eating disorders are among the highest risk patients and would benefit from collaboration across disciplines to identify healthy goal weight ranges, formulate nutritional plans, and encourage strong parental involvement with nutritional support and gender affirmation (Donaldson et al., 2018).

Speech language therapists deliver voice and communication therapy for TGNB youth and adolescents with voice incongruence. Voice therapy is effective in raising voice pitch and increasing externally rated vocal femininity (Gelfer & Tice, 2013). For vocal feminization, it is highly satisfactory and noninvasive in comparison to phonosurgery such as cricothyroid approximation to increase vocal cord tension, vocal cord shortening, and laser reduction glottoplasty to reduce vocal cord mass (Nolan et al., 2019). Testosterone therapy is the primary treatment for vocal masculinization but may not always result in cisgender male vocal frequencies after one year of treatment (Ziegler, Henke, Wiedrick, & Helou, 2018). Voice and communication therapy may improve voice-gender incongruence, help achieve desired speech expression, and reduce gender dysphoria in TGNB adolescents.

### *Schools and communities in multidisciplinary gender-affirming care*

School counselors can help TGNB students navigate complex social issues with gender identity and be advocates for their belonging by establishing an inclusive, affirming school environment as well as by ensuring general education, awareness of marginalized gender identities, and use of preferred name and pronouns (Byrd & Hays, 2012; Hatchel & Marx, 2018; Kurt, 2017). For transgender youth of color, peer victimization is associated with diminished school belonging while school belonging is associated with better mental health (Hatchel, Valido, De Pedro, Huang, & Espelage, 2019). When schools take action to reduce harassment, students have greater connections to school personnel and feel safe (McGuire, Anderson, Toomey, & Russell, 2010). Efforts to build and promote positive peer social support, often due to initiatives driven by school staff, can have a positive impact on suicidal ideation and attempts in TGNB youth (Miller, Esposito-Smythers, & Leichtweis, 2015). TGNB youth report positive impacts from teacher intervention to stop harassment, provision of knowledge and curricula on LGBT issues, extra-curricular activities or groups such as Gay Straight Alliances (GSA), and TGNB inclusive school policies (McGuire et al., 2010).

Community groups provide safe spaces for TGNB youth and adolescents to meet one another, build social support, and foster community, which can positively impact social development, mental health, self-esteem, and lower substance use (Fish, 2020). Locally in Michigan, *Stand with Trans* is a federally approved not-for-profit organization that provides tools to empower and support transgender youth and their families. Similar programs exist nationwide and many online resources, such as the Human Rights Campaign and The Trevor Project, offer suicide and crisis services, social networking for LGBTQ youth, and support centers with information on adolescent health. Youth who access community resources are more likely to be transgender,

people of color, and accessing free-or-reduced lunch and may represent those with limited access and barriers to health care (Fish, Moody, Grossman, & Russell, 2019).

Family support and affirmation of TGNB youths' gender forms a critical scaffold for gender-affirming care. Multiple therapeutic modalities exist to help support families including parental coaching and education, support groups, and child and family therapy (Malpas, 2011). School counselors can also help foster acceptance, engagement, and partnerships between school communities and families of TGNB children (Beck & Wikoff, 2019). Family therapy can help TGNB adolescents navigate family relationships and their family members process feelings about their child's gender identity, learn to accept, support, and advocate for their child, and explore their gender expression and treatment options (Coolhart & Shipman, 2017; Menvielle & Rodnan, 2011). The Family Acceptance Project is a national research, education, and training program that provides online resources to providers, religious leaders, and other community agencies to improve LGBTQ children's well-being.

Legal aid and attorneys can assist with name changes, discrimination in school or other settings, as well as navigating complex cases on parent or guardian consent for gender-affirming medical treatment for children and adolescents who are not of legal age. On a broader level, physicians and lawyers can play a critical role in advocating for increased social and legal acceptance of TGNB people to ensure legal recognition and protection (Minter, 2012). Data analysis from the 2015 U.S. Trans Survey demonstrates that living in states with more protective transgender-specific policies is associated with reduced odds of avoiding health care due to fear of mistreatment (Goldenberg, Reisner, Harper, Gamarel, & Stephenson, 2020). Human Rights Campaign, Pride Law Fund, and Lambda Legal are just a few of the numerous legal organizations that promote and advocate for the legal rights of TGNB people. Policy-level interventions are also a critical component to addressing the mental health of TGNB youth and adolescents (Fish, 2020).

### *Longitudinal outcomes*

In a description of adolescents treated at the Amsterdam Clinic in the Netherlands, 41% started puberty suppression and 32.3% directly started GAHT due to their age at presentation (Wiepjes et al., 2018). The first 70 youth treated with GnRHa between 2000 and 2008 showed improved psychological functioning and none discontinued pubertal suppression (Spack et al., 2012). Subsequent outcomes data show that adolescents with gender dysphoria who received puberty suppression had improved behavioral, emotional, and depressive symptoms with psychometric testing (Spack et al., 2012). Overall, longitudinal studies from Amsterdam Clinic patients document that only 1.9% of adolescents stopped puberty suppression and did not

go on to start GAHT (Wiepjes et al., 2018). Youth treated at the Amsterdam Clinic who were 16 to 18 years old and received GAS reported a significant decrease in gender dysphoria and increased body satisfaction (Waal & Cohen-Kettenis, 2006). Overall, 0.6% of these transgender woman and 0.3% of transgender men reported regret after anywhere from 46 to 271 months following gonadectomy (Wiepjes et al., 2018).

A long-term study of 55 transgender adolescents who received puberty suppression followed by GAHT and then GAS in early adulthood showed complete resolution of gender dysphoria and psychological outcomes that were similar or better than cisgender, age-matched young adults (de Vries et al., 2014; Lopez et al., 2017). Of note, none of these patients regretted their decision to transition.

### *Future directions*

Research on large-scale prevention, intervention, and health promotion programs that specifically address the mental health of LGBTQ youth is limited (Fish, 2020). There are only nine evidence-supported interventions for sexual and gender minority youth mental health, the majority of which entails individual-level psychological and pharmacological/medical treatment (Coulter et al., 2019). Evidence-based care is lacking with regard to psychological assessment and treatment within the team-based care model and descriptions of which youth would benefit from these interventions (Chen et al., 2018). Further exploration is needed regarding transgender youth psychological distress with respect to gender dysphoria, parent and peer interactions, and co-occurring psychopathology (Chen et al., 2018; Spivey & Edwards-Leeper, 2019).

## Implications for practice

Registered dieticians' knowledge on TGNB individuals is limited and emphasizes the need for continuing education to provide competent, inclusive nutritional care (Douglass, 2020). Clinical curricula and medical competency with regard to dietician programs on TGNB identities is lacking (Douglass, 2020). There is also a lack of validated adolescent measures and protocols for voice and communication therapy (Russell & Abrams, 2019). There is no nationally standardized training for transgender voice and communication services in speech-language pathology, but some universities are now including and promoting this topic (Jakomin, Ziegler, Rio, & Suddarth, 2020). In addition to individual-level treatment strategies, school-based programs, and state-level policies that address TGNB disparities in mental health and well-being continue to be a critical gap in supporting the development of these youth (Fish, 2020).

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Ex. 19


# Pubertal Suppression in Transgender Youth

COURTNEY FINLAYSON

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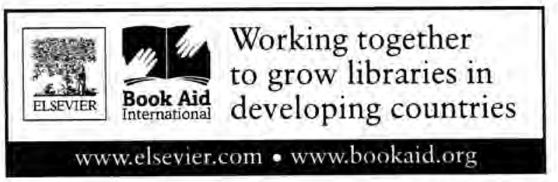


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# Contents

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CHAPTER 10

# Duration of Pubertal Suppression and Initiation of Gender-Affirming Hormone Treatment in Youth

HADRIAN MYLES KINNEAR, BA • DANIEL EVAN SHUMER, MD, MPH

Gender identity describes a person's deeply held feelings of being a boy or girl, man or woman, or another nonbinary understanding of their gender.[1] The adolescent with gender dysphoria has a gender identity incongruent with their sex assigned at birth causing distress.[2] Current management of children and adolescents with gender dysphoria has its roots in the so-called "Dutch Protocol", whereby puberty was suppressed at pubertal (Tanner) stage 2, followed by treatment with gender-affirming hormones later in adolescence.[3] In this way, the transgender adolescent was treated sequentially with medications which had been previously used for both precocious puberty and for delayed puberty.[4,5]

The "Dutch Protocol" was subsequently used as a basis for recommendations outlined by professional organizations such as the World Professional Association for Transgender Health (WPATH) and the Endocrine Society. The WPATH Standards of Care (SOC) for the Health of Transsexual, Transgender, and Gender-Nonconforming People (version 7, 2012)[6] and the Endocrine Society Clinical Practice Guideline for Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons (2017)[7] outline treatment recommendations pertaining to the use of these medical interventions. However, since the "Dutch Protocol" was first described, there have been dramatic shifts in how transgender and gender-nonconforming youth are accessing care, and how individuals are conceptualizing gender. For example, patients who fit the treatment paradigm initially described by the Dutch had gender dysphoria presenting prior to the start of puberty. In practice, the majority of adolescents present to clinic later than pubertal stage 2.[8] In addition, individuals are increasingly expanding beyond the male/female, boy/girl, man/woman binary ideas of sex and gender.[9] In parallel, estimates of the prevalence of transgender identities are rapidly changing. Previous estimates using data from the 1970s calculated the prevalence of transgender identities at 1:30,000 for natal males, and 1:100,000 for natal females;[10] however, an adult sample from Massachusetts placed the combined estimate at 0.5% in 2012.[11] This 2012 finding has been further supported by two groups using data from the 2014 US Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System to place the estimates at 0.53%[12] and 0.6%[13] of the US population (1.4 million US adults). Furthermore, at our children's hospital-based gender clinic, consultations with transgender boys now outpace consultations with transgender girls at a rate of 2:1, a ratio anecdotally similar to peer institutions. Finally, pubertal suppression medications as well as most other treatment used in the "Dutch Protocol" were covered by their national insurance program, whereas this very expensive medication may or may not be covered by current health insurance depending on the area of practice.[14] In addition, an implicit assumption was made that transgender adults would (1) desire and (2) be able to afford gonadectomy, whereas in clinical practice neither one of these assumptions may be true.

As the field of transgender medicine works to keep pace with epidemiologic shifts and social changes, clinicians are left with clinical questions, which may not be adequately outlined by current guidelines and SOC. Central to these clinical questions remain the following:

1. When should a patient begin pubertal suppression treatment?
2. When should a patient begin gender-affirming hormones?
3. When should a patient discontinue use of pubertal suppression treatment?

The goal of this chapter is to outline and contextualize current treatments and protocols, explore primary research around these topics, and provide a series of case examples for multiple clinical situations.

## PUBERTAL SUPPRESSION AND GENDER-AFFIRMING HORMONE THERAPIES

The hypothalamus produces spikes of gonadotropin-releasing hormone (GnRH), which stimulates the pituitary to produce pulsatile luteinizing hormone (LH) and follicle-stimulating hormone (FSH), in turn stimulating the gonads. Specifically, LH stimulates the Leydig cells in the testes to produce testosterone and the thecal cells in the ovary to produce androgens which are converted to estradiol in granulosa cells.[15] The model for pubertal suppression treatment uses GnRH agonists, commonly leuprolide acetate and histrelin acetate, which are generally used for precocious puberty.[16] GnRH agonists work by providing a basal level of GnRH, which, somewhat counterintuitively, inhibits the pituitary secretion of LH and FSH. In turn, the production of the sex steroids in the gonads is suppressed.[17]

Following pubertal suppression with GnRH agonists, gender-affirming hormone therapy with sex steroids is used for pubertal induction. Transmasculine individuals are typically prescribed testosterone either as a parenteral testosterone ester or transdermal testosterone gel or patch. Transfeminine individuals are typically prescribed estrogen (oral, transdermal, or parenteral) in addition to an antiandrogen or a GnRH agonist.[7] Gender-affirming hormones are used for pubertal induction and then continued indefinitely into adulthood.

Inhibition of sex hormone production by administration of GnRH agonists can serve three proximal goals in hormonal management of transgender persons. First, the development of isosexual secondary sex characteristics can be inhibited. Second, reduction in isosexual sex hormones may make use of cross-sex hormones more effective at promoting a hormonal transition, or may make the required dosage of cross-sex hormones for effective transition lower and perhaps safer. In our practice, this "block and replace" strategy is used primarily in transgender women, who may have more successful and safe feminization on a GnRH agonist plus low-dose estrogen compared to higher dose estrogen without a GnRH agonist. Third, the effects of ongoing production of isosexual sex hormones in a transgender person, which may be causing dysphoric symptoms in a pubertal or postpubertal person, could be reduced. Examples of this include suppression of testosterone in a transgender woman who is experiencing dysphoric erections, or the suppression of estrogen in a transgender man who is experiencing dysphoric menses.

In practice, the use of GnRH agonists is often complicated by cost and insurance coverage. Therefore, there may be more notable benefits for use of GnRH agonists in some situations when compared to others, and this may have logistical impacts on practice. For example, a transgender boy at the start of puberty (early breast budding) would have a significant benefit from a GnRH agonist with no suitable alternative if the goal is to prevent development of breasts. Alternatively, a transgender boy at pubertal stage 5 (full breast development) could theoretically use a GnRH agonist to suppress menses while considering starting testosterone. However, this patient could alternatively trial simpler approaches to suppress menses, such as depo-medroxyprogesterone, or a daily oral progestin (Fig. 10.1).

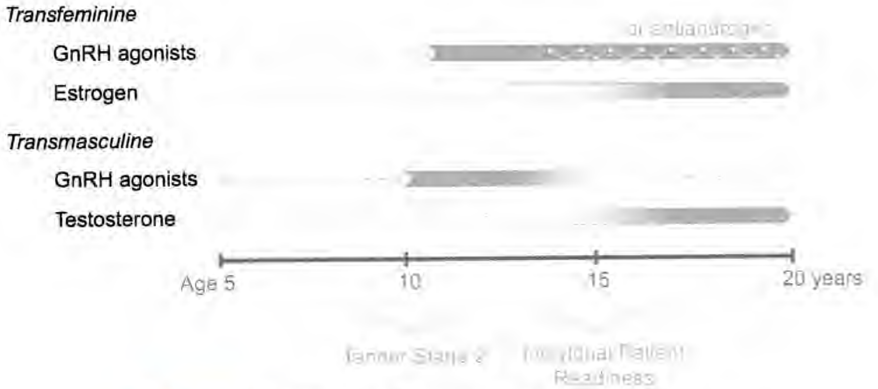


FIG. 10.1 Timeline. *GnRH*, gonadotropin-releasing hormone.

## RELEVANT TIME POINTS IN CLINICAL GUIDELINES AND PROTOCOLS

Clinicians and patients considering pubertal suppression need to decide when to (1) start GnRH agonist treatments, (2) start gender-affirming sex steroid treatment, (3) stop GnRH agonist treatments, and (4) when to consider alternative approaches if GnRH agonist treatments are not available to an individual patient. Each of these questions requires consideration of the goals of therapy for the individual patient.

We will examine how current clinical guidelines and protocols address these specific time points. We will compare the "Dutch Protocol", the WPATH SOC (version 7), the University of California San Francisco's (UCSF) primary care guidelines, and the 2017 Endocrine Society Clinical Practice Guidelines.

### The "Dutch Protocol"

The seminal work around pubertal suppression for transgender youth occurred in the Netherlands. The timeline set forth by the Amsterdam Gender Clinic in 2006 was as follows: eligible adolescents may begin GnRH agonists at Tanner stage 2 or 3 *and* older than 12 years.[3] In the Netherlands, the age of 12 years was chosen as an age when adolescents may make medical decisions together with their caretakers.[18] The assumption was made that the onset of puberty helps to clarify whether gender dysphoria will persist. Additionally, they noted that this protocol could be applied to adolescents in later phases of pubertal development to halt future progression of puberty. At the age of 16 years, sex steroids were initiated, followed by the option for genital surgery and gonad removal at the age of 18 years. Sixteen years of age was established for beginning sex steroid hormone therapy, as 16-year-olds are considered legal adults for medical decision-making in the Netherlands. Gender-affirming pubertal development was initiated by the use of increasing sex steroid dosage every 6 months until the adult dose was reached. GnRH agonist treatment was continued at least until maintenance level of sex steroids was reached with a preference to continue until gonadectomy. Additionally, in 2006 in the Netherlands, changing the birth certificate (the source for other personal documents) was only possible after the patient had their gonads removed.[3] However, as of 2014, it is now possible to change official documents in the Netherlands without gonadectomy. In qualitative analyses of transgender youth in the Netherlands, statements such as the following were documented: "I don't care about hysterectomy because changing gender on official documents is nowadays possible without this surgical procedure" (p. 1701),[19] highlighting the intersection between the medical and legal spheres.

In review of the "Dutch Protocol," some important considerations are worth addressing. First, the Dutch authors did make note that provision of hormonal treatment to adolescents is a controversial topic. Despite the controversy, Cohen-Kettenis et al., in 2008, made the case that nonintervention is not a neutral decision for a clinician.[20] Second, the societal and legal context in the Netherlands helped to frame how different ages were selected for making treatment decisions. As much of the published literature around pubertal suppression came from the Netherlands, other clinicians began to benchmark their timing toward similar ages: Tanner stage 2 or 3 *and* 12 years of age for starting GnRH agonists, gender-affirming hormones not until at age of 16 years, and continuation of GnRH agonist treatment with removal of the gonads not before the age of 18 years. That said, the use of age cutoffs for what are essentially decisions predicated on patient and family readiness may or may not make sense in modern contexts. Finally, it is worth restating that nearly all gender-affirming treatment was covered by insurance in the Netherlands resulting in limited consideration to costs for these interventions.[21]

### World Professional Association for Transgender Health

The WPATH SOC is based on professional consensus using the best data available to provide flexible guidelines for clinicians. Originally published in 1979, the current version (version 7) was published in 2012. The SOC separates treatments for adolescents into fully reversible (pubertal suppression), partially reversible (sex steroids), and irreversible (surgical) interventions. Fully reversible interventions intend to delay or suppress puberty and often include GnRH agonists. Other reversible medications include progestins (medroxyprogesterone) and spironolactone (to decrease androgen effects). WPATH comments on two relevant time points: (1) starting puberty suppression and (2) starting sex steroid therapy. Puberty-suppressing hormone eligibility may begin as soon as adolescents have the onset of puberty to Tanner stage 2, which they note may occur as early as 9 years of age, although it is stated that the evaluation of this approach has only been studied for adolescents who were at least 12 years old. The goals of suppression include giving more time for the adolescent to explore gender while preventing difficult-to-reverse development of secondary sex characteristics. For timing of gender-affirming hormones, the WPATH SOC offers more general guidance, noting

that the age of consent may be relevant, as well as hormone regimens adapted to account for adolescent development. Additionally, little is offered around the appropriate time to stop treatment with GnRH agonist medication. GnRH agonists are also mentioned for adult endogenous hormone suppression, on a list of possible antiandrogens for use in transgender women and in the context of masculinizing hormone therapy for transgender men to assist with menstrual cessation if needed.[6]

## University of California San Francisco Primary Care Guidelines

Johanna Olson-Kennedy, Stephen Rosenthal, Jennifer Hastings, and Linda Wesp authored the section of the UCSF Guidelines for Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People entitled "Health considerations for gender nonconforming children and transgender adolescents" (p. 186).[22] In understanding the medical care for transgender youth, they separate youth into two cohorts—early pubertal youth (Tanner stages 2–3) and late pubertal youth (Tanner stages 4–5). They note that GnRH agonists are ideally initiated at the earliest stages of puberty (Tanner 2–3) to avoid development of undesired secondary sexual characteristics and discuss that there is limited study on administration of GnRH agonists at younger than 12 years of age. The UCSF Primary Care Guidelines note that the onset of puberty may occur much sooner than 12 years of age,[22] drawing on the work of Biro et al. demonstrating that at the age of 7 years, 10% of white, 23% of black non-Hispanic, and 15% of Hispanic girls had obtained breast stage ≥Tanner stage 2.[23]

With respect to the initiation of gender-affirming hormones, the UCSF Guidelines discuss consideration of hormone initiation prior to the age of 16 years related to several factors. These include the length of time on a GnRH agonist as potentially relevant to bone density, the upheaval that may come from experiencing puberty in late high school or early college, and data suggesting that youth who reach adolescence and experience gender dysphoria are likely to persist.[22] This persistence is supported by findings that pubertal suppression did not ameliorate gender dysphoria for the first 70 eligible candidates treated at the Amsterdam gender identity clinic of the VU University Medical Center.[24]

The discontinuation of GnRH agonists is also discussed in regard to the "Dutch Protocol," which historically has aligned this to gonadectomy. Genital surgeries and gonadectomy may be more complicated to obtain and afford in the United States and other countries, and also may not be desirable for many transgender individuals. These guidelines discuss potential continuation of a GnRH agonist concurrently with gender-affirming hormones into late adolescence or early adulthood, particularly to reduce required doses of estradiol in transgender girls. Finally, the UCSF Guidelines discusses strategies for the management of hormone therapy, particularly for late pubertal use, with or without the use of GnRH agonists.[22]

## Endocrine Society Clinical Practice Guidelines

The Endocrine Society offers updated clinical practice guidelines published in September 2017. These guidelines recommend treating gender-dysphoric/gender-incongruent adolescents with GnRH agonists when they have reached Tanner stage 2. Tanner stage 2 is defined as "breast and papilla elevated as small mound; areolar diameter increased"; and "slight enlargement of penis, enlarged scrotum, pink, texture altered, testes 4–6 mL" (p. 13).[7]

Regarding initiation of gender-affirming hormones, the clinical guidelines dictate that clinicians may begin sex steroids after a multidisciplinary team confirms persistent gender dysphoria/gender incongruence and the patient has sufficient mental capacity for informed consent. It is noted that there may be "compelling reasons" (p. 2) for beginning treatment with sex steroids before the age of 16 years, although there has been limited literature published on treating patients prior to 13.5/14 years of age.[7]

These guidelines also note that rigorous study and evaluation is needed to determine the effects of prolonged pubertal delay on bones, gonads, and brain development. Additionally, they highlight that GnRH agonists are the preferred treatment option (there are also GnRH antagonists without sufficient data around their safety and efficacy in adolescents). The Endocrine Society guidelines list the time to stop GnRH agonist treatment as gonadectomy, although it is acknowledged that this may not be a procedure chosen by the patient. The alternative time points for stopping GnRH agonist treatment include once the adult dose of testosterone has been reached in transgender men. However, it is noted that combined testosterone and GnRH agonists could potentially allow for lower doses of testosterone. For discontinuing GnRH agonist treatment in transgender women, it is noted that some adjunctive therapy is needed in addition to physiologic doses of estrogen and that other antiandrogens may be used, such as spironolactone and cyproterone acetate in addition to

| Guidelines | Start GnRH agonists | Start Sex Steroids | Stop GnRH agonists |
|---|---|---|---|
| Dutch Protocol (2006)[3] | Tanner stage 2 or 3 and older than 12 years | Age of 16 years | Gonadectomy (eligible at 18 years of age) |
| WPATH SOC (2012)[6] | Tanner stage 2 | Relevant to age of consent and adolescent development | Unclear, may be used in adults |
| UCSF Primary Care Guidelines (2016)[22] | Tanner stage 2 | Consider prior to 16 years of age relevant to bone density & upheaval of late puberty | Can continue into adulthood, particularly for trans-feminine individuals |
| Endocrine Society Clinical Practice Guidelines (2017)[7] | Tanner stage 2 | May treat before the age of 16 years, limited literature prior to 13.5/14 years | At gonadectomy *or* Transmasculine: adult dose of testosterone reached; Transfeminine: use with estrogen or replace with other antiandrogen |

FIG. 10.2 Guidance summary diagram.

GnRH agonists.[7] It should be noted that cyproterone acetate is not available for use in the United States (Fig. 10.2).

## UNRESOLVED QUESTIONS

The four guidelines discussed above (Dutch Protocol, WPATH, UCSF, and Endocrine Society) are clear on the use of GnRH agonist medications beginning in early puberty. This treatment forestalls the onset of secondary sex characteristics, avoiding the accompanying dysphoria of this development in the transgender child. In addition, the older transgender adolescent or adult who never developed secondary sex characteristics of their sex assigned at birth may have a more straightforward time presenting themselves as their affirmed gender. Finally, the treatment allows for protected time to explore gender and to make a balanced decision on the use of gender-affirming hormones in later adolescence. However, the published guidelines offer less nuance and guidance around topics commonly encountered when treating transgender youth. For example, if GnRH agonists are started in early puberty, when should they be discontinued, especially if gonadectomy is not practical or desired? What about the large percentage of adolescents seeking medical care well after the onset of puberty—are GnRH agonists helpful for these patients? If so, should GnRH agonists be considered for adult transgender patients presenting for care?

While peer-reviewed studies attempting to tackle these questions are sparse, we've attempted to guide the reader through the various situations when GnRH agonists could be considered, and when the use of GnRH agonists may or may not be helpful. In writing this section, we have relied on personal clinical experience, input from other experts in the field, published clinical guidance, and the limited available data on medical treatment and outcomes for transgender individuals.

## CASE EXAMPLES

### Case 1: the 9-Year-Old Prepubertal Boy or Girl at Pubertal Stage 1

Families of transgender or gender nonconforming youth may present to primary care providers or multidisciplinary gender clinics looking for guidance on topics related to gender. For example, a 9-year-old and their parents may present to their primary care provider to discuss the right timing to make a social transition. The family may request referral to a therapist with experience in gender to help sort through topics of gender exploration, or to navigate challenges related to making a social transition. Often, we see prepubertal children

referred to our multidisciplinary gender clinic. These children will undergo a comprehensive gender and psychosocial assessment by one of our clinic's mental health professionals. The clinician will provide gender-related education and support to the family, and also to the child at an age-appropriate level. There may be a recommendation to connect with a therapist in the patient's community with experience in gender, or referral to a psychiatrist if the child has comorbid psychopathology such as anxiety or depression that may require a medical intervention. The family may also wish to meet with one of the clinic's physicians for discussion of hormonal interventions for gender dysphoria. Additionally, the family may not know whether the child is perhaps in early puberty, and a careful pubertal staging exam is required.

The current guidance from WPATH and the Endocrine Society does not support treatment of prepubertal youth with GnRH agonists for purposes of pubertal suppression. Treatment before pubertal stage 2 is not necessary, as pubertal hormone production does not yet occur prior to this stage. Furthermore, it is thought that early puberty can have some diagnostic value—if gender dysphoria persists or intensifies in early puberty, it is more likely to persist as adolescence continues; if it dissipates, then treatment may not be necessary. In a Dutch study aimed toward understanding persistence of gender dysphoria, older children were found to be more likely to persist.[25] Furthermore, some of the changes in early puberty up to Tanner stage 2 show regression with GnRH agonists, including reductions in testicular volume and varying degrees of breast development regression.[26]

In medical visits with prepubertal youth, it is our practice to discuss topics of gender including validating the child's gender experience, assessing mental health needs, and providing information at an age-appropriate level about puberty and the option of intervention with pubertal suppression in the future. A pubertal staging exam can be performed to confirm that the child remains at pubertal stage 1. Frequency of visits can vary depending on the age of the child. A very young child may not need to see a hormone provider for years and can continue to follow with their supportive primary care provider. Peripubertal children could be followed at closer intervals for pubertal staging exams, or this could be accomplished using a team approach with the primary care provider. Parents and children can also be given guidance on contacting their health professional if they note early breast development or testicular enlargement, the hallmarks of pubertal stage 2, between visits, with instruction to contact the office should these findings develop. Parents anxious to avoid even the very start of puberty may request GnRH agonist treatment for their child prior to the start of puberty; however, this is not the recommended treatment by current guidelines, and it is not our practice to intervene in this manner.

## Case 2: the 11-Year-Old Transgender Boy at Pubertal Stage 2

Breast budding is the hallmark of pubertal stage 2 in natal females. The average age of breast budding (pubertal stage 2) varies throughout the population and ranges from 8.9 to 11.2 years across studies.[27] The current definition of precocious puberty in natal females is the onset of central puberty prior to 8 years of age[28]; the definition of delayed puberty is the lack of central puberty at the age of 13 years.[29] The transgender boy who is currently at pubertal stage 2 and meets criteria for gender dysphoria is eligible to receive pubertal suppression using a GnRH agonist.[6,7]

There are several rationales for treatment. Continued development of secondary sexual characteristics can exacerbate gender dysphoria. Additionally, development of secondary sex characteristics that are permanent may require surgical treatment in the future. Specifically, treatment with GnRH agonists at pubertal stage 2, followed by future treatment with testosterone, can obviate the potential need for masculinizing chest surgery. Furthermore, because GnRH agonist therapy is considered a "reversible" intervention (i.e., puberty would commence if the medication is discontinued), the adolescent can continue to explore their gender identity prior to making a commitment to the "partially irreversible" intervention of testosterone therapy.

When starting GnRH agonist therapy in a transgender boy at pubertal stage 2, multiple important considerations should be explored. First, the child and family should be counseled that the treatment will affect the normal timing of the pubertal growth spurt. Children treated with GnRH agonists continue to grow at a prepubertal speed. It would be expected that growth acceleration would commence once the child is withdrawn from GnRH agonist therapy, or once testosterone treatment is initiated. Preliminary study has shown slowed height velocity gain during pubertal suppression, with growth spurts shown after administration of testosterone but not estrogen.[3]

Second, bone metabolism is affected by pubertal suppression. Pubertal hormones are important modulators of the relative increase in bone strength that occurs in adolescence. Bone density accrual will continue in a prepubertal fashion while on treatment; however, the adolescent acceleration in bone density will be postponed until withdrawal from GnRH agonist

medication or treatment with testosterone. Experiences of the first 21 patients treated with the Dutch Protocol demonstrated no significant changes (although reduced calculated z-score) in bone mineral density during pubertal suppression for the lumbar spine, femoral neck, and total body. Significant increases in bone density were also shown following sex steroid treatment.[3] Another longitudinal study demonstrated reduction in lumbar spine absolute bone mineral density z-scores for 34 adolescents (using natal sex reference values) when compared prior to the start of GnRH agonists and then for follow-up at the age of 22 years (after treatment with GnRH agonists, sex steroids, and gonadectomy). These findings were interpreted to be related to delayed or reduced peak bone mass potential.[30]

Third, menarche will not occur while on treatment with a GnRH agonist. This is likely reassuring to transgender boys. However, this eliminates the potential for oocyte harvesting in interested patients by controlled ovarian stimulation. Fertility preservation in a prepubertal female is not a standardly available procedure, as ovarian tissue cryopreservation is currently considered experimental, although it may be moving toward broader clinical implementation.[31] Therefore, while treatment with GnRH agonist does not, itself, cause infertility, the patient may be progressing down a road toward possible infertility by embarking on GnRH agonist therapy prior to menarche with the intention of future sex steroid treatment. Fertility for transgender men on sex steroid treatment (testosterone) has not been well studied. Current guidelines assume loss of fertility with testosterone treatment and encourage prior oocyte or embryo cryopreservation.[7] Despite assumed fertility loss, there are accounts in the literature where some transgender men have paused testosterone and carried pregnancies, while others have unintentionally become pregnant while taking testosterone therapy.[32]

Finally, there are several other health considerations for transgender adolescents considering GnRH agonist therapy. There have been several reported cases in the literature of GnRH agonist-induced arterial hypertension in transgender boys.[33] Additionally, fat percentage increased and lean body mass percentage decreased during the first year of treatment with GnRH agonists for both transgender boys and transgender girls.[26] Therefore, in review of these multiple important considerations, careful discussion of the risks and benefits of GnRH agonist therapy is necessary before proceeding.

The transgender boy who starts on GnRH agonists at pubertal stage 2 becomes eligible for testosterone treatment later in adolescence provided that their gender identity as a boy persists over time. Timing of testosterone therapy is debated. Historically, 16 years of age had been used, correlating to the Dutch age of consent. However, the psychological impact of delaying puberty to the age of 16 years can be challenging for transgender boys who are watching their peers complete puberty by this age. Contemporary practice in the United States is trending toward clinicians being primarily focused on patient readiness, maturity, and the ability to understand risks and benefits of testosterone treatment. The 2017 version of the Endocrine Society Clinical Practice Guideline recognizes that there may be reasons to begin sex hormone treatment before the age of 16 years, with the acknowledgement that there are limited published studies prior to the age of 13.5–14 years.[7]

A transgender adolescent boy on testosterone may no longer require GnRH agonist medication. The suppressive effect of testosterone on the adolescent's hypothalamic–pituitary–ovarian axis may obviate the need for concurrent treatment with a GnRH agonist and testosterone. It is therefore our practice to discontinue GnRH agonist therapy once testosterone dosing is increased to the adult dose. The estradiol level and clinical exam can guide whether discontinuation of a GnRH agonist after initiation of testosterone level is effective. Estradiol levels in the female range or clinical progression of breast development may necessitate an increase in the testosterone dose or resumption of GnRH agonist therapy. If GnRH agonist therapy is needed concurrently with testosterone treatment, it could be discontinued if the patient elects for hysterectomy/oophorectomy as an adult.

In some instances, a natal female on GnRH agonist therapy may express a desire to continue GnRH agonist therapy indefinitely, rather than discontinue it and proceed through female puberty or start testosterone. This desire may be founded on a rejection of a binary gender identity or identification as agender. While understandable, the importance of pubertal hormones for physical health and bone health necessitate that adolescents do get exposure to puberty. The indefinite withholding of puberty is not recommended.

### Case 3: the 11-Year-Old Transgender Girl at Pubertal Stage 2

Testicular enlargement is the hallmark of pubertal stage 2 in natal males. Testicular enlargement occurs due to stimulation of the testes by gonadotropins and is accompanied by testosterone production. This pubertal stage is often less obvious to patients and parents than breast budding in natal females. For this reason, pubertal staging exams by a physician can be

helpful in the identification of the start of male puberty in transgender girls. The average age of testicular enlargement >3 mL was reported to be 11.6 years, with a range of 9.6–13.7 years in a recent Danish study.[34] Similarly, the average age for genital Tanner stage 2 was 10.1, 9.1, and 10.0 years in non-Hispanic white, African-American, and Hispanic youth, respectively, as found by an office-based study from the American Academy of Pediatrics.[35] Precocious puberty in natal males is defined as the onset prior to the age of 9 years, and delayed puberty is defined as no pubertal development by the age of 14 years.[28,29]

Transgender girls at pubertal stage 2 are eligible for treatment with a GnRH agonist. Rationales for treatment are similar to the rationales for transgender boys. Continued development of male secondary sexual characteristics may exacerbate gender dysphoria. Many of these changes, such as the deepening of the voice and development of a prominent Adam's apple, growth of facial and body hair, and masculinization of the face, would be permanent. The intervention with a GnRH agonist is "reversible" and allows time for further gender identity exploration prior to committing to feminizing medications.

Initiation of treatment with a GnRH agonist in a transgender girl at pubertal stage 2 requires discussion about several other considerations. The adolescent will continue to grow, but at a prepubertal speed, while on GnRH agonist therapy. If estrogen is initiated later in adolescence, a growth spurt and subsequent growth arrest will occur, likely resulting in a shorter final adult height than if no intervention was pursued. Similarly to transgender boys, bone density accrual will continue in a prepubertal fashion while on treatment; however, the adolescent acceleration in bone density will be postponed until withdrawal from GnRH agonist medication or treatment with estrogen. Spermatogenesis will not occur if puberty is suppressed.[36] Therefore, a child treated with GnRH agonist medication followed by estrogen would not have the opportunity to preserve sperm using the standard methods.

The transgender girl who starts on GnRH agonist therapy at pubertal stage 2 would become eligible for estrogen treatment in later adolescence if her gender identity as a girl persists. As discussed in Case 2, the age of initiation of estrogen treatment was historically set at 16 years, but there has been a shift toward treatment at younger ages based on individual patient readiness.

After initiation of estrogen, the transgender girl may benefit from continued pubertal suppression using a GnRH agonist—a departure from the guidance for transgender boys. Concurrent treatment with a GnRH agonist plus estradiol, the so-called "block and replace" strategy, allows for smaller doses of estrogen to achieve normal female puberty. In our experience, the dose of estradiol required for normal female puberty in a patient on concurrent GnRH agonist treatment is similar to the dosing used in cisgender girls with ovarian insufficiency—oral 17-β estradiol, 2 mg orally daily, or transdermal estradiol patches 0.1 mg/24 h. This is in contrast to much higher doses often required in transgender girls not on GnRH agonist treatment—oral 17-β estradiol 6–8 mg orally daily, or transdermal estradiol patches up to 0.4 mg/24 h.[22] When treating a transgender adolescent or young adult with estrogen, the Endocrine Society suggests goals of therapy as maintaining a serum estradiol level between 100 and 200 pg/mL, and a serum testosterone level less than 50 ng/dL.[7] It is clear that achieving these goals is easier when using the "block and replace" strategy. That said, in practice, as previously stated, GnRH agonist medications are expensive and often insurance coverage is difficult to obtain. For this reason, we often advocate strongly for coverage for the transgender girl at pubertal stage 2 *at least* until estrogen treatment commences, and then continue treatment with a GnRH agonist if possible, but with less urgency.

In the patient with initiation of GnRH agonist treatment at pubertal stage 2, followed by continued concurrent treatment with GnRH agonist and estrogen treatment in later adolescence, the GnRH agonist treatment could be discontinued at the time of gonadectomy, if surgery is desired in young adulthood. There is some concern that technical aspects of vaginoplasty are made more difficult when the surgery is performed on a young adult who has never gone through male puberty—the phallic size is smaller in these patients, and there is less tissue available for certain surgical methods used to create the neovagina.[20]

As outlined in Case 2, there may be instances where a natal male on GnRH agonist therapy may express a desire to continue GnRH agonist therapy indefinitely, without proceeding through male puberty or starting estrogen. Again, the importance of pubertal hormones for physical health and bone health necessitate that adolescents do get exposure to puberty, and indefinite withholding of puberty is not recommended.

## Case 4: the 15-Year-Old Transgender Boy at Pubertal Stage 4

Many transgender adolescents do not present for care at the time of onset of puberty. In our clinic, for example,

approximately two-thirds of patients are presenting for care at pubertal stage 4 or 5. A transgender boy presenting at pubertal stage 4 requires different medical considerations than a transgender boy presenting at pubertal stage 2. The most obvious physical difference between stage 4 and 2 is breast development. The transgender boy at pubertal stage 4 has breasts nearing adult size and contour. The adolescent is likely menarchal, and if not, will be having menarche soon.

In considering treatment options for the transgender boy at pubertal stage 4, one must first consider goals of treatment. Goals may include (1) to start a masculinizing puberty, (2) to stop menses or prevent menses from starting, and (3) to limit further breast development.

The patient may or may not be ready to start treatment testosterone. If the adolescent meets readiness criteria for initiation of testosterone, we recommend starting testosterone and not initiating treatment with a GnRH agonist (see Case 2). If the adolescent is not ready to start testosterone treatment, GnRH agonist medication would be helpful in suppressing menses and limiting further breast development. That said, breast development already present would not resolve, and masculinizing chest surgery would likely still be required in the future for chest-based dysphoria. In addition, there are other hormonal methods that could be employed to suppress menses besides GnRH agonist treatment. In this situation, given the high cost of GnRH agonist medication for marginal utility, we employ progesterone for purposes of menstrual suppression in the late-pubertal transgender boy not ready for testosterone treatment. Norethindrone or other progestin-only oral pills, or depo-medroxyprogesterone acetate 150 mg intramuscularly every 3 months can be used in this patient population with the primary goal of suppression of dysphoric menses.[37] If testosterone treatment is subsequently initiated, progesterone treatment can be discontinued.

### Case 5: the 15-Year-Old Transgender Girl at Pubertal Stage 4

Likewise, a transgender girl presenting at pubertal stage 4 requires different medical considerations than a transgender girl presenting at pubertal stage 2. This patient will have had almost complete masculinization of the external genitalia and deepening of the voice. However, there are several important processes that occur in late male puberty that are of significant consequence to the transgender girl. First, fullness of facial hair and body hair are late-developing processes in male puberty. Second, full masculinization of the face is another late-developing process, such that natal males with almost complete pubertal genital development, or even natal males at genital stage 5, often have a young appearing face, which will continue to masculinize into late adolescence and early adulthood. Therefore, we are more aggressive in our attempt to treat transgender girls in later puberty with GnRH agonist medications. As outlined in Case 3, we would consider treatment with GnRH agonist regardless of whether estrogen was being initiated concurrently for these patients and consider continuing this treatment until gonadectomy if desired in young adulthood, and dependent on their ability to obtain coverage for the medication.

Spironolactone, a weak androgen receptor antagonist, can also be used in this patient population if GnRH agonists are not used. The medication, prescribed at dosing ranging from 100 to 300 mg/day orally,[7] blunts the effect of androgens and can be helpful at slowing development of unwanted facial and body hair, or other masculinizing effects of male puberty. Other medications that suppress androgen action, including cyproterone acetate, flutamide, nilutamide, and bicalutamide, have been reported for use in transgender women as well.[38]

### Case 6: the 17-Year-Old Transgender Boy at Pubertal Stage 5, or the Adult Transgender Man

Treatment considerations for the postpubertal transgender boy are similar to considerations for the transgender boy presenting at pubertal stage 4. Monotherapy with testosterone could be considered based on patient readiness. Progesterones could be considered for menstrual suppression for patients with dysphoric menses not ready for testosterone treatment.

### Case 7: the 17-Year-Old Transgender Girl at Pubertal Stage 5, or the Adult Transgender Woman

Treatment considerations for the postpubertal transgender girl are similar to considerations for the transgender girl presenting at pubertal stage 4. Estrogen can be started based on patient readiness. Adjunctive treatment with a GnRH agonist can be helpful, if available, using the "block and replace" strategy described in Case 3. If GnRH agonists are not used, and especially if monotherapy with estrogen is not achieving adequate clinical results and/or ideal blood levels of estrogen and testosterone, adjunctive therapy with antiandrogens can also be considered (i.e., spironolactone, cyproterone

acetate, bicalutamide. When GnRH agonists are used in conjunction with estrogen, this intervention could be discontinued at the time of gonadectomy, if desired.

### Case 8: The Gender Nonconforming Child in Early Puberty

Gender nonconforming children are increasingly presenting to gender clinics to discuss treatment with GnRH agonist medications. For example, a natal male or a natal female may present to the clinic at the age of 13 years after parental discussion around their identification as genderqueer. Some parents may research interventions and request GnRH agonist medications while their child works through their gender identity. In our experience, the current generation of youth is expanding the boundaries of sexuality and gender, and often times rejecting binary ideas of gender, sex, and sexuality. This requires careful consideration by clinicians as to when medical intervention is appropriate.

We define gender identity as a deeply held internal sense of oneself as a boy or girl, man or woman, another gender (e.g., genderqueer, nonbinary), or no gender at all (e.g., agender). Gender expression is the way one manifests one's gender by the way that one acts, dresses, and presents oneself socially. Sexual orientation is defined as emotional, romantic, and sexual attraction to one, multiple, all, or no sexes/genders.

The first step in assessing eligibility for a medical intervention is gaining a better understanding of the youth's understanding of their sex, gender, and gender expression. This is best accomplished with careful assessment by a mental health professional with experience in working with youth around topics of gender. Important considerations to explore include the following: When did the child or adolescent begin considering gender in more detail? How is the youth experiencing pubertal changes? Are pubertal changes causing distress or anxiety? What is the youth's current understanding of how medical interventions work, and what would they expect to happen to their bodies if medical interventions are used? How do their parents perceive their gender identity now and historically? What is the level of support for gender exploration in the youth's home and in the youth's community? Are there co-occurring mental health comorbidities present such as anxiety and depression and are these comorbidities in reasonable control? Does the child meet Diagnostic and Statistical Manual of Mental Disorders, 5th edition, criteria for gender dysphoria?

Regardless of the answers to these questions, there is little in the medical literature and clinical guidelines around endocrine treatment for the gender-expansive or gender nonbinary youth. The original utility of using GnRH agonists was, in essence, to buy time for the adolescent to make a balanced decision about gender without the stress of the progression of dysphoric puberty. We would argue that gender-expansive, genderqueer, or gender nonbinary youth would not be good candidates for GnRH agonists unless there is dysphoria related to the current progression, or the anticipated progression of isosexual puberty. If a GnRH agonist was felt to be appropriate for an individual under these circumstances, indefinite suppression of puberty without endogenous puberty or exogenous sex steroid treatment is not recommended.

### Financial Considerations

Guidelines are only theoretical if they recommend treatments that are unavailable. GnRH agonist medications are extremely expensive and not affordable to most families if not covered by medical insurance. While providers in various geographical locations have had different success with respect to coverage, it is clear that access to GnRH agonist treatment is not universal.[14] Barriers to universal coverage of GnRH agonist treatment for transgender youth may include (1) it is not Food and Drug Administration approved for use outside of treatment for youth with precocious puberty, (2) long-term data on safety and efficacy is deemed not robust by some, and (3) gender-affirming treatment is not mandated for coverage in all areas. Approval or denial of GnRH agonist treatment has serious practical implications for the individual patient and may significantly impact the care plan.

For a child in early puberty, who is eligible for, but cannot afford GnRH agonist treatment, limited options exist. One consideration would be exploration of different formulations of GnRH agonists. For example, the GnRH agonist designed for use in adults with prostate cancer (Vantas, Endo Pharmaceuticals) is much less expensive than the formulation used in children with precocious puberty (Supprelin, Endo Pharmaceuticals).[14] Additionally, treatment of transgender youth with medroxyprogesterone to suppress puberty has also been described.[39] Lastly, and concerningly, the adolescent who would otherwise be started on GnRH agonist treatment to delay pubertal decisions regarding sex steroid therapy, but who cannot afford the blocker, may prompt more urgent discussion about readiness for initiation of gender-affirming hormones.

## INITIATION OF GENDER-AFFIRMING HORMONES

Gender-affirming hormones, testosterone and estrogen, are used to promote development of secondary sex characteristics aligned with a person's gender identity. As discussed above, age of initiation is a topic of ongoing conversation in the field of transgender medicine. Historically, 16 years of age was used in the "Dutch Protocol" as this is the age of consent in the Netherlands. This historical tradition was carried forward in the WPATH SOC and the Endocrine Society Guidelines. That said, the revised version of the Endocrine Society Guidelines (2017) notes that delaying treatment with these hormones until 16 years of age may not be in the best interest for all patients.[7] In order to assess this historical practice, we should consider the risks and benefits of delaying treatment.

Perhaps the original impetus for delaying treatment to 16 years of age in the Netherlands was to allow for legal consent for treatment. However, this rationale only applies to the Netherlands or other countries where the age of medical consent is 16 years. If the same rationale were applied to the United States, perhaps patients would need to wait until 18 years of age to consent for testosterone or estrogen. It is important to note that delaying puberty until the age of 16 years is not physiologic. Thus, waiting to begin puberty until the age of 18 years would alter the normal timing of puberty to an even more dramatic extent and is not a practical course of treatment. Furthermore, there is concern that the longer an adolescent remains prepubertal on GnRH analog suppression, the higher the risk for low bone mineral density. Finally, withholding pubertal hormones until the age of 16 years may be socially and emotionally difficult for an adolescent, making pubertal timing delayed compared to their peers.

In his description of endocrine considerations for transgender youth, Rosenthal notes that at the time of writing (2014), his institution (UCSF) was studying the impact of cross-sex hormone treatment at the age of 14 years, which is an age similar to the upper end of normal pubertal onset.[37]

An alternative approach considers patient and family readiness, rather than any particular age cutoff, as the most important factor for the initiation of gender-affirming hormones. This approach would allow for initiation of testosterone or estrogen at any age after pubertal onset. This approach takes into account the fact that a 12-year-old on a GnRH agonist since the age of 9 years, who perhaps made a social transition at the age of 6 years, may be a better candidate for testosterone or estrogen than a 15-year-old who is in the early stages of exploring their gender identity.

Ultimately, it is our opinion that arbitrary age cutoffs are not particularly helpful on the individual level and that an individualized approach is preferred based on patient readiness, assessed by a mental health professional with expertise in gender identity. However, prior to the accrual of long-term data, providers should be cautious when starting gender-affirming hormones in early adolescence.

## TESTOSTERONE

Transgender men and boys are prescribed testosterone to promote development of male secondary sex characteristics. Testosterone is most often prescribed as an intramuscular or subcutaneous injection (testosterone cypionate or testosterone enanthate) once weekly or once every 2 weeks. The adult dose of injectable testosterone is typically 50–100 mg/week or 100–200 mg/2 weeks. When treating transgender boys who have been treated with GnRH agonists, or even adolescents who have not been on GnRH agonists, the goal is to mimic normal puberty, which begins gradually. Therefore, dosing often starts lower, perhaps at 12.5 mg/week or 25 mg/2 weeks, and increases over time to the adult dose.[37] Titration of dosing is based on the development of desired masculinizing effects, suppression of menses if not co-treated with a GnRH agonist, and monitoring of testosterone levels with a goal of an age-appropriate male testosterone level.

Alternative formulations of testosterone include transdermal patches or testosterone gel. These formulations are most often prescribed once the full adult dose has been reached using injectable testosterone; however, these can also be considered in the patient with needle phobia.[37] Testosterone treatment likely increases the risk of polycythemia, sleep apnea, weight gain, and cystic acne and possibly increases the risk of elevated liver enzymes, hyperlipidemia, and hypertension.[6]

## ESTROGEN

Transgender girls and women are treated with estrogen in order to achieve feminine secondary sex characteristics. 17-β-estradiol is the preferred formulation of estrogen and is available as a transdermal patch, oral tablet, or as an injectable. In pediatric patients, transdermal patches and oral tablets are most commonly prescribed. The dosing of estrogen, as described above, varies depending on co-treatment with a GnRH agonist. The

required dose of 17-β-estradiol is much lower for the suppressed patient. For the suppressed transgender woman, the typical adult dose of 17-β-estradiol is typically 2 mg when given as an oral tablet, and 0.1 mg/24 h patch when given as a transdermal patch. However, when not suppressed, the required dose may be as high as 6–8 mg orally, or 0.4 mg/24 h transdermal patch.[22] Similarly to testosterone, younger patients on GnRH agonist treatment typically start at lower doses and gradually increase to the adult dose. Titration of dosing is based on the development of desired feminizing effects, suppression of testosterone effects such as erections and facial/body hair development, and testosterone and estrogen levels in the age-appropriate female range.[37] Estrogen treatment likely increases the risk of thromboembolic disease (particularly synthetic ethinyl estradiol), hypertriglyceridemia, gallstones, elevated liver enzymes, and weight gain and may increase the risk of hypertension and hyperprolactinemia.[6]

## CONCLUSIONS

The field of transgender medicine is growing, and arguably maturing from its infancy into its adolescence. Endocrine treatment of transgender youth began with the observation that earlier treatment, including pubertal blockade, could provide significant reduction in dysphoria in adolescence and improved physical and mental health outcomes. As these observations became Guidelines and SOC, logistical and safety questions emerged, which have not been fully resolved. While current guidelines provide a framework for treatment, they fail to address important questions that commonly arise in clinical care. It is our hope that this chapter fills some of these gaps. Clearly, further research is needed to inform best practices in the care of the transgender adolescent. Simultaneously, financial barriers to care must be addressed in order for all transgender youth to receive access to gender-affirming treatment.

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Ex. 20

Annals of Internal Medicine

ORIGINAL RESEARCH



# Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons

## A Cohort Study

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**Background:** Venous thromboembolism (VTE), ischemic stroke, and myocardial infarction in transgender persons may be related to hormone use.

**Objective:** To examine the incidence of these events in a cohort of transgender persons.

**Design:** Electronic medical record–based cohort study of transgender members of integrated health care systems who had an index date (first evidence of transgender status) from 2006 through 2014. Ten male and 10 female cisgender enrollees were matched to each transgender participant by year of birth, race/ethnicity, study site, and index date enrollment.

**Setting:** Kaiser Permanente in Georgia and northern and southern California.

**Patients:** 2842 transfeminine and 2118 transmasculine members with a mean follow-up of 4.0 and 3.6 years, respectively, matched to 48 686 cisgender men and 48 775 cisgender women.

**Measurements:** VTE, ischemic stroke, and myocardial infarction events ascertained from diagnostic codes through the end of 2016 in transgender and reference cohorts.

**Results:** Transfeminine participants had a higher incidence of VTE, with 2- and 8-year risk differences of 4.1 (95% CI, 1.6 to 6.7) and 16.7 (CI, 6.4 to 27.5) per 1000 persons relative to cisgender men and 3.4 (CI, 1.1 to 5.6) and 13.7 (CI, 4.1 to 22.7) relative to cisgender women. The overall analyses for ischemic stroke and myocardial infarction demonstrated similar incidence across groups. More pronounced differences for VTE and ischemic stroke were observed among transfeminine participants who initiated hormone therapy during follow-up. The evidence was insufficient to allow conclusions regarding risk among transmasculine participants.

**Limitation:** Inability to determine which transgender members received hormones elsewhere.

**Conclusion:** The patterns of increases in VTE and ischemic stroke rates among transfeminine persons are not consistent with those observed in cisgender women. These results may indicate the need for long-term vigilance in identifying vascular side effects of cross-sex estrogen.

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Transgender persons are a diverse group whose gender identity differs from a male or female sex designation, which usually is assigned at birth (1). Although some transgender persons may not self-identify on the basis of binary definitions (2), a person whose gender identity differs from a male sex designation at birth often is referred to as male-to-female, transfeminine, or trans woman, and a person whose gender identity differs from a female sex designation at birth often is referred to as female-to-male, transmasculine, or trans man (3, 4). Some transgender persons undergo medical treatment to align their physical appearance with their gender identity (5, 6).

A specific area of concern in transgender health is the risk for acute cardiovascular events (ACVEs), including venous thromboembolism (VTE), ischemic stroke, and myocardial infarction, which might plausibly be related to cross-sex hormone therapy (7). As reviewed elsewhere (8–11), the direct evidence addressing this issue is sparse and inconsistent because of the predominance of small studies with very few reported events.

A direct evaluation of the evidence regarding the incidence of ACVEs requires a longitudinal study that includes large numbers of transfeminine and transmasculine participants, with sufficient follow-up, appropriate control groups, and documented cross-sex hormone use among participants (12). Integrated health care systems with electronic medical records (EMRs) allow efficient identification and follow-up of hard-to-reach population subgroups, such as transgender persons. Our objective was to compare ACVE incidence rates in a cohort of transgender persons enrolled in 3 such health care systems with rates observed in age-, race-, site-, and membership-matched cisgender men and women (reference cohorts).

## Methods

### Cohort Ascertainment

This study took place at Kaiser Permanente sites in Georgia, northern California, and southern California

**See also:**

*Web-Only*
Supplement

*Table 1.* Characteristics of the Transgender and Matched Reference Cohorts*

| Characteristic | Transfeminine Cohort, *n* (%) | | | Transmasculine Cohort, *n* (%) | | |
|---|---|---|---|---|---|---|
| | Transfeminine Cohort (*n* = 2842) | Reference Men (*n* = 27 906) | Reference Women (*n* = 27 968) | Transmasculine Cohort (*n* = 2118) | Reference Men (*n* = 20 780) | Reference Women (*n* = 20 807) |
| **Membership site** | | | | | | |
| KPNC | 1585 (56) | 15 620 (56) | 15 650 (56) | 1382 (65) | 13 572 (65) | 13 599 (65) |
| KPSC | 1180 (42) | 11 528 (41) | 11 553 (41) | 678 (32) | 6631 (32) | 6630 (32) |
| KPGA | 77 (2.7) | 758 (2.7) | 765 (2.7) | 58 (2.7) | 577 (2.8) | 578 (2.8) |
| **Race/ethnicity** | | | | | | |
| Non-Hispanic white | 1544 (54) | 15 149 (54) | 15 198 (54) | 1281 (60) | 12 532 (60) | 12 557 (60) |
| Non-Hispanic black | 185 (6.5) | 1810 (6.5) | 1825 (6.5) | 192 (9.1) | 1885 (9.1) | 1890 (9.1) |
| Asian/Pacific Islander | 263 (9.3) | 2600 (9.3) | 2596 (9.3) | 143 (6.8) | 1415 (6.8) | 1421 (6.8) |
| Hispanic | 523 (18) | 5147 (18) | 5157 (18) | 294 (14) | 2900 (14) | 2893 (14) |
| Other/unknown | 327 (12) | 3200 (11) | 3192 (11) | 208 (10) | 2048 (10) | 2046 (10) |
| **Age at index date** | | | | | | |
| 18–25 y | 642 (23) | 6246 (22) | 6293 (23) | 737 (35) | 7189 (35) | 7210 (35) |
| 26–35 y | 584 (21) | 5715 (20) | 5726 (20) | 701 (33) | 6872 (33) | 6880 (33) |
| 36–45 y | 572 (20) | 5630 (20) | 5624 (20) | 344 (16) | 3392 (16) | 3389 (16) |
| 46–55 y | 547 (19) | 5401 (19) | 5401 (19) | 215 (10) | 2125 (10) | 2123 (10) |
| >55 y | 497 (17) | 4914 (18) | 4924 (18) | 121 (5.7) | 1202 (5.8) | 1205 (5.8) |
| **Smoking status** | | | | | | |
| Current smoker | 434 (15) | 4006 (14) | 2339 (8.4) | 382 (18) | 3167 (15) | 1757 (8.4) |
| Not current smoker | 2408 (85) | 23 900 (86) | 25 629 (92) | 1736 (82) | 17 613 (85) | 19 050 (92) |
| **BMI** | | | | | | |
| Normal weight (<25.0 kg/m$^2$) | 1100 (39) | 6699 (24) | 10 397 (37) | 767 (36) | 6051 (29) | 8717 (42) |
| Overweight (25.0–29.9 kg/m$^2$) | 821 (29) | 9269 (33) | 6846 (24) | 548 (26) | 6762 (33) | 4799 (23) |
| Obese (≥30.0 kg/m$^2$) | 659 (23) | 7814 (28) | 7453 (27) | 657 (31) | 5414 (26) | 5355 (26) |
| Unknown | 262 (9.2) | 4124 (15) | 3272 (12) | 146 (6.9) | 2553 (12) | 1936 (9.3) |
| **Total blood cholesterol level** | | | | | | |
| Normal (<5.2 mmol/L [<200 mg/dL]) | 1589 (56) | 9937 (36) | 10 353 (37) | 1233 (58) | 6298 (30) | 7149 (34) |
| Borderline (5.2–6.2 mmol/L [200–239 mg/dL]) | 528 (19) | 4201 (15) | 4707 (17) | 345 (16) | 2266 (11) | 2253 (11) |
| High (>6.2 mmol/L [≥240 mg/dL]) | 170 (6.0) | 1671 (6.0) | 1845 (6.6) | 109 (5.2) | 892 (4.3) | 784 (3.8) |
| Not done (missing, age <40 y) | 374 (13) | 8696 (31) | 8114 (29) | 369 (17) | 9888 (48) | 9280 (45) |
| Unknown (missing, age ≥40 y) | 181 (6.4) | 3401 (12) | 2949 (11) | 62 (2.9) | 1436 (6.9) | 1341 (6.4) |
| **Blood pressure** | | | | | | |
| Normal (systolic: ≤120 mm Hg; diastolic: ≤80 mm Hg) | 1110 (39) | 8083 (29) | 13 810 (49) | 1070 (51) | 6268 (30) | 11 408 (55) |
| Borderline (systolic: 121–139 mm Hg; diastolic: 81–89 mm Hg) | 1187 (42) | 11 607 (42) | 8976 (32) | 787 (37) | 8859 (43) | 6262 (30) |
| Elevated (systolic: ≥140 mm Hg; diastolic: ≥90 mm Hg) | 461 (16) | 4476 (16) | 3131 (11) | 196 (9.3) | 2828 (14) | 1658 (8.0) |
| Unknown | 84 (3.0) | 3740 (13) | 2051 (7.3) | 65 (3.1) | 2825 (14) | 1479 (7.1) |
| **History of any ACVE before index date** | | | | | | |
| Yes | 54 (1.9) | 791 (2.8) | 581 (2.1) | 35 (1.7) | 243 (1.2) | 246 (1.2) |
| No | 2788 (98) | 27 115 (97) | 27 387 (98) | 2083 (98) | 20 537 (99) | 20 561 (99) |

ACVE = acute cardiovascular event; BMI = body mass index; KPGA = Kaiser Permanente Georgia; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California.
* We refer to referents as cisgender for expediency but were unable to verify that each of these members was not transgender. Percentages may not sum to 100 due to rounding.

and was coordinated by Emory University. All activities were reviewed and approved by the institutional review boards of the 4 institutions. The methods of cohort ascertainment were described in detail previously (13, 14). As summarized in the **Supplement** and **Supplement Figure 1** (available at Annals.org), cohort selection involved a 3-step algorithm: an initial EMR search to identify cohort candidates (step 1), validation of transgender status (step 2), and determination of transmasculine or transfeminine status (step 3).

Ten male and 10 female cisgender Kaiser Permanente enrollees were matched to each member of the final validated transgender cohort by race/ethnicity (non-Hispanic white, non-Hispanic black, Asian/Pacific Islander, Hispanic, and other), year of birth (within a 5-year interval), study site, and calendar year of membership based on the index date. Index date was defined as the first recorded evidence of transgender status. We used both male and female cisgender reference groups because hormone serum concentrations

among transgender persons may range from normal physiologic male to normal physiologic female levels, depending on receipt and dosage of hormone therapy as well as individual characteristics (15). A 10:1 ratio was used to allow stratified analyses (for example, by hormone therapy type) while ensuring a sufficient number of cisgender referents for each cohort member. Each transgender cohort member was linked to matched referents via a unique cluster identification number (ID) to allow subanalyses.

### Data Collection and Analysis

Only persons aged 18 years or older at their index date who were determined to be transmasculine or transfeminine, along with their matched referents, were included. All study participants were characterized with respect to their Kaiser Permanente enrollment history and their cigarette smoking status, body mass index (BMI; kilograms per square meter), blood pressure, and total blood cholesterol level at baseline. Variable categorization is presented in the footnotes to the tables and in the **Supplement**.

Transgender hormone treatment was determined through EMR linkages to prescription data by using national drug codes. Linkages with the International Classification of Diseases, Ninth Revision and 10th Revision (ICD-9 and ICD-10), and Current Procedural Terminology codes were used to ascertain surgeries and other interventions. Feminizing drugs (such as estradiol and spironolactone) in a participant recorded as male at birth and masculinizing drugs (such as testosterone) in a participant documented as female at birth were considered evidence of hormone therapy.

In both the transgender and the reference cohorts, ACVEs were ascertained on the basis of ICD-9 or ICD-10 codes. The lists of codes and numbers of cases ascertained by each code are specified in **Supplement Table 3** (available at Annals.org). Only ACVEs with a diagnosis date during follow-up were used in the analyses. History of ACVEs was defined as having an event with a diagnosis date before the start of follow-up.

### Statistical Analysis

All transgender cohort members were characterized as transfeminine or transmasculine and grouped further according to their history of cross-sex hormone use. Follow-up in the overall analysis extended from the index date until the first occurrence of the event of interest, disenrollment from the plan for more than 90 days, death, or the end of the study period (30 November 2016). For participants who began hormone therapy at Kaiser Permanente after the index date (hormone initiation cohort), additional analyses were conducted. In these analyses, follow-up started on the date of the first filled prescription for estrogen or testosterone for transfeminine or transmasculine participants, respectively. Matched referents were assigned the same start date for follow-up.

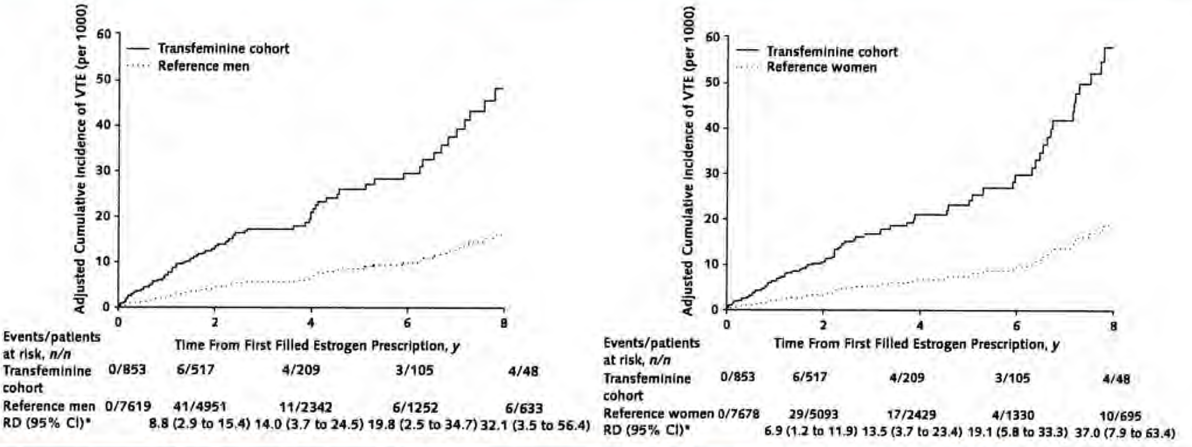
Missing covariate values for BMI, blood pressure, and total cholesterol level were assigned by using multiple imputation methods ($n = 5$ imputations). Incidence rates were calculated as the number of cases per 1000 person-years, and the corresponding 95% CIs were calculated by using the Poisson distribution. Both unadjusted Kaplan–Meier curves and weighted cumulative incidence curves adjusted for covariates at the population means were constructed to compare the incidence of each ACVE type in the transmasculine and transfeminine participants with those in the corresponding matched reference cohorts. Risk differences at 2, 4, 6, and 8 years were calculated directly from the adjusted cumulative incidence curves. The 95% CI for each risk difference estimate was calculated via a bootstrapping procedure using 1000 random samples with replacement.

***Table 2.*** Incidence Rates and Adjusted HRs for ACVEs Among Transfeminine Cohort Members Compared With Matched Reference Cohorts From KPNC, KPSC, and KPGA, 2006–2016

| Cohort and Event of Interest | Transfeminine Cohort | | Adjusted HR (95% CI)* | |
|---|---|---|---|---|
| | ACVEs, *n* | Incidence Rate (95% CI)† | Versus Reference Men | Versus Reference Women |
| **Transfeminine overall cohort ($n = 2842$)** | | | | |
| VTE | 61 | 5.5 (4.3-7.0) | 1.9 (1.4-2.7) | 2.0 (1.4-2.8) |
| Ischemic stroke | 54 | 4.8 (3.7-6.3) | 1.2 (0.9-1.7) | 1.9 (1.3-2.6) |
| Myocardial infarction | 33 | 2.9 (2.1-4.1) | 0.9 (0.6-1.5) | 1.8 (1.1-2.9) |
| **Transfeminine estrogen initiation cohort ($n = 853$)** | | | | |
| VTE‡ | 17 | 6.6 (4.1-10.6) | 3.2 (1.5-6.5) | 2.5 (1.2-5.0) |
| At 0-2 y of follow-up | 6 | 4.3 (1.9-9.6) | 1.5 (0.5-5.1) | 1.7 (0.5-5.5) |
| At >2 y of follow-up | 11 | 9.3 (5.2-16.8) | 5.1 (2.1-12.6) | 3.2 (1.3-7.6) |
| Ischemic stroke‡ | 17 | 6.6 (4.1-10.6) | 2.3 (1.2-4.3) | 2.9 (1.5-5.5) |
| At 0-6 y of follow-up | 9 | 3.8 (2.0-7.3) | 1.3 (0.6-2.9) | 2.3 (1.0-5.4) |
| At >6 y of follow-up | 8 | 36.2 (18.1-72.4) | 9.9 (3.0-33.1) | 4.1 (1.5-11.4) |
| Myocardial infarction in the cohort overall | 4 | 1.5 (0.6-4.1) | 1.0 (0.3-3.2) | 2.4 (0.6-9.4) |

ACVE = acute cardiovascular event; HR = hazard ratio; KPGA = Kaiser Permanente Georgia; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; VTE = venous thromboembolism.
* Stratified by cluster identification number and history of any ACVE; body mass index (normal, overweight, or obese), smoking status (current vs. not current), blood pressure (elevated, borderline, or normal), and total blood cholesterol level (normal, not done [for persons <40 y], borderline, or high) are included in the model as covariates (see the **Supplement** [available at Annals.org] for details of variable characterization).
† Calculated as number of cases per 1000 person-years.
‡ Models were extended because of violation of proportional hazards assumptions.

***Figure 1.*** Adjusted cumulative incidence curves comparing rates of VTE among transfeminine cohort members who initiated estrogen therapy after the index date with matched reference men (*left*) and reference women (*right*) from KPNC, KPSC, and KPGA, 2006–2016.




Adjustment for covariates was made at the population mean values. KPGA = Kaiser Permanente Georgia; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; RD = risk difference; VTE = venous thromboembolism.
* Per 1000 persons.

In the primary analysis, we used multivariable Cox proportional hazards models to compare ACVE rates in the overall transfeminine and transmasculine cohorts and among members of the hormone initiation cohorts with those in the matched cisgender reference groups, after controlling for history of any ACVE, smoking status, BMI, blood pressure, and blood cholesterol level ascertained near the index date. Each model was stratified by cluster ID to account for matching. Proportional hazards assumptions were tested by examining log-minus-log plots for each variable in the model and by performing a goodness-of-fit test using Schoenfeld residuals (16). The results of the Cox models were expressed as adjusted hazard ratios with corresponding 95% CIs. Because the weighted cumulative incidence curves could not account for matching, hazard ratios from models that were not stratified by cluster ID were also calculated and are included in **Supplement Tables 4** and **5** (available at Annals.org). When evidence (such as log-minus-log survival plots) suggested that the proportional hazards assumption was violated, stratified Cox models were used to control for covariates, and extended Cox models with time-dependent hazard ratio estimates were used for the main independent variables of interest (16).

Although the cohort size precluded detailed analyses by specific hormone therapy regimens, some examination of treatment subcategories was possible. These secondary exploratory analyses focused on transfeminine cohort subgroups defined on the basis of administration route (oral or other) and estrogen type (estradiol or other). In addition, the highest daily hormone dosages were summarized for participants who had an event of interest and in those who received hormone therapy but remained ACVE-free.

We examined the effect of different case and exposure definitions, risk factors, and analytic approaches by conducting a series of sensitivity analyses (**Supplement**). To investigate the effects of unaccounted confounding, we calculated a range of E-values for the main results and the lower limits of their 95% CIs observed in Cox regression models (17). The data analyses were performed with SAS, version 9.4 (SAS Institute). E-values were obtained by using an online calculator for hazard ratios with an outcome prevalence of less than 15%.

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## RESULTS

A total of 6456 transgender cohort members were identified in the EMR. After persons younger than 18 years at their index date ($n$ = 1347), those with unknown sex designation at birth ($n$ = 75), and those with no follow-up data ($n$ = 74) were excluded, the study group included 4960 transgender participants and matched reference cohorts of 48 686 cisgender men and 48 775 cisgender women.

The transgender cohort comprised 2842 (57%) transfeminine and 2118 (43%) transmasculine persons (**Table 1**). More than 50% of participants in both groups were non-Hispanic whites; Hispanics represented 18% of transfeminine and 14% of transmasculine partici-

pants, whereas the remainder of the study population was distributed approximately equally among non-Hispanic blacks, Asians/Pacific Islanders, and persons whose race/ethnicity was marked as other or unknown. The proportion of newly identified cohort members increased over time, with approximately 40% of participants identified in the 3 most recent years. About 38% of the transgender cohort had a normal BMI around the index date, which was greater than the proportion of reference men but less than that of reference women. Fewer than 20% of participants were current smokers at or around the index date, with the highest proportion observed in the transmasculine group (**Table 1**).

The average follow-up was 4.0 (SD, 3.0) years in the transfeminine group and 4.4 (SD, 3.1) years in the matched reference cohort. For transmasculine participants and their matched reference cohort, the mean follow-up was 3.6 (SD, 2.7) and 3.9 (SD, 2.9) years, respectively.

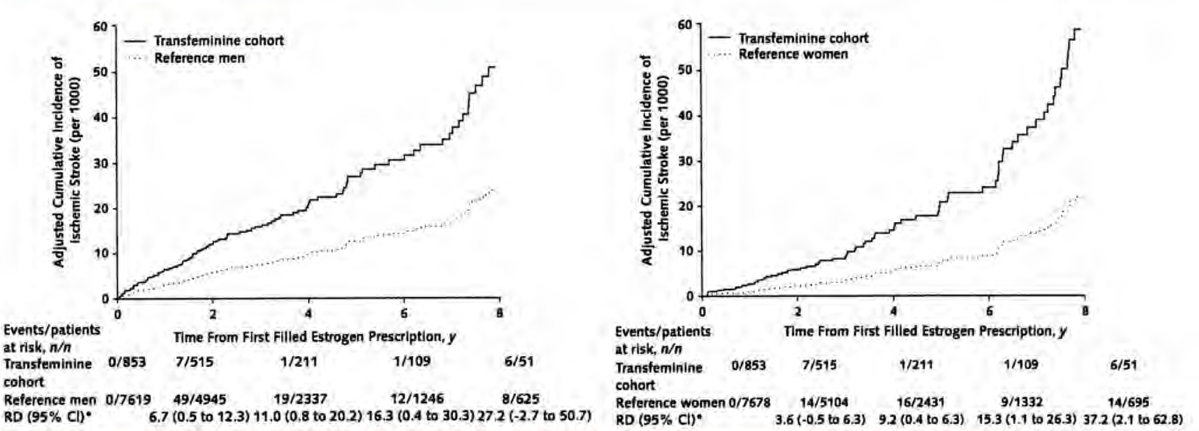
The transfeminine participants had 148 ACVEs since the index date: 61 VTEs, 54 ischemic strokes, and 33 myocardial infarctions. In the transmasculine cohort, 23 VTEs, 16 ischemic strokes, and 9 myocardial infarctions occurred.

The transfeminine cohort had an increase in post-index date incidence of VTE compared with either reference cohort, and the difference seemed more pronounced with increased follow-up, with 2- and 8-year risk differences of 4.1 (95% CI, 1.6 to 6.7) and 16.7 (CI, 6.4 to 27.5) per 1000 persons relative to cisgender men and 3.4 (CI, 1.1 to 5.6) and 13.7 (CI, 4.1 to 22.7) per 1000 persons relative to cisgender women (**Table 2** and **Supplement Figure 2**, *A* and *D*, available at Annals.org). The incidence of ischemic stroke was about the same in all 3 cohorts (**Table 2** and **Supplement Figure 2**, *B* and *E*, available at Annals.org). The incidence of myocardial infarction in the transfeminine cohort was greater than in reference women but no different from the incidence in reference men (**Table 2** and **Supplement Figure 2**, *C* and *F*, available at Annals.org).

In the analyses limited to transfeminine persons who initiated estrogen therapy after the index date (estrogen initiation cohort), the differences in VTE and ischemic stroke incidence rates compared with either reference cohort were evident. The adjusted survival curves, and particularly the Kaplan–Meier curves (**Supplement Figure 3**, available at Annals.org), suggested inflection points around 2 years of follow-up for VTE (**Figure 1**) and at 6 years of follow-up for ischemic stroke (**Figure 2**). The corresponding adjusted cumulative incidence curves for myocardial infarction in the estrogen initiation cohort did not show statistically significant differences (**Figure 3**), but the hazard ratio estimates in **Table 2** are imprecise because few events ($n$ = 4) occurred in the exposed group.

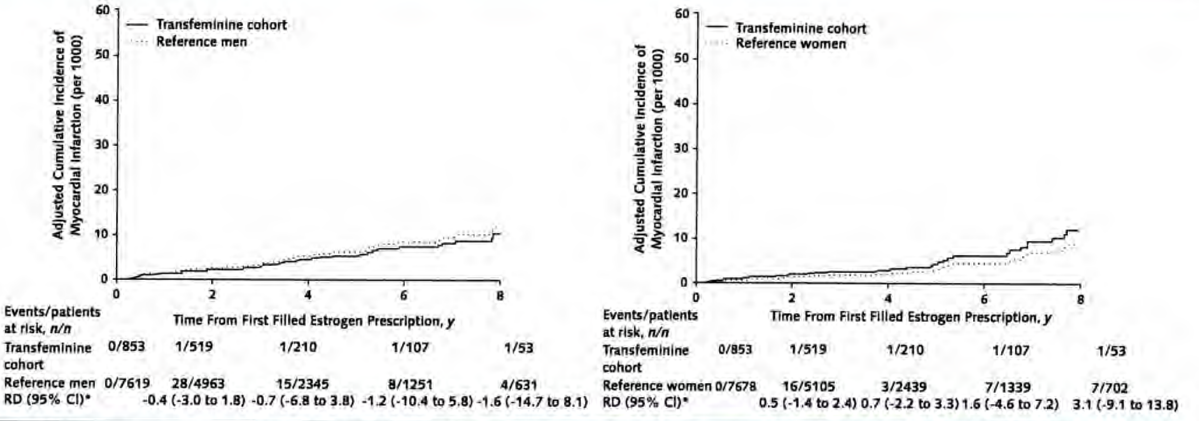
Although results of the Schoenfeld goodness-of-fit test were not statistically significant, changes in relative rates over time and a violation of the proportional hazards assumption were suggested by log-minus-log plots (**Supplement Figure 4**, available at Annals.org) in the analyses for VTE and ischemic stroke in the estrogen initiation cohort. For this reason, the hazard ratios for VTE in this category of participants are presented separately for follow-up of 2 years or less and for follow-up longer than 2 years, whereas the analyses for ischemic stroke used 6 years as the cutoff. As shown in **Table 2**, the hazard ratio estimates–after adjustment for cluster ID, BMI, history of ACVE of interest, blood pressure, blood cholesterol level, and smoking–in the 0- to 2-year follow-up for VTE and the 0- to 6-year follow-up for ischemic stroke were closer to the null than the corresponding estimates in the later pe-

***Figure 2.*** **Adjusted cumulative incidence curves comparing rates of ischemic stroke among transfeminine cohort members who initiated estrogen therapy after the index date with matched reference men (*left*) and reference women (*right*) from KPNC, KPSC, and KPGA, 2006–2016.**




Adjustment for covariates was made at the population mean values. KPGA = Kaiser Permanente Georgia; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; RD = risk difference.
* Per 1000 persons.

***Figure 3.*** Adjusted cumulative incidence curves comparing rates of myocardial infarction among transfeminine cohort members who initiated estrogen therapy after the index date with matched reference men (*left*) and reference women (*right*) from KPNC, KPSC, and KPGA, 2006-2016.




Adjustment for covariates was made at the population mean values. KPGA = Kaiser Permanente Georgia; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; RD = risk difference.
* Per 1000 persons.

riods; this was consistent with the inflection points observed on log-minus-log plots.

The cumulative incidence curves for most analyses in the transmasculine cohort closely followed those of the 2 matched reference cohorts (**Supplement Figure 5**, available at Annals.org). These curves were consistent with the results of the multivariable Cox regression analyses (**Table 3**). The hazard ratio estimates for VTE in the overall transmasculine cohort that used cisgender men and cisgender women as the reference categories were 1.6 (CI, 0.9 to 2.9) and 1.1 (CI, 0.6 to 2.1), respectively. The corresponding results were 1.1 (CI, 0.6 to 2.0) and 1.3 (CI, 0.7 to 2.5) for ischemic stroke and 0.7 (CI, 0.3 to 1.8) and 1.3 (CI, 0.5 to 3.9) for myocardial infarction. Analyses restricted to the testosterone initiation cohort were limited because of relatively few events (**Table 3**).

Hormone dosages are described only for members of the estrogen initiation cohort who received oral estradiol alone, the most common formulation–route combination. The average maximum daily dosage of estradiol received during follow-up was 4.1 mg (range, 1 to 10 mg) for transfeminine participants with either VTE or ischemic stroke ($n$ = 11) and 4.2 mg (range, 0.3 to 10 mg) for those with neither event ($n$ = 391). Among transfeminine participants who had either event, the average maximum daily dosage during the first 2 years of follow-up was lower (3.6 mg; range, 1.0 to 7.0 mg) than the corresponding dosage after 2 years of follow-up (5.6 mg; range, 2.0 to 10.0 mg). The mean values for transfeminine participants with no ACVE were similar before and after 2 years of follow-up (4.1 vs. 4.4 mg), and the dose ranges for the 2 intervals were the same (0.3 to 10 mg).

The results of most sensitivity analyses were similar to those of the main analyses (**Supplement Tables 6 and 7**, available at Annals.org). However, the precision of some estimates decreased because of fewer events. **Supplement Table 8** (available at Annals.org) presents E-value calculations for the main associations observed in this study, with the focus on statistically significant results. The E-values for observed point estimates ranged from 1.7 to 19.3. The corresponding E-values for lower estimates of 95% CIs that excluded 1.0 ranged from 1.7 to 5.5.

## DISCUSSION

The results of this EMR-based cohort study of transgender persons indicate that transfeminine participants had higher rates of VTE and, to a lesser extent, ischemic stroke relative to the corresponding rates among cisgender men and women. Myocardial infarction rates were greater among transfeminine participants than in matched cisgender women but were similar to those observed among cisgender men. The evidence was insufficient to draw conclusions about increased risk for any of the ACVEs of interest among transmasculine participants.

Results further indicate that the increases in VTE and ischemic stroke rates were most pronounced among transfeminine participants who initiated estrogen therapy during follow-up and that the patterns of these increases differed substantially from those reported in previous research. For example, in a clinical trial of hormone replacement therapy in postmenopausal women, VTE rates increased relatively rapidly after the intervention began and seemed to decline and then plateau by 5 years of follow-up (18). Likewise, in a case-control study of VTE and estradiol use in Sweden, the risk was elevated only during the first year after the start of therapy (19). In contrast, in our estro-

gen initiation cohort, VTE rates increased only after 2 years of follow-up and continued to rise for another 5 to 6 years. Likewise, the ischemic stroke rates in the estrogen initiation and 2 reference cohorts did not differ during the first 6 years of follow-up but clearly diverged afterward.

Previous studies of cisgender women demonstrated that the presence and magnitude of the association between estrogen hormone therapy and both VTE and ischemic stroke may differ by medication type, drug combinations, and administration routes (20–26). Although the data on hormone replacement therapy in cisgender women come from high-quality studies, including large randomized placebo-controlled clinical trials, the results of these studies may not apply to transgender persons.

Unlike research of hormone replacement therapy in cisgender populations, placebo-controlled clinical trials of transgender hormones may not be ethically acceptable (12). For this reason, evidence pertaining to the risks and benefits of hormone therapy in transgender persons must be obtained from observational studies (27–31). One of the largest studies to date included a cohort of 816 transfeminine participants who received oral ethinyl estradiol (100 mcg/d) or transdermal estradiol and 293 transmasculine patients who received parenteral testosterone esters or oral testosterone undecanoate (30). The study participants were seen in the outpatient department of Free University Hospital in Amsterdam between 1975 and 1994. Among the transfeminine participants, 45 cases of VTE occurred, only 5 of which arose after surgery. With the general male population of the Netherlands used as a reference, this number of VTE cases was 20-fold higher than expected. Only 1 case of VTE was observed in transmasculine cohort members. A cross-sectional study in Belgium examined morbidity in transgender patients who received transgender care at Ghent University Hospital (31). Transfeminine ($n$ = 214) and transmasculine ($n$ = 138) patients who had at least 3 months of cross-sex hormone therapy between 1986 and 2012 were each age matched to 3 cisgender men and 3 cisgender women. Most transfeminine patients received 2 mg/d of oral estradiol valerate (43%), transdermal estradiol gel (36%), or estradiol patches (14%). Prevalence estimates for history of VTE among transfeminine and transmasculine persons were 6.7% and 1.5%, respectively. No cases of VTE occurred in any of the referent participants.

A distinguishing feature of our study is that it represents one of the largest cohorts of transgender persons in the United States and, to our knowledge, is the only study of this size that carefully validated transfeminine or transmasculine status in the participants. Although the information on hormone therapy and surgical transgender treatment received within the Kaiser Permanente system is relatively high quality, one of the study's main limitations was the inability to determine from the data which participants received care elsewhere. This limitation restricted our ability to identify a subcategory of transgender cohort members with no history of transgender treatment of any kind. Our results suggest that some persons with no evidence of hormone therapy at Kaiser Permanente may have received it from other sources. This observation has both research and clinical implications because it illustrates the challenges of reconstructing the full, lifetime history of hormone therapy use.

Even with the relatively large group of patients who initiated hormone therapy at Kaiser Permanente, many useful subanalyses evaluating risks associated with specific types of hormone treatment were not feasible because of sparse drug- and dose-specific strata. In a set of exploratory analyses, we could examine the data on subgroups of patients who received estrogen orally, the most common route of administration. We also could study the estradiol-only estrogen group and the group that received other estrogen formulations. These exploratory analyses do not provide evidence of substantial heterogeneity across subcohorts, but limited

*Table 3.* Incidence Rates and Adjusted HRs for ACVEs Among Transmasculine Cohort Members Compared With Matched Reference Cohorts From KPNC, KPSC, and KPGA, 2006–2016

| Cohort and Event of Interest | Transmasculine Cohort | | Adjusted HR (95% CI)* | |
|---|---|---|---|---|
| | ACVEs, *n* | Incidence Rate (95% CI)† | Versus Reference Men | Versus Reference Women |
| **Transmasculine overall cohort ($n$ = 2118)** | | | | |
| VTE | 23 | 3.1 (2.0–4.6) | 1.6 (0.9–2.9) | 1.1 (0.6–2.1) |
| Ischemic stroke | 16 | 2.1 (1.3–3.5) | 1.1 (0.6–2.0) | 1.3 (0.7–2.5) |
| Myocardial infarction | 9 | 1.2 (0.6–2.3) | 0.7 (0.3–1.8) | 1.3 (0.5–3.9) |
| **Transmasculine testosterone initiation cohort ($n$ = 585)** | | | | |
| VTE | 4 | 3.3 (1.3–8.9) | 2.7 (0.6–12.1) | 1.5 (0.4–5.6) |
| Ischemic stroke | 2 | 1.7 (0.4–6.7) | NC‡ | NC‡ |
| Myocardial infarction | 0 | - | - | - |

ACVE = acute cardiovascular event; HR = hazard ratio; KPGA = Kaiser Permanente Georgia; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; NC = not calculated; VTE = venous thromboembolism.
* Stratified by cluster identification number and history of any ACVE; body mass index (normal, overweight, or obese), smoking status (current vs. not current), blood pressure (elevated, borderline, or normal), and total blood cholesterol level (normal, not done [for persons <40 y], borderline, or high) are included in the model as covariates (see the **Supplement** [available at Annals.org] for details of variable characterization).
† Calculated as number of cases per 1000 person-years.
‡ Because of small numbers.

conclusions may be drawn because of the paucity of counts in some of the smaller strata. We also found some evidence that dosages increased for participants who had a VTE or an ischemic stroke but not for those who were event-free. No statistical comparisons of the dosage distributions were possible because of the small numbers of events. Of note, the documented dosages in our cohort exceeded those reported in the European studies (30, 31), which also found greater risks for VTE.

Although the current analysis was adjusted for several covariates, some information on possible confounders was not available. For example, we did not have data on statin use or various comorbid conditions. In addition, because transgender persons receive much of their care from a select group of health care providers who do not necessarily practice in the same clinics as providers with primarily cisgender patients, we could not account for differences by clinical site. However, sensitivity analyses indicate that the most important observed associations, such as those reported for VTE, are probably not a result of any potential effect of unmeasured confounders.

It is important to keep in mind that no single study may be considered sufficient for answering all relevant research questions regarding comparative risks and benefits of various treatment options. This is true particularly in observational research, in which the ability to examine specific formulation-route-dosage combinations or rates of rare events depends on the available data. For example, although we did not observe statistically significantly elevated rates of some of the less common events, such as myocardial infarction among transfeminine or any ACVEs among transmasculine patients, interpreting these data as conclusive evidence of no association would be premature. In particular, our analyses suggest that transmasculine persons receiving testosterone may be at higher risk for myocardial infarction, but the number of events was insufficient because of the relatively young age of the transmasculine cohort. A larger cohort and extended follow-up will allow additional analyses of more specific treatment options (such as various combinations of estradiol with antiandrogens and progesterone) and less common events, such as myocardial infarction among trans men or different subtypes of VTE among trans women.

In summary, the present study demonstrated that cross-sex estrogen is a risk factor for VTE and probably ischemic stroke among transfeminine persons. We also observed that patterns of VTE and ischemic stroke incidence among transfeminine persons receiving hormone therapy were different from those reported in cisgender women receiving hormone replacement therapy. If confirmed, these results may indicate the need for increasing vigilance in identifying long-term vascular side effects of estrogen therapy in transgender patients. In the meantime, it is critical to keep in mind that the risk for ACVEs in this population must be weighed against the benefits of treatment.

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Ex. 21



chromosome material has been observed in about 10% of patients. As such, the presence of the Y chromosome material in patients with Turner syndrome poses an increased risk of gonadoblastoma and malignant transformation (Baer et al. 2017).

**Case:** Our case report entails a 13 y.o. female who initially presented with short stature and progressively worsening facial/body hair and deepened voice without menarche or thelarche. Evaluation was notable for 46X karyotype, elevated FSH (41.5) and LH (16.8), as well as DHEAS (421) and Testosterone (128), and lipid panel. Patient had normal estradiol (24), 17 Hydroxyprogesterone, Hemoglobin A1c, prolactin, cortisol, and renal/adrenal and pelvic imaging by both ultrasound and MRI. Normal uterus, cervix, and ovaries/gonads were noted. ACTH testing had suppressed and normal adrenal testing, and unsuppressed/unchanged testosterone levels. No SRY gene was identified on initial karyotype testing. Given a lack of clear source of her hyperandrogenism, she underwent laparoscopic gonadectomy, with final pathology notable for compound gonad with fibrous streak ovary on surface of Sertoli-only testis with Sertoli cell nodule and Leydig cell hyperplasia. FISH analysis noted that none of the examined nuclei showed the presence of Y (DYZ1) or SRY signals. 52% of 200 interphase nuclei examined contained an XX chromosome signal pattern and 47.5% contained a single X chromosome signal pattern.

**Comments:** Our case demonstrates a gonadal cause of hyperandrogenism in a patient with Turner's syndrome without any SRY component on initial karyotype testing. Given the lack of obvious peripheral, adrenal or central causes of hyperandrogenism our decision to proceed with gonadectomy in this instance revealed surprising results. It highlights the importance of karyotype mosaicism, and specifically the possibility of atypical findings on gonadal tissue not previously seen on karyotype testing, to explain otherwise unclear etiology of hyperandrogenism. Significantly, it may also predispose to similar risks of malignancy, thus further research is warranted to fully elucidate this issue.

## 72. Revision Gender Affirming Surgery for Trans Women

Philippa Brain, Sarah McQuillan

*University of Calgary*

**Background:** In Canada there is a single Center that performs gender affirming surgery for transwomen. While a business case has been put forward to the provincial government to develop a program in Alberta, until funding is obtained, anywhere from 20-40 patients per year to travel to Quebec for this surgery. The care of the grafted vagina is complicated and requires a unique skill set that is inherent in the training in pediatric gynecology and our service now routinely see these patients postoperatively. Common complications include infection, hematomas, urinary incontinence and retention as well as granulation tissue, and fibrin, and recovery includes support through the dilation process. Any postoperative complications can result in longer term complications such as loss of the graft, complete stenosis of the vagina as well as introital stenosis at a published rate of five percent. Saving the graft and upper vagina requires unique stenting solutions. Transwomen have varying results from their original procedure which may or may not include the development of a vagina and have requested consults for revision surgery.

**Case:** In this paper we will present our experience of 5 patients undergoing revision surgery which includes the use pedicled full thickness grafts from redundant scrotal/vulvar skin as a grafted neovagina, inverted Y grafts and rotated skin flaps to provide increased introital capacity, as well as the use of bucchal grafts to enhance both introital stenosis and complete vaginal stenosis. The patients were 10 -24 months post their original surgeries. At six months postoperatively all patients are satisfied with width and depth except for one patient who continues to have difficulty with introital pain and stenosis interfering with dilation.

**Comments:** Realizing the variance in postop care of the neovagina and the differences in pedagogue between formal training in Peds Gyne and Urology, including the use of stents or dilation in the functional maintenance of a grafted neovagina has been invaluable in maintaining patency of the neovagina with difficult postop complications. Applying various postoperative techniques improves the care we provide to more traditional peds gyne surgery such as the surgical correction of transverse vaginal septum, McIndoe procedures and other less common but often more complicated congential anomalies such as urogenital sinuses, and congential adrenal hyperplasia with significant vulvar virilization. The provision of this care requires a team of multidisciplinary expertise and the shared learning between plastics, urology, both adult and pediatric, psychiatry and dedicated family physicians in trans care has been invaluable.

## 73. "I think sex is different for everybody" - Sexual Experiences and Expectations in Transgender Youth

Adrian Araya, Daniel Shumer, Rebecca Warwick, Ellen Selkie

*University of Michigan*

**Background:** There is a paucity of data on sexual experiences of transgender adolescents, yet this population is at high risk for sexually transmitted infections and unintended pregnancy. Characterizing the lived experiences of these youth can provide insight to guide clinicians' best practices and refine evidence-based family and school-centered sexual education. The purpose of this phenomenological qualitative study was to describe sexual experiences and sexual health education of transgender youth.

**Methods:** 30 transgender adolescents were recruited from a Midwestern university-based child and adolescent gender services clinic to participate in semi-structured interviews exploring sexual experiences and perceptions of sexual education from schools, parents, and health care providers. Interviews were audio recorded, transcribed, and coded utilizing NVivo 12 software for thematic analysis.

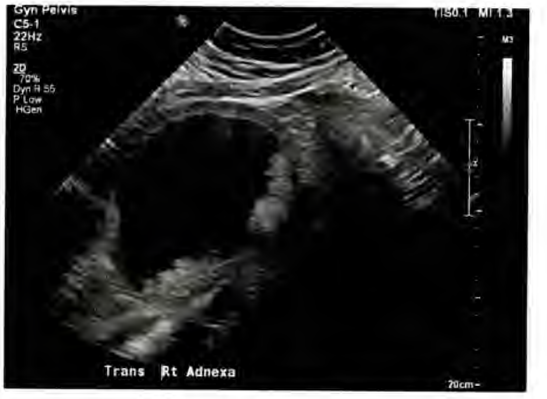
**Results:** 18 transmasculine and 12 transfeminine adolescents ages 15-20 were interviewed. Participants were predominantly White (87% of participants) and described socioeconomic status as "pretty well off" (43%).

Table 1

| Theme | Quote |
|---|---|
| Effects on libido and sexual identity attributed to gender affirming hormone therapy | I have lost 100% of my sex drive. All of it. –17-year-old transwoman<br><br>I do notice that before starting testosterone, I was more attracted to girls and since, you know, I don't know if it's correlation or causation or whatever, that has definitely shifted to guys—17-year-old transman |
| Inconsistent or ineffective sexual education from families | My parents didn't say anything to me. So uh, you know I had friends who were like, my mom just talked to me about having sex and it was the weirdest thing ever. I was like oh that's funny, and months and years would go by and none of them had said anything to me. I was like, ok it is not funny anymore. –18-year-old transman |
| Pervasive heteronormative sexual education from parents and schools | I would say no, because it was only about two heterosexual cis-people having sex with other heterosexual cis people, and I'm neither cis nor heterosexual, so I don't. I never learned anything about how my body works, obviously being a transgender girl, my body doesn't work the same way cis boys or girl's body work and sex doesn't work the same way. –19-year-old transwoman |
| Varying definitions of sex | To be honest, I don't think it has to be like technically any kind of insertion. I just kind of think sex can be a lot of things. I feel like sex can be whatever act you want to do you can define as sex. –18-year-old transman<br><br>Personally, I view it as more penetration kind of activity, but you can also have sex by not penetrating, I guess. –20-year-old transwoman<br><br>Yeah, I mean, contact with other people's genitals, I guess, in any way shape or form that is intentional and like consensual. –17-year-old transman |
| Inconsistent screening for STI and use of barrier method | Since then, since having sex, I never found myself concerned if I did find myself having a sexual disease. I don't know what it's about, I've just never been scared that I could actually have a disease. –18-year-old transwoman<br><br>I always used protection with him and then with the other people that I've had sexual encounters with they've all had female assigned parts when they were born so I didn't really have to worry about it at first, and then I realized there were some things that I still had to worry about. –17-year-old transman |
| Insufficient clinician sexual health counseling and reliance on gender services clinician | No, nobody has really asked except for [gender services doctor] the first few visits, trying to figure out what's your relationships status, are you sexually active, how does that work, that type of thing. Other than that, no typical doctor. – 17-year-old transman |

28 adolescents at time of recruitment were treated with gender affirming hormone therapy. Participants' varying sexual orientations included heterosexual, homosexual, bisexual, pansexual, or asexual identities. Age of sexual debut ranged from 14 to 18 years of age. Number of lifetime sexual partners ranged from 0 to 15. Grade at first sexual education occurred from 4th to 12th grade. Thematic analysis demonstrated: 1) effects on libido and sexual identity attributed to gender affirming hormone therapy; 2) inconsistent or ineffective sexual education from families; 3) pervasive heteronormative sexual education from parents and schools; 4) varying definitions of sex; 5) inconsistent screening for sexually transmitted infections and use of barrier protection; and 6) insufficient sexual health counseling from clinicians and reliance on gender services physician. Representative quotations are displayed in Table 1.

**Conclusions:** This study highlights a need for inclusive sexual education at the level of the home and school. Sexual practices of this population are varied and may not be effectively captured on current medical screening tools. Physicians should tailor their interviewing and education to consider non-heteronormative sexual behaviors.




### 74. A Large Mass and an Even Larger Discussion: Management of a Serous Borderline Ovarian Tumor in a Trans-male Adolescent

Katherine Hayes, Amanda French

*Boston Children's Hospital*

**Background:** Gender dysphoria is increasingly recognized and treated in adolescents. Many patients will use hormone therapy to develop secondary sex characteristics more aligned with their gender identity. Providers may fail to consider the potential role of these hormones in the pathogenesis and recurrence of rare ovarian pathology. We present the case of a 17-year-old transgender male with acute adnexal torsion of a serous borderline ovarian tumor with androgen receptor positivity to highlight the decision making surrounding ongoing surveillance and gender affirming care for this patient and others like him.

**Case:** A 17-year-old transgender male receiving testosterone therapy for twelve weeks presented with severe right lower quadrant pain and nausea. Ultrasound showed a 20 cm mass with solid and cystic components and no vascular flow. He was taken to the operating room for emergent management with oophorectomy per patient and family preference. Torsion was confirmed. Pathology demonstrated an intact serous borderline tumor without micropapillary features and immunohistochemical staining positive for androgen receptors. Norethindrone acetate was continued for menstrual suppression to minimize dysphoria. Testosterone therapy was initially held after surgery, but restarted approximately two months postoperatively.

**Comments:** Borderline ovarian tumors in adolescents account for 10-30% of epithelial neoplasms and less than 1% of all ovarian neoplasms. These tumors have an excellent prognosis in adolescents when managed by fertility-sparing surgery, but patients must be monitored due to the recurrence risk, which extends for 10-20 years after initial diagnosis. Typically, surveillance is done with serial transvaginal ultrasonography which may not be well tolerated in the transmasculine population. Discussion of post-operative gender-affirming hormone therapy was complicated by the androgen receptor status of this tumor. A multi-disciplinary team elected to restart treatment for this patient as the ovary was completely removed and recurrence risk in the contralateral ovary is low. His current surveillance strategy will likely evolve as his gender affirmation journey progresses. This case illustrates the complicated interplay between gender-affirming hormonal and surgical treatment and long-term follow up of serous borderline ovarian tumors. A literature search using the terms testosterone, transgender, and borderline ovarian tumor failed to identify any similar cases, although there were three reported cases of ovarian malignancy in adult trans-males. Given the rarity of ovarian neoplasms in transmasculine individuals, we propose creating a registry to monitor incidence and long-term outcomes.

### 75. Achieving Literacy through Education and Simulation (ALIES) in Transgender Healthcare

Kimberly Huhmann [1], Victoria Wang [1], Thao Thieu [1], Laura Grubb [2]

[1] *Tufts Medical Center*
[2] *Floating Hospital for Children at Tufts Medicine Center*

**Background:** The LGBTQ community faces health disparities for a multitude of reasons, from social stigma to legal discrimination. Among the LGBTQ community, transgender individuals encounter some of the starkest deficiencies in access to care with key reasons they do not seek medical care being lack of access to gender-affirming care and knowledgeable providers. Achieving Literacy through Education and Simulation (ALIES) in transgender healthcare is a unique and robust curriculum developed with the aim to become stronger allies and better providers.

**Methods:** This is an IRB approved curriculum involving Obstetric and Gynecology residents and rotating medical students over four one-hour didactic sessions and a half-day of simulated training. Lecture topics included definitions, mental health, medical transition, and clinic-based care. Simulated training with standardized patients who identify as transgender or non-binary allowed participants to role play in a controlled and supportive environment as well as watch their peers interact in real-time and provide each other feedback. The effectiveness of the curriculum was measured by pre- and post- intervention surveys given at four time intervals: the first day of didactic learning, after simulation training, at 3-months and 6-months following the curriculum. The survey assesses

Ex. 22

NEWS

# Duke Health emerges as Southern hub for youth gender transition

DAVID LARSON

AUGUST 31, 2022

LISTEN TO THIS STORY *(8 minutes)*

*Editor's note: Graphic language*

The debate around childhood gender transitions has become a cultural flashpoint in 2022. Arkansas, Alabama, Arizona, and Texas **passed bans** on youth gender surgeries and hormone treatments — with 15 other states considering such bans — while **California** and **New York** are considering laws making themselves places of "refuge" for youth gender transition.

The tide in Europe seems to be turning strongly against providing puberty blockers, hormones, and surgeries to minors experiencing gender dysphoria. This summer, the United Kingdom announced it would **shut down** its only gender clinic for minors, the Tavistock Clinic, over fears the treatments were dangerous, experimental, and provided without enough scrutiny. **Sweden** and **Finland** also made strong moves against the practice, banning hormones, puberty blockers, and gender reassignment surgeries as treatments for gender dysphoria.

Amidst this contentious cultural landscape, North Carolina's own Duke Health has emerged as a Southern regional hub of "gender-affirming care" for minors experiencing gender dysphoria. Many are choosing to travel long distances from Southern states with stricter laws to seek treatment at Duke.

"Duke is the only medical school in the southern states with a child and adolescent gender clinic, an adult gender clinic, a sexual and gender minorities primary care clinic, a top public policy school and global health institute," said a February 2020 Duke Health **statement** announcing the opening of the Duke Sexual and Gender Minority Health Program.

The statement said that "The vision for the Duke Sexual and Gender Minority Health Program (DSHP) is to transform research and healthcare for millions of sexual and gender minority individuals—that is, members of the LGBTQIA+ community—and to become the leader in research, patient care, education and policy for sexual and gender minority health in the southern U.S. and the Global South."

And the effort is quickly bearing fruit. At the DSHP's 2022 Sexual and Gender Health Symposium, co-director of adult gender medicine Carly Kelley laid out the explosion of interest in the clinic among both adults and children. The DSHP has already had more than 1,000 patients, and both the adult and pediatric practices have a 6-month waiting list. This spike comes as clinics across the world are seeing a recent flood of new interest in gender services, including a **4,000% increase** in youth seeking gender transitions in the U.K. over the past decade.

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"The demand for gender-affirming treatment is increasing, and you can see from the graphs here, as a result of the demand, our program is growing," Kelley said.

At the 2022 symposium, there were a number of panels bringing together top minds in the field from across the country and around the world. The "Teen Transitions" panel had Dr. Marci Bowers, who has done more than 2,250 transition surgeries, likely more than anyone else on the planet. Bowers is also the president-elect of WPATH, the global medical body that creates best-practices for youth transgender care, making her a minor celebrity among those in the specialty. Bowers also recently appeared on *The Daily Wire's* satirical documentary "What is a Woman?" as one of the experts duped into giving an interview.

During Duke's panel, Bowers made note of a few major concerns that have cropped up for "gender-affirming" surgeons. One is the increase in "detransitioners," people who had hormonal and surgical treatments to transition towards their preferred gender and then came to regret that decision. Bowers said that this was not necessarily negative and might just be "part of their journey," likening the phenomenon to someone had a breast augmentation and later regretted it.

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The detransitioner movement has been growing, though, with **one online community** alone hosting over 37,000 people who claim to regret a gender transition. And many of these detransitioners claim they were not properly made aware of the risks and challenges they would face.

Bowers seemed to acknowledge these challenges, saying that "really about zero" biological males who block puberty at the typical Tanner 2 Stage of puberty (around 11 years old) will go on to ever achieve an orgasm and that their penises will never develop enough tissue "to create a female vulva" surgically later in the transition process.

Bowers suggested that because this was all a new field, these were all "to-be-answered questions" needing more experimentation, possibly solved by allowing puberty to proceed a little further or adding testosterone later in the transition process.

Bowers also said that all this needs to be better communicated with patients as a part of informed consent and that maybe patients should be encouraged to keep their penises and think of them as more of "a large clitoris" instead.

Duke Health's Dane Whicker, a psychologist at the gender clinic, seemed to push back on this, saying that the risks of not transitioning, like being bullied, outweighed having the risks Bowers mentioned centered during informed consent discussions with the child. He also suggested the sexual dysfunction caused by SSRI medications for depression were analogous to the lack of orgasms and fertility caused by the transition process, and if patients were scared off from transitioning, they may end up on these medications.

Another hot topic at the symposium was the increasing evidence of a link between autism-spectrum disorders and transgenderism. Before the United Kingdom shut down the Tavistock Clinic, there was **controversy** over a report that of the 1,069 patients under 18 served by the clinic, 372 (or 35%) had moderate to severe autism.

A larger **study** of 640,000 people found 24% of the transgender population to be autistic, with the remainder being five-times more likely than the general population to believe they have undiagnosed autism. They also had higher rates of all six major psychological conditions tested, including bipolar disorder and schizophrenia.

Only about 1% of the global population is estimated to be autistic (and 2% of the American population **according to the CDC**), making these numbers orders of magnitude greater than the population at large. With autism being defined as a spectrum of disorders affecting the ability to socialize and communicate, the British government ordered investigations to look into whether this vulnerable community somehow came to see a transgender identity as an easy explanation for their social difficulties.

A panel during the symposium explored this intersection of gender diversity and autism but pushed back at the suggestion that the connection had anything to do with confusion.

Dr. Nick Walker, an autistic male who identifies as a woman, said that these stats are convincing people that the overlap between transgender and autistic people is evidence that "this is some trend that autistic people's terrible disorder is causing them to fall for." But Walker suggested this is a weaponization of autistophobia and that the autistic and queer identities are as valid as gendernormativity and neuronormativity and therefore should not be policed.

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On Aug. 26, Carolina Journal reached out to Dr. Deanna Adkins, the child and adolescent lead for DSHP; and Dr. Dane Whicker, the mental health and education lead for DSHP — both of whom were on the Teen Transitions panel with Bowers — to ask if they agreed with Bowers' assessments on lack of sexual functioning after puberty blockers and the need for better informed consent. CJ also asked at what age DSHP begins offering surgeries and hormonal treatments.

Neither Adkins nor Whicker responded in time for publication.

Ex. 23

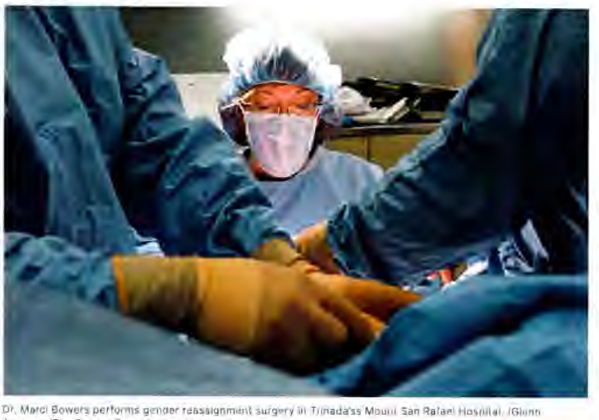
THE FREE PRESS

Wednesday, March 13, 2024 3:52 PM

FOR FREE PEOPLE







Dr. Marci Bowers performs gender reassignment surgery in Trinidad's Mount San Rafael Hospital. (Glenn Asakawa/The Denver Post via Getty Images)

# Top Trans Doctors Blow the Whistle on 'Sloppy' Care

*In exclusive interviews, two prominent providers sound off on puberty blockers, 'affirmative' care, the inhibition of sexual pleasure, and the suppression of dissent in their field.*

**By Abigail Shrier**
October 4, 2021

For nearly a decade, the vanguard of the transgender-rights movement — doctors, activists, celebrities and transgender influencers — has defined the boundaries of the new orthodoxy surrounding transgender medical care: What's true, what's false, which questions can and cannot be asked.

They said it was perfectly safe to give children as young as nine puberty blockers and insisted that the effects of those blockers were "fully reversible." They said that it was the job of medical professionals to help minors to transition. They said it was not their job to question the wisdom of transitioning, and that anyone who did — including parents — was probably transphobic. They said that any worries about a social contagion among teen girls was nonsense. And they never said anything about the distinct possibility that blocking puberty, coupled with cross-sex hormones, could inhibit a normal sex life.

Their allies in the media and Hollywood reported stories and created content that reaffirmed this orthodoxy. Anyone who dared disagree or depart from any of its core tenets, including young women who publicly detransitioned, were inevitably smeared as hateful and accused of harming children.

But that new orthodoxy has gone too far, according to two of the most prominent providers in the field of transgender medicine: Dr. Marci

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Bowers, a world-renowned vaginoplasty specialist who operated on reality-television star Jazz Jennings; and Erica Anderson, a clinical psychologist at the University of California San Francisco's Child and Adolescent Gender Clinic.

In the course of their careers, both have seen thousands of patients. Both are board members of the World Professional Association for Transgender Health (WPATH), the organization that sets the standards worldwide for transgender medical care. And both are transgender women.

Earlier this month, Anderson told me she submitted a co-authored op-ed to The New York Times warning that many transgender healthcare providers were treating kids recklessly. The Times passed, explaining it was "outside our coverage priorities right now."

Over the past few weeks, I have spoken at length to both women about the current direction of their field and where they feel it has gone wrong. On some issues, including their stance on puberty blockers, they raised concerns that appear to question the current health guidelines set by WPATH — which Bowers is slated to lead starting in 2022.

WPATH, for instance, recommends that for many gender dysphoric and gender non-conforming kids, hormonal puberty suppression begin at the early stages of puberty. WPATH has also insisted since 2012 that puberty blockers are "fully reversible interventions."

When I asked Anderson if she believes that psychological effects of puberty blockers are reversible, she said: "I'm not sure." When asked whether children in the early stages of puberty should be put on blockers, Bowers said: "I'm not a fan."

When I asked Bowers if she still thought puberty blockers were a good idea, from a surgical perspective, she said: "This is typical of medicine. We zig and then we zag, and I think maybe we zigged a little too far to the left in some cases." She added "I think there was naivete on the part of pediatric endocrinologists who were proponents of early [puberty] blockade thinking that just this magic can happen, that surgeons can do anything."

I asked Bowers whether she believed WPATH had been welcoming to a wide variety of doctors' viewpoints — including those concerned about risks, skeptical of puberty blockers, and maybe even critical of some of the surgical procedures?

"There are definitely people who are trying to keep out anyone who doesn't absolutely buy the party line that everything should be affirming, and that there's no room for dissent," Bowers said. "I think that's a mistake."

* * *

Bowers is not only among the most respected gender surgeons in the world but easily one of the most prolific: she has built or repaired more than 2,000 vaginas, the procedure known as vaginoplasty. She rose to celebrity status appearing on the hit reality-television show "I Am Jazz," which catalogues and choreographs the life of Jazz Jennings, arguably the country's most famous transgender teen.

In January 2019, Jeanette Jennings threw her famous daughter a "Farewell to Penis" party. Over a million viewers looked in on guests feasting on meatballs and miniature wieners in the Jennings' Mediterranean-style Florida home. Family and friends cheered as Jazz sliced into a penis-

shaped cake. The rather complicated upcoming procedure came to seem as little more than a Sweet Sixteen.

By that point, Jazz was already Time magazine's top 25 most influential teen, the co-author of a bestselling children's book and the inspiration for a plastic doll. She had served as youth ambassador to the Human Rights Campaign, and she had about one million Instagram followers. Hers was no longer just a personal story but an advertisement for a lifestyle and an industry.

On the day of the procedure — dutifully recorded for Instagram — Jazz's sister, Ari, teasingly wiggled a sausage in front of the camera. As Jazz was about to be wheeled into the operating room, she snapped her fingers and said, "Let's do this!"

The vaginoplasty she underwent is what surgeons call a "penile inversion," in which surgeons use the tissue from the penis and testicles to create a vaginal cavity and clitoris. With grown men, a penile inversion was eminently doable. With Jazz, it was much more difficult.

Like thousands of adolescents in America treated for gender dysphoria (severe discomfort in one's biological sex), Jazz had been put on puberty blockers. In Jazz's case, they began at age 11. So at age 17, Jazz's penis was the size and sexual maturity of an 11-year-old's. As Bowers explained to Jazz and her family ahead of the surgery, Jazz didn't have enough penile and scrotal skin to work with. So Bowers took a swatch of Jazz's stomach lining to complement the available tissue.

At first, Jazz's surgery seemed to have gone fine, but soon after she said experienced "crazy pain." She was rushed back to the hospital, where Dr. Jess Ting was waiting. "As I was getting her on the bed, I heard something go pop," Ting said in an episode of "I Am Jazz." Jazz's new vagina — or neovagina, as surgeons say — had split apart.

✦ ✦ ✦

Gender dysphoria, which Jazz had suffered from since age two, is very real, and by all accounts, excruciating. For the nearly 100-year diagnostic history of gender dysphoria, it overwhelmingly afflicted boys and men, and it began in early childhood (ages two to four). According to the DSM-V, the latest edition of the historical rate of incidence was .01 percent of males (roughly one in 10,000).

For decades, psychologists treated it with "watchful waiting" — that is, a method of psychotherapy that seeks to understand the source of a child's gender dysphoria, lessen its intensity, and ultimately help a child grow more comfortable in her own body.

Since nearly seven in 10 children initially diagnosed with gender dysphoria eventually outgrew it — many go on to be lesbian or gay adults — the conventional wisdom held that, with a little patience, most kids would come to accept their bodies. The underlying assumption was children didn't always know best.

But in the last decade, watchful waiting has been supplanted by "affirmative care," which assumes children *do* know what's best. Affirmative care proponents urge doctors to corroborate their patients' belief that they are trapped in the wrong body. The family is pressured to help the child transition to a new gender identity — sometimes having been told by doctors or activists that, if they don't, their child may eventually commit suicide. From there, pressures build on parents to

begin concrete medical steps to help children on their path to transitioning to the "right" body. That includes puberty blockers as a preliminary step. Typically, cross-sex hormones follow and then, if desired, gender surgery.

The widespread use of puberty blockers can be traced to the Netherlands. In the mid-1990s, Peggy Cohen-Kettenis, a psychologist in Amsterdam who had studied young people with gender dysphoria, helped raise awareness about the potential benefits of blockers — formerly used in the chemical castration of violent rapists. Pharmaceutical companies were happy to fund studies on the application of blockers in children, and, gradually, what's called the Dutch Protocol was born. The thinking behind the protocol was: Why make a child who has suffered with gender dysphoria since preschool endure puberty, with all its discomforts and embarrassments, if that child were likely to transition as a young adult? Researchers believed blockers' effects were reversible — just in case the child did not ultimately transition.

Cohen-Kettenis later grew doubtful about that initial assessment. "It is not clear yet how pubertal suppression will influence brain development," she wrote in the European Journal of Endocrinology in 2006. Puberty is not merely a biochemical development; it is also "a psycho-social event that occurs in concert with one's peers," Doctor William Malone, an endocrinologist and member of the Society for Evidence Based Gender Medicine, told me. Hormones do not merely stimulate sex organs during puberty; they also shower the brain.

But at the very moment when Dutch researchers were beginning to raise concerns about puberty blockers, American health providers discovered it. In 2007, the Dutch Protocol arrived at Boston Children's Hospital, one of the preeminent children's hospitals in the nation. It would soon become the leading course of treatment for all transgender-identified children and adolescents in the United States. One of them was Jazz Jennings.

* * *

In 2012, a surgeon implanted a puberty blocker called Supprelin in Jazz's upper arm to delay the onset of facial hair and the deepening of her voice, among other things. Without these conventional masculine features, it would be easier, down the road, for doctors to make her look more feminine — more like the budding young woman she felt she was deep inside.

At the time, doctors knew less than they do now about the effects of puberty blockers. "When you enter a field like this where there's not a lot of published data, not a lot of studies, the field is in its infancy, you see people sometimes selling protocols like puberty blockers in a dogmatic fashion, like, 'This is just what we do,'" Bowers told me.

Once an adolescent has halted normal puberty and adopted an opposite-sex name, Bowers said: "You're going to go socially to school as a girl, and you've made this commitment. How do you back out of that?"

Another problem created by puberty blockade — experts prefer "blockade" to "blockage" — was lack of tissue, which Dutch researchers noted back in 2008. At that time, Cohen-Kettenis and other researchers noted that, in natal males, early blockade might lead to "non-normal pubertal phallic growth," meaning that "the genital tissue available for vaginoplasty might be less than optimal."

But that hair-raising warning seems to have been lost in the trip across the Atlantic.

Many American gender surgeons augment the tissue for constructing neovaginas with borrowed stomach lining and even a swatch of bowel. Bowers draws the line at the colon. "I never use the colon," she said. "It's the last resort. You can get colon cancer. If it's used sexually, you can get this chronic colitis that has to be treated over time. And it's just in the discharge and the nasty appearance and it doesn't smell like vagina."

The problem for kids whose puberty has been blocked early isn't just a lack of tissue but of sexual development. Puberty not only stimulates growth of sex organs. It also endows them with erotic potential. "If you've never had an orgasm pre-surgery, and then your puberty's blocked, it's very difficult to achieve that afterwards," Bowers said. "I consider that a big problem, actually. It's kind of an overlooked problem that in our 'informed consent' of children undergoing puberty blockers, we've in some respects overlooked that a little bit."

Nor is this a problem that can be corrected surgically. Bowers can build a labia, a vaginal canal and a clitoris, and the results look impressive. But, she said, if the kids are "orgasmically naive" because of puberty blockade, "the clitoris down there might as well be a fingertip and brings them no particular joy and, therefore, they're not able to be responsive as a lover. And so how does that affect their long-term happiness?"

Few, if any, other doctors acknowledge as much. The Mayo Clinic, for instance, does not note that permanent sexual dysfunction may be among puberty blockers' risks. St. Louis Children's Hospital doesn't mention it, either. Oregon Health & Science University Children's Hospital and University of California at San Francisco don't. Nor was there any mention of sexual dysfunction in a recent New York Times story, "What Are Puberty Blockers?"

Jack Turban, the chief fellow in child and adolescent psychiatry at Stanford University School of Medicine, wrote, in 2018: "The only significant side effect is that the adolescent may fall behind on bone density."

But lack of bone density is often just the start of the problem. Patients who take puberty blockers almost invariably wind up taking cross-sex hormones — and this combination tends to leave patients infertile and, as Bowers made clear, sexually dysfunctional.

On an episode of "I Am Jazz," Jazz revealed that she had never experienced an orgasm and may never be able to. But she remains optimistic. "I know that once I fall in love and I really admire another individual that I'm going to want to have sex with them," Jazz said at 16, in an episode that aired in July of 2017.

In the year after her operation, Jazz would require three more surgeries, and then defer Harvard College for a year to deal with her depression. In 2021, she opened up about a binge-eating disorder that caused her to gain nearly 100 pounds in under two years.

Jazz has insisted she has "no regrets" about her transition. (I reached out to Jazz for an interview and never heard back). But subjecting patients to a course of serious interventions that cannot be scrutinized — even by experts — without one risking being tarred as anti-trans seems unlikely to be in anyone's best interest.

Bowers told me she now finds early puberty blockade inadvisable. "I'm not a fan of blockade at Tanner Two anymore, I really am not," she told me, using the clinical name of the moment when the first visible signs of

puberty manifest. "The idea all sounded good in the very beginning," she said. "Believe me, we're doing some magnificent surgeries on these kids, and they're so determined, and I'm so proud of so many of them and their parents. They've been great. But honestly, I can't sit here and tell you that they have better — or even as good — results. They're not as functional. I worry about their reproductive rights later. I worry about their sexual health later and ability to find intimacy."

Bowers knows what the loss of fertility and sexual intimacy might entail: She has three children, all born before she transitioned, and she spent a decade tending to victims of female genital mutilation. "Those women, a lot of them experience broken relationships because they cannot respond sexually," she said. "And my fear about these young children who never experience orgasm prior to undergoing surgery are going to reach adulthood and try to find intimacy and realize they don't know how to respond sexually."

* * *

In 2007, the year the U.S. began implementing the Dutch Protocol, the U.S. had one pediatric gender clinic, and it overwhelmingly served patients like Jazz: natal males who expressed discomfort in their bodies in the earliest stages of childhood. (At age 2, Jazz reportedly asked Jeanette when the good fairy would turn him into a girl. Jazz's own social transition did not appear to proceed from peer influence and predated social media.)

Today, the U.S. has hundreds of gender clinics. Most patients are not natal males, like Jazz, but teenage girls. I wrote a book about these girls, "Irreversible Damage," which was based on interviews with them and their families. Peer influence and exposure to trans influencers on social media play an outsized role in their desire to escape womanhood. Unlike the patients of the Dutch Protocol, who were screened for other mental health comorbidities, these young women almost always suffer from severe anxiety and depression or other significant mental health problems — and those problems are often overlooked or ignored.

When public health researcher and former Brown University Professor Lisa Littman dubbed this phenomenon "rapid onset gender dysphoria" in 2018, the university apologized for her paper and ultimately pushed her out. Activists called the hypothesis of a social contagion among teen girls a "poisonous lie used to discredit trans people."

But Littman's research about the sudden spike in teen girl trans-identification has become increasingly difficult to deny: A recent survey by the American College Health Association showed that, in 2008, one in 2,000 female undergraduates identified as transgender. By 2021, that figure had jumped to one in 20.

While both Anderson and Bowers pointed out that "ROGD" has yet to be accepted as a diagnosis, Anderson said: "At our clinic at UCSF, for two years now running, we're running two to one natal females to natal males." Two to one.

"As for this ROGD thing," Bowers said, "I think there probably are people who are influenced. There is a little bit of 'Yeah, that's so cool. Yeah, I kind of want to do that too.'"

Anderson agreed that we're likely to see more regret among this teenage-girl population. "It is my considered opinion that due to some of the — let's see, how to say it? what word to choose? — due to some of the, I'll call it just 'sloppy,' sloppy healthcare work, that we're going to have more young

adults who will regret having gone through this process. And that is going to earn me a lot of criticism from some colleagues, but given what I see — and I'm sorry, but it's my actual experience as a psychologist treating gender variant youth — I'm worried that decisions will be made that will later be regretted by those making them."

What, exactly, was sloppy about the healthcare work? "Rushing people through the medicalization, as you and others have cautioned, and failure — *abject* failure — to evaluate the mental health of someone historically in current time, and to prepare them for making such a life-changing decision," Anderson said.

I asked Bowers about the rise of detransitioners, young women who have come to regret transitioning. Many said they were given a course of testosterone on their first visit to a clinic like Planned Parenthood. "When you have a female-assigned person and she's feeling dysphoric, or somebody decides that she's dysphoric and says your eating disorders are not really eating disorders, this is actually gender dysphoria, and then they see you for one visit, and then they recommend testosterone — red flag!" Bowers said. "Wake up here."

*Abigail Shrier is the author of "Irreversible Damage," which the Economist named one of the best books of 2020. Read more of her work at her newsletter, The Truth Fairy.*

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Steven N. Oct 4, 2021
At 2 years old, Jazz did not experience gender dysphoria, Jazz's parents did.
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ThinkPieceOfPie Oct 4, 2021
They're not creating a vagina by inverting a penis, anymore than a surgeon is creating a younger person by performing a facelift. At best it's a facsimile, at worst it's a disaster--the necessity for follow up surgeries is very high, from 40-60%, with as noted, limited function. Of course, a child doesn't understand what is at risk when they are 2, or 4 or 11. As Abigail has written elsewhere, some of these adolescent girls having breast amputated & taking testosterone haven't had a first kiss.
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# Continuation of Gender-affirming Hormones Among Transgender Adolescents and Adults

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## Abstract

**Introduction:** Concerns about future regret and treatment discontinuation have led to restricted access to gender-affirming medical treatment for transgender and gender-diverse (TGD) minors in some jurisdictions. However, these concerns are merely speculative because few studies have examined gender-affirming hormone continuation rates among TGD individuals.

**Methods:** We performed a secondary analysis of 2009 to 2018 medical and pharmacy records from the US Military Healthcare System. We identified TGD patients who were children and spouses of active-duty, retired, or deceased military members using International Classification of Diseases-9/10 codes. We assessed initiation and continuation of gender-affirming hormones using pharmacy records. Kaplan-Meier and Cox proportional hazard analyses estimated continuation rates.

**Results:** The study sample included 627 transmasculine and 325 transfeminine individuals with an average age of 19.2 ± 5.3 years. The 4-year gender-affirming hormone continuation rate was 70.2% (95% CI, 63.9-76.5). Transfeminine individuals had a higher continuation rate than transmasculine individuals 81.0% (72.0%-90.0%) vs 64.4% (56.0%-72.8%). People who started hormones as minors had higher continuation rate than people who started as adults 74.4% (66.0%-82.8%) vs 64.4% (56.0%-72.8%). Continuation was not associated with household income or family member type. In Cox regression, both transmasculine gender identity (hazard ratio, 2.40; 95% CI, 1.50-3.86) and starting hormones as an adult (hazard ratio, 1.69; 95% CI, 1.14-2.52) were independently associated with increased discontinuation rates.

**Discussion:** Our results suggest that >70% of TGD individuals who start gender-affirming hormones will continue use beyond 4 years, with higher continuation rates in transfeminine individuals. Patients who start hormones, with their parents' assistance, before age 18 years have higher continuation rates than adults.

**Key Words:** transgender gender dysphoria, sex-hormones, treatment, adolescent, adult

**Abbreviations:** ICD, International Classification of Diseases; MHS, Military Healthcare System; TGD, transgender and gender-diverse

Approximately 1 in 250 adults or almost 1 million adults in the United States identify as transgender (1). The frequency of adults, and especially younger adults, reporting a gender-diverse identity has increased over time (1). Some persons who identify as transgender or gender-diverse (TGD) will seek treatment with gender-affirming hormones to align their bodies more closely with their gender identity (2). Medical treatment of people who identify as transgender improves body satisfaction, quality of life, and mental health (2, 3). However, many of these treatments are not entirely reversible (4).

Some adolescents or adults who take gender-affirming hormones subsequently elect to stop treatment (5, 6). Most adults who stop gender-affirming hormones report doing so for reasons unrelated to a change in gender identity, such as pressure from family, difficulty obtaining employment, or discrimination (7). Also, discontinuation of gender-affirming hormones does not necessarily represent a failure in treatment or initial decision-making. Some TGD adolescents and adults who start and then discontinue gender-affirming hormones experience use of hormones as an important part of consolidating their gender identity and experience no regret over the use of hormones despite some permanent effects (5, 7, 8). However, a portion of TGD individuals who pursue gender-affirming medical or surgical affirmation do express regret over the permanent effects of treatment (5, 9, 10). In a

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metanalysis of 7928 TGD individuals who had gender confirmation surgery, 1% expressed regret after surgery (9). The most prevalent reason for regret was psychosocial circumstances, particularly from a lack of social support or negative reactions from family and employers (9). Concerns about future regret after medical or surgical affirmation and the capacity of adolescents to provide informed assent for this treatment, with the assistance of their families, have led legislators and members of the judiciary in some locations to attempt to limit access to these interventions for youths (11-14). For example, in the United States, 16 states do not provide coverage for gender-affirming medical care through public insurance for those with incomes below the federal poverty line (Medicaid). Two states have outlawed gender-affirming care for minors, another state has taken administrative action to classify gender-affirming medical care for minors as child abuse, and 20 state legislatures are considering laws to make some or all aspects of gender-affirming medical care for minors illegal during the 2022 legislative session (13, 14). In the United Kingdom, a court ruled that gonadotropin-releasing hormone analogues could not be administered to transgender patients younger than age 16 years without obtaining a court order and suggested that older TGD adolescents should be required to obtain a court order before starting gender-affirming hormones (12).

Clinical guidelines for medical affirmation of persons who identify as TGD suggest that the rate of "de-transition" among postpubertal adolescents and adults is rare, but few studies have assessed the actual rate of treatment discontinuation (6, 7, 10). In a cross-sectional study of a self-selected sample of 27 715 TGD adults in the United States, 61.9% reported a history of social affirmation (ie, changing name, pronouns, appearance), 44.8% reported medical affirmation with hormones, and 19.5% reported surgical affirmation (7). A history of stopping affirmation and reverting to living in their sex assigned at birth for at least a little while was more common among people who only engaged in social affirmation (30.8%) than among people who had started medical (9.1%) or surgical (6.9%) affirmation (7). Among TGD adults who stopped affirmation, 82.5% reported at least 1 external factor, such as pressure from family and community or difficulty with employers as a reason to stop and 15.9% reported at least 1 internal factor, such as psychological distress and uncertainty or fluctuation in gender identity as a reason to stop. Only 5% of people who stopped affirmation reported stopping because they realized that changing gender was no longer desired. At the time of the survey, 68% of people who had discontinued affirmation had subsequently restarted (7). In a 1-year chart review of 174 adults treated at a national gender clinic in the United Kingdom, 12 (6.9%) patients discontinued medical affirmation during a 1-year period. Of these 12 patients, 4 later reengaged in gender-affirming care (6). At the Center of Expertise on Gender Dysphoria, a specialized gender clinic that provides > 95% of all gender-affirming medical and surgical care in the Netherlands, > 75% of TGD adults who started gender-affirming hormones between 1972 and 2014 had completed 1.5 years of gender-affirming hormones and met criteria for gonadectomy by the end of 2015 (10). However, this study did not assess hormone continuation rates directly.

Prior studies of treatment discontinuation rates among TGD adults undergoing medical affirmation have been limited to small samples of patients from specialized gender clinics who stopped coming in for appointments or a cross-sectional study of self-reported de-transition rates among adults who continue to identify as TGD and obtained hormonal therapy both in and outside the health care system (6, 7, 15). These studies found low levels of treatment discontinuation. The discontinuation that did occur was frequently temporary and unrelated to a change in gender identity. However, none of these studies have examined discontinuation rates among minors or assessed objective measures of medication continuation. Therefore, in the current study, we assessed the rate of treatment discontinuation after starting gender-affirming hormones among TGD adolescents and adults and identified demographic groups at higher risk of discontinuation of gender-affirming hormones. We hypothesized that gender-affirming hormone continuation rates will not differ between individuals who start hormones before or after reaching the age of legal majority.

## Methods

This study is a secondary analysis of US Military Healthcare System's (MHS) medical and pharmacy billing records from October 2009 to September 2018 for family members of active-duty service members. Data were extracted from the Military Healthcare Data Repository, which includes insurance billing records of all inpatient and outpatient care and outpatient prescriptions provided to individuals enrolled in the military's health care benefit (TRICARE) both domestically and abroad at military and civilian treatment facilities.

We used the following inclusion criteria for our study:

- The patient was a child or spouse of an active duty, retired, or deceased servicemember at the time of the initial TGD-related diagnosis
- Patient had 2 or more medical encounters for a TGD-related diagnosis on different days (International Classification of Diseases [ICD] codes: ICD-9 302.6, 302.85 302.50, 302.51, 302.52, 302.53, and ICD-10 F64.0, F64.1, F64.2, F64.8, F64.9, Z87.890)
- Patient received an initial prescription for gender-affirming hormones between 30 days before the date of their first TGD-related medical encounter and 90 days after their date of his or her last TGD-related medical encounter
- Patient received at least 2 prescriptions for gender-affirming hormones.

We excluded active-duty servicemembers and military retirees from our analysis because servicemembers are required to obtain permission from the military service to transition while on active duty (16) and follow rules governing gender affirmation and use of gender-affirming hormones. We felt this would make them a distinctly different population from their family members and it would be inappropriate to combine them.

Use of ICD 9/10 codes to identify TGD individuals is a validated methodology. In a previous study, these codes were well-matched with clinical text notes in identification of TGD individuals (17, 18). We required patients to have 2 or more encounters with an associated TGD diagnosis to limit false-positive identifications.

We used medical and pharmacy records to identify TGD individuals who started gender-affirming hormones. We identified a TGD individual's sex assigned at birth using the sex recorded at the first encounter, for any reason, in our dataset. Then, we used pharmacy billing records to identify prescriptions and days supplied of gender-affirming hormones for both initial prescriptions and refills. We defined gender-affirming hormone prescriptions as prescriptions for testosterone issued to individuals coded as female at their first encounter and prescriptions for estrogens issued to individuals coded as male at their first encounter. We attempted to limit our sample to patients using gender-affirming hormones by requiring patients to obtain at least 2 prescriptions for gender-affirming hormones and obtain the initial prescription for gender-affirming hormones between 30 days before the date of their first TGD-related medical encounter and 90 days after their date of their last TGD-related medical encounter.

We collected patient age at the initial TGD-related encounter, age at the time of the first prescription for gender-affirming hormones, family role (spouse vs offspring), determined if the patient started gender-affirming hormones before or after gender-affirming health care became an officially covered military benefit for family members on September 1, 2016, and military rank of the insurance sponsor (16). We used military rank (enlisted vs officer) of the patient's insurance sponsor at the time of the last medical encounter in our dataset as a proxy for family income. Officers are required to have a 4-year college degree before military service, whereas enlisted servicemembers are only required to have a high school degree or equivalent. Officers also have a higher average base pay than enlisted servicemembers. In 2019, the average base salary for servicemembers with 10 years of military service was $48 864 for enlisted servicemembers and $86 832 for officers (19).

We used Kaplan-Meier analyses to estimate the rate of discontinuation of gender-affirming hormones after starting treatment (20). We identified patients as discontinuing their gender-affirming hormones if they failed to obtain another prescription for gender-affirming hormones more than 90 days after completing their most recent prescription. Patients were censored from further analysis if they were no longer obtaining health care in the MHS (reached the date of their most recent medical encounter in the database).

We used the log-rank test to assess the influence of sex assigned at birth, age at initiation of gender-affirming hormones (< 18 years vs 18 years of age and older), family income (officer vs enlisted insurance sponsor), family role (spouse vs offspring), and if the patient started gender-affirming hormones before or after gender-affirming care became an official TRICARE benefit on September 1, 2016 (16). We limited our analysis of the influence of official insurance coverage to the first 22 months after starting gender-affirming hormones because we only had 22 months of data after the change occurred. We also used Cox proportional hazard analysis to determine the independent influence of our demographic factors on discontinuation rates. This study was institutional review board-approved as a secondary analysis of preexisting records. Statistical significance was defined as $P < 0.05$.

## Results

Of the 952 individuals in our study, 66% were assigned female at birth, 61% were ≥ 18 years old, 71% had an enlisted insurance sponsor, and 90% were children of active duty, retired, or deceased servicemembers (Table 1, Fig. 1). Patients who discontinued obtaining refills of gender-affirming hormones continued to obtain medical care in the MHS for an average of 324 days (SD, 274; range, 91-1602) after they completed their final prescription for gender-affirming hormones (Table 1). The number of patients initiating gender-affirming hormones increased during the study period, and 58% of patients had their first appointment for transgender-related care during the last 22 months of our study (September 2016-June 2018), after gender-affirming care was included as an officially covered TRICARE benefit for family members (14) (Table 1 and Fig. 2).

In our sample, 70.2% (95% CI, 63.9-76.5) of patients who started medical affirmation continued to fill prescriptions for gender-affirming hormone for at least 4 years (Fig. 1). Transfeminine individuals were more likely to continue obtaining gender-affirming hormones in the MHS than transmasculine individuals. The 4-year continuation rate for transfeminine individuals was 81.0% (95% CI, 72.0-90.0) vs 64.4% (95% CI, 56.0-72.8) for transmasculine individuals (log-rank test $\chi^2$, 11.860) (Fig. 3). Patients who were younger than 18 years of age when starting hormones were less likely to discontinue use than patients who were 18 years of age and older. The 4-year continuation rate among people who started treatment under 18 years of age was 74.4% (95% CI, 66.0-82.8) and the rate among people who were ≥ 18 years was 64.4% (95% CI, 56.0-72.8) (log-rank test $\chi^2$, 4.461) (Fig. 4). Family income (enlisted vs officer insurance sponsor; log-rank test $\chi^2$, 0.013) and family member type (spouse vs child; log-rank test $\chi^2$, 1.002) had no influence on continuation rates. Starting hormones before or after official coverage of gender-affirming medical care by TRICARE on September 1, 2016, also had no influence on continuation rates (log-rank test $\chi^2$, 0.728).

**Table 1.** Sample demographics (n = 952)

| Demographic group | % |
|---|---|
| Gender identity | |
| Transfeminine | 34.1 |
| Transmasculine | 65.9 |
| Age at Initiation of Gender-Affirming Hormones | |
| <18 years old | 39.1 |
| ≥18 years old | 60.9 |
| Insurance sponsor rank | |
| Enlisted (high school or some college) | 70.6 |
| Officer (college education and beyond) | 29.4 |
| Family member type | |
| Dependent child | 90.1 |
| Spouse | 9.9 |
| Started gender-affirming hormones before or after approval of gender-affirming care as an official TRICARE benefit | |
| Before approval (October 2009-August 2016) | 42 |
| After approval (September 2016-June 2018) | 58.0 |
| | Mean ± SD (range) |
| Days between stopping gender-affirming hormones and last visit | 324 ± 274 (91-1602) |

Gender-affirming medical care became an authorized TRICARE benefit for dependents on September 1, 2016.

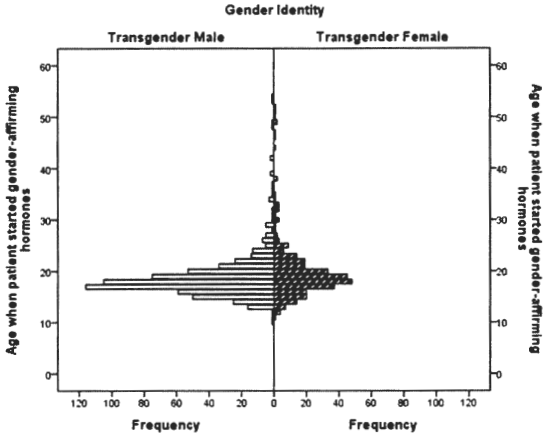


**Figure 1.** Age at initiation of gender-affirming hormones by sex assigned at birth.

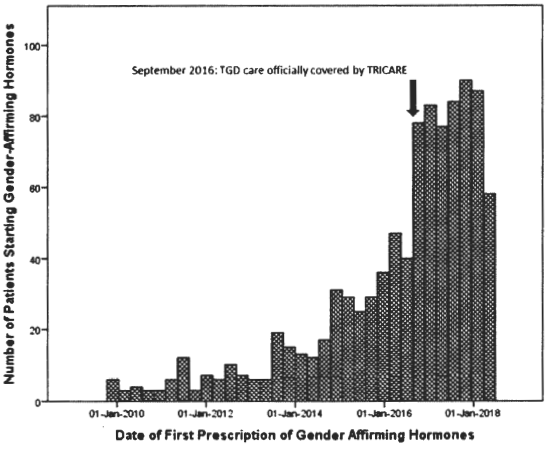


**Figure 2.** Incidence of gender-affirming hormone initiation over time.

In a Cox regression model containing assigned gender and age at initiation of hormones, transmasculine individuals were more than twice as likely to stop obtaining hormones in the MHS compared with transfeminine individuals (hazard ratio 2.40; 95% CI, 1.50-3.86) and people who started hormones after turning 18 years of age were more likely to stop obtaining gender-affirming hormones compared with people who started hormones *before age* 18 years (hazard ratio, 1.69; 95% CI, 1.14-2.52) (Table 2).

## Discussion

Our study documented higher gender-affirming hormone continuation rates among transfeminine individuals and by patients who started hormones before reaching the age of legal majority in a population with universal insurance and access to low or no-cost medical and pharmaceutical care. Family socioeconomic status, family member type, and the official status of gender-affirming care as a TRICARE-covered benefit at the time the patient began taking gender-affirming hormones had no influence on continuation of gender-affirming hormones.

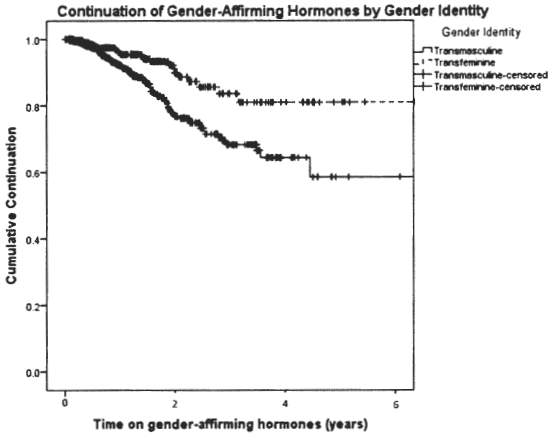


**Figure 3.** Continuation of gender-affirming hormones by gender identity.

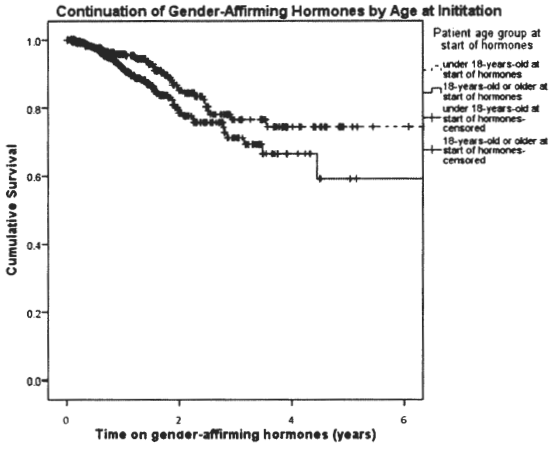


**Figure 4.** Continuation of gender-affirming hormones by age at initiation.

**Table 2.** Multivariate regression: independent association of age and gender identity on discontinuation of gender-affirming hormones

| Demographic factor | Risk of discontinuing of gender-affirming hormones |
|---|---|
| Gender identity | Hazard ratio (95% CI) |
| Transfeminine | Reference |
| Transmasculine | 2.40 (1.50-3.86) |
| Age at initiation of gender-affirming hormones | |
| <18 years old | Reference |
| ≥18 years old | 1.69 (1.14-2.52) |

We noted a higher hormone continuation rate among TGD individuals who were younger than 18 years old at the time of first use of gender-affirming hormones compared with those who were aged 18 years and older when starting hormones. This has not been documented in previous studies.

The patients who started before turning 18 years would require parental consent for this treatment, whereas those aged 18 years and older do not. Parents who consent to use

of gender-affirming hormones likely have a higher level of support for their child's gender affirmation on average than parents who do not. Parental support plays an important role in the mental health of TGD youth (21). A prior study of adults found that lack of family support for a TGD individual's gender was associated with a history of discontinuing social or medical gender affirmation (7). Higher parental support may explain the higher continuation rate among patients who start gender-affirming hormones as minors compared with people who start as adults.

Regardless of the reason for the higher hormone continuation rate among TGD youth, this finding provides support for the idea that TGD individuals below the age of legal majority, with the assistance of their parents or legal guardians and health care providers, can provide meaningful informed assent for gender-affirming hormones and do not appear to be at a higher risk of future discontinuation of gender-affirming hormones because of their young age alone.

There was a higher gender-affirming hormone continuation rate among transfeminine individuals compared with transmasculine individuals in our study. This has not been observed in previous studies. The reasons for this difference cannot be determined using the data from this study. If confirmed in future studies, this would suggest a need to ensure routine screening of transmasculine patients for osteoporosis risk after oophorectomy, especially if this procedure occurs at a younger age.

As in a previous study, there was an increase in the number of patients presenting for gender-affirming care over time (10, 22). However, unlike previous studies, the coverage status of gender-affirming care in our study changed over time. We noted a large increase in patients presenting for care after designation of gender-affirming care as a covered benefit in the MHS.

This leads to a concern that patients and providers who were engaging in gender-affirming care in the MHS before it was officially sanctioned were different than the patients and providers who did not start engaging in gender-affirming care in the MHS until after it was officially sanctioned. However, we did not see a difference in continuation rates between these 2 groups.

The large number of adolescents in our study, the longitudinal data for TGD individuals in a naturalistic and varied clinical setting, use of objective measures of ongoing hormone use, and comparison of gender-affirming hormone use among adolescents and adults are unique strengths of our study, but there are several limitations that must be noted.

We only collected information on medication refills obtained using a single insurance plan. If patients elected to pay out of pocket for hormones, accessed hormones through nonmedical channels, or used a different insurance plan to pay for treatment before and/or after obtaining gender-affirming hormones using TRICARE insurance, we did not capture this information. This means that our findings are likely an underestimate continuation rates among transgender patients.

We attempted to address our concern about overestimating discontinuation rates by only recording cessations among patients who stopped obtaining prescriptions for gender-affirming hormones while continuing to receive medical care using TRICARE insurance for more than 90 days. We would miscategorize patients as terminations if patients elected to obtain their gender-affirming medications using alternative payment options while continuing to receive other medical care using TRICARE.

However, the medication copay for generic medications purchased using TRICARE is quite low at $0 to $3 per prescription when compared with other private insurance programs in the United States. For example, a transgender woman using TRICARE insurance would pay a total of $0 to $72 for a 1-year supply of estrogen and spironolactone. For transgender women with private insurance in the United States, the out-of-pocket expenses for gender-affirming medications would be $230 per year and $500 per year for transgender men with insurance (23). This cost difference makes it less likely that a patient would continue to use TRICARE for medical care but elect to use a different insurer to obtain gender-affirming hormones.

This study was limited by reliance on accuracy of billing data and lack of patient-level data. We cannot know why patients in our study stopped obtaining refills of gender-affirming hormones using their TRICARE insurance. Many factors inform an individual patient's desire or ability to continue obtaining refills of gender-affirming hormones including gender identity, treatment intentions, difficulty finding a provider who offers gender-affirming care, satisfaction with treatment outcomes, or social context.

In a previous study, only 16% of TGD individuals who stopped gender-affirming hormones cited a change in gender identity or mental health concerns as a reason to discontinue social or medical gender affirmation (7). Many of the individuals who reported stopping gender-affirming hormones reported subsequently restarting treatment or the intention to restart treatment (7).

The lack of patient level detail in our study makes it impossible to predict individual patient outcomes with our findings. However, our findings can still be useful to inform policy makers or legislators when assessing the risk of transgender care for minors.

A related limitation is our reliance on the gender marker at the first medical encounter as a proxy for sex assigned at birth. It is possible that this information is wrong or reflects a change in gender marker that occurred before the beginning of our study interval. We attempted to address this concern using our inclusion criteria. For example, with our inclusion criteria, we would incorrectly include a cis-male patient who was assigned male at birth, changed the sex recorded in the electronic medical record to female, received a transgender-related diagnosis at 2 different medical encounters, and then elected to fill 2 prescriptions for testosterone during the same time period he had the 2 transgender-related medical encounters. This combination would likely be a rare event and, if present, have a minimal impact on the findings of the study.

Before September 2016, gender-affirming care was not an officially covered health care benefit under TRICARE (16). Patients may have had trouble finding a TRICARE-approved clinician who would prescribe hormones or a pharmacy that would fill the prescription in their area, especially in cases where they initiated care in 1 location and then they or their family moved. However, we did not see a difference in continuation rates between patients who started hormones before or after gender-affirming care becoming an officially covered benefit.

Determining if these differences in continuation rates exist in other groups of TGD individuals and determining if there

are differences in reasons for discontinuation by gender identity or age is an important topic for future studies. Future prospective studies should investigate the rate of hormone discontinuation between transfeminine and transmasculine individuals to determine whether the same pattern of discontinuation is observed. The reasons for discontinuing treatment and whether patients anticipate restarting treatment at a future date would also be important to assess. Finally, it would be useful to prospectively assess the number of TGD individuals who experience regret after starting gender-affirming hormones and if there are any associated factors that can be used to identify patients at a higher risk of regret. This would assist clinicians in providing nuanced counseling regarding treatment options to TGD individuals before starting hormones.

## Conclusion

In our study, transmasculine individuals were more likely to discontinue use of gender-affirming hormones during the first 4 years of use than transfeminine individuals. We also found that individuals who start gender-affirming hormones before reaching the age of legal majority are less likely to subsequently discontinue use when compared with individuals who start hormones after becoming a legal adult. If replicated in future studies, the improved continuation rate among patients who are not legal adults at the time of treatment should provide some reassurance to those concerned about the ability of minors to provide informed assent to use of gender-affirming hormones. A higher continuation rate among minors could also be used to inform the actions of legislators and judges who wish to prohibit gender-affirming treatment for minors to protect them from the consequences of health care decisions they make with the assistance of their parents and health care providers.

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## Disclosures

The authors report no competing interests.

## Data Availability

A deidentified copy of the dataset for this study is available from the authors on reasonable request

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Ex. 25



# Continuation of gender-affirming hormones in transgender people starting puberty suppression in adolescence: a cohort study in the Netherlands

Maria Anna Theodora Catharina van der Loos, Sabine Elisabeth Hannema, Daniel Tatting Klink, Martin den Heijer, Chantal Maria Wiepjes


## Summary

**Background** In the Netherlands, treatment with puberty suppression is available to transgender adolescents younger than age 18 years. When gender dysphoria persists testosterone or oestradiol can be added as gender-affirming hormones in young people who go on to transition. We investigated the proportion of people who continued gender-affirming hormone treatment at follow-up after having started puberty suppression and gender-affirming hormone treatment in adolescence.

**Methods** In this cohort study, we used data from the Amsterdam Cohort of Gender dysphoria (ACOG), which included people who visited the gender identity clinic of the Amsterdam UMC, location Vrije Universiteit Medisch Centrum, Netherlands, for gender dysphoria. People with disorders of sex development were not included in the ACOG. We included people who started medical treatment in adolescence with a gonadotropin-releasing hormone agonist (GnRHa) to suppress puberty before the age of 18 years and used GnRHa for a minimum duration of 3 months before addition of gender-affirming hormones. We linked this data to a nationwide prescription registry supplied by Statistics Netherlands (Centraal Bureau voor de Statistiek) to check for a prescription for gender-affirming hormones at follow-up. The main outcome of this study was a prescription for gender-affirming hormones at the end of data collection (Dec 31, 2018). Data were analysed using Cox regression to identify possible determinants associated with a higher risk of stopping gender-affirming hormone treatment.

**Findings** 720 people were included, of whom 220 (31%) were assigned male at birth and 500 (69%) were assigned female at birth. At the start of GnRHa treatment, the median age was 14·1 (IQR 13·0–16·3) years for people assigned male at birth and 16·0 (14·1–16·9) years for people assigned female at birth. Median age at end of data collection was 20·2 (17·9–24·8) years for people assigned male at birth and 19·2 (17·8–22·0) years for those assigned female at birth. 704 (98%) people who had started gender-affirming medical treatment in adolescence continued to use gender-affirming hormones at follow-up. Age at first visit, year of first visit, age and puberty stage at start of GnRHa treatment, age at start of gender-affirming hormone treatment, year of start of gender-affirming hormone treatment, and gonadectomy were not associated with discontinuing gender-affirming hormones.

**Interpretation** Most participants who started gender-affirming hormones in adolescence continued this treatment into adulthood. The continuation of treatment is reassuring considering the worries that people who started treatment in adolescence might discontinue gender-affirming treatment.


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## Introduction

Transgender people diagnosed with gender dysphoria experience distress due to gender incongruence—ie, a discrepancy between their gender identity and sex assigned at birth. Many transgender people desire to align their physique to match their gender identity. Consequently, the development of secondary sex characteristics during puberty can aggravate distress for transgender adolescents.

Around 1998, a revolutionary treatment protocol to suppress pubertal development was introduced in the Netherlands for transgender adolescents.[1,2] Following a thorough diagnostic evaluation, suppression of pubertal development is usually achieved with use of a gonadotropin-releasing hormone agonist (GnRHa). Such suppression of puberty can avert stressful changes in physical characteristics while providing time for a young person's exploration of their gender identity, and bridging the time until a person becomes eligible for gender-affirming hormones. The effects of GnRHa on the gonadal axis are fully reversible.[3]

This protocol became known as the Dutch Protocol and has become part of routine care for adolescents diagnosed with gender dysphoria in many gender identity clinics internationally. However, puberty suppression for individuals under 18 years has recently become a subject of public debate and legal measures have even been taken to ban its use.[4,5] Although short-term studies have shown beneficial effects of puberty

## Research in context

### Evidence before this study

Medical treatment consisting of puberty suppression and gender-affirming hormones for people younger than 18 years diagnosed with gender dysphoria has been surrounded by controversy since it was introduced around 20 years ago. Although there has been a steep increase in people requesting this treatment, concerns exist regarding possible regret and discontinuation of gender-affirming hormones in adulthood. To collect evidence on this topic, we searched PubMed with "gender dysphoria", "puberty suppression", and related terms, for literature published between database inception and Aug 31, 2022. A previous study found that 74·4% of individuals who had started gender-affirming hormones before age 18 years were still on gender-affirming hormone treatment 4 years after starting medical treatment. However, it remains unclear what proportion of people who started medical treatment for gender dysphoria specifically with puberty suppression before age 18 years, and who then received gender-affirming hormones, continue gender-affirming hormone treatment into adulthood.

### Added value of this study

We found that most (98%) individuals diagnosed with gender dysphoria who started medical treatment with puberty suppression when younger than 18 years and went on to receive gender-affirming hormones were still receiving gender-affirming hormones at follow-up. Studies on continuation rates of medical treatment in this particular population were absent. Our findings could help guide the public and legal debate regarding initiation of medical treatment for gender dysphoria in young people.

### Implications of all the available evidence

Discontinuation of medical treatment for gender dysphoria in adulthood, among those who start treatment before age 18 years appears to be uncommon in the Netherlands.

suppression for mental and physical outcomes,[6] the treatment is regarded by some people as experimental because long-term follow-up is lacking.

As increasing numbers of adolescents are referred to gender identity clinics around the globe, it is important to answer outstanding questions, such as whether the desire for gender-affirming treatment in adolescence lasts throughout adult life.[7–9] Steensma and colleagues reported in 2011 that 45% of adolescents (ages 14–18 years) with gender incongruence in childhood no longer wanted to transition when they reached adolescence or adulthood.[10] In contrast, a recent study of children (ages 3–12 years) who had socially transitioned (ie, live in their identified gender) found that only 7% did not continue to identify as transgender after 5 years.[11] However, this study did not assess long-term continuation rates of gender-affirming hormone treatment in people who started treatment at a young age. Furthermore, in recent years, an increase in referrals of predominantly people assigned female at birth has been recorded; however, the reason for this is not yet clarified.[12–14]

The aim of this study was therefore to assess the proportion of people who continue gender-affirming hormone treatment in adulthood, after they started GnRHa and gender-affirming hormone treatment in adolescence according to the Dutch Protocol. Additionally, we set out to study whether timing of treatment initiation, reflected by age at first visit, age and puberty stage at start of medical treatment, duration of GnRHa monotreatment (ie, the period between start of GnRHa treatment and addition of gender-affirming hormones) were correlated with gender-affirming hormone treatment discontinuation rates. We also aimed to assess whether sex assigned at birth, year of first visit, and year in which gender-affirming hormone treatment was started were associated with discontinuation of treatment. We additionally investigated whether people who had undergone gonadectomy were more likely to continue treatment.

## Methods

### Study population and design

In this cohort study, we used data from the Amsterdam Cohort Of Gender dysphoria (ACOG).[15] All individuals—children, adolescents, and adults—visiting the gender identity clinic of the Amsterdam UMC, location Vrije Universiteit Medical Center, Netherlands, at least once between its establishment (1972) and Dec 31, 2018, were included in the ACOG dataset. The ACOG dataset contains demographic and clinical data on all of its 8831 participants, extracted from medical records. The ACOG dataset did not include people with disorders of sex development. We included only people receiving a minimum duration of 3 months of GnRHa, which was started when younger than age of 18 years, preceding the start of gender-affirming hormone treatment (start of gender-affirming hormone treatment when younger than 18 years was not a requirement for inclusion).

### Procedures and outcomes

Adolescent individuals could be medically treated at our gender identity clinic if referred by a physician, usually a general practitioner, and were diagnosed with gender dysphoria (Diagnostic and Statistical Manual of Mental Disorders [DSM-IV-TR 2000 or DSM-5 2013], American Psychiatric Association) by the gender identity clinic. People could start on intramuscular or subcutaneous triptorelin, a GnRHa, 3·75 mg every 4 weeks or 11·25 mg every 12 weeks when a Tanner genital stage II or higher for people assigned male at birth or Tanner breast stage II

or higher for those assigned female at birth was reached, usually around age 12 years. If gender dysphoria remained present after treatment was started, and participants met all criteria as defined by the Endocrine Society's guideline for treatment of people with gender dysphoria,[16,17] gender-affirming hormones could be added to induce puberty in eligible adolescents 16 years or older. Gender-affirming hormone treatment consists of oestrogen in people assigned male at birth, and testosterone in those assigned female at birth.[17] Over time, the Dutch Protocol was adapted, enabling adolescents who had already been treated with GnRHa for several years to start gender-affirming hormones from age 15 years. Occasionally, some people started gender-affirming hormones at a younger age than 15 years, for example to reduce growth in case a tall adult height was predicted. GnRHa was usually discontinued in people assigned female at birth when they were on the full, adult dose of testosterone. In people assigned male at birth, GnRHa treatment was continued until gonadectomy. After at least 1 year of gender-affirming hormone treatment, and at a minimum age of 18 years, people became eligible for gender-affirming surgeries. After gonadectomy, treatment with sex hormones become indicated lifelong.

The main outcome of this study was a prescription for gender-affirming hormones at the end of data collection (Dec 31, 2018), which was used as an indicator of ongoing use of gender-affirming hormones. A prescription at the end of data collection was defined in one of two ways: firstly, a gender-affirming hormone prescription in the hospital's prescription registry in 2018. However, at the gender identity clinic of the Amsterdam UMC, long-term follow-up visits are advised at least once every 3 years but some people choose to have these evaluations at another clinic and therefore might have received a prescription from clinicians elsewhere. Therefore, secondly, we (MATCvdL and CMW) linked our study population to data supplied by the national statistical office, Statistics Netherlands (Centraal Bureau voor de Statistiek; CBS) that contained information regarding all drug prescriptions reimbursed under basic health insurance. In the Netherlands health insurance covering basic medical expenses is mandatory for everyone living or working in the country. All gender-affirming hormone treatment must be prescribed by a medical doctor and is fully covered by this basic health insurance. Therefore, all gender-affirming hormones prescribed in the Netherlands are available in the CBS data. In addition, gender-affirming hormone medication is readily available at local pharmacies. It was therefore unlikely that, contrary to some other countries, gender-affirming hormones in the Netherlands are obtained through other resources after the first prescription.

Drug prescriptions in the CBS-database are classified by the Anatomical Therapeutic Chemical (ATC) system.[18] We (MATCvdL and CMW) searched for hormone prescriptions within the following subgroups: A14A, G03A, G03B, G03C, G03D, G03F, G03H, G03X, G04C, H01C, L02A, and L02B. We only searched for people for whom a prescription could not be found in the hospital's 2018 prescription registry.

### Statistical analyses

We reported continuous variables as mean (SD) for normally distributed data. Non-normally distributed data were described as median with IQR. Dichotomous variables were presented as proportions. We used a Cox proportional-hazards model to analyse data. We calculated analysis time as the number of years between the start of gender-affirming hormone treatment and the first terminating event for each participant. Terminating events were either date of last found prescription in people who did not have a prescription at the end of follow-up (Dec 31, 2018) or, where no prescription was found, the date of last visit to the clinic. We censored data for people who had prescriptions at the end of the study. We also censored data of individuals who were deceased or had moved abroad at the time of death or emigration; if the date of death or emigration was not available, the date of last visit to the clinic was used.

Independent variables were sex assigned at birth, age at first visit to the clinic, age at start of GnRHa and at start of gender-affirming hormone treatment, puberty stage at start of GnRHa treatment, duration of GnRHa monotreatment, year of start of gender-affirming hormone treatment, year of first visit, and whether a gonadectomy was done. We did both a univariable analysis and a multivariable analysis. In the multivariable model, we excluded people who had already started hormone treatment elsewhere because year of first visit did not reflect their initial visit to a gender identity clinic, and this would bias the results. Individuals with missing data were also excluded from the particular analysis. The proportional-hazards assumption was tested on the basis of the Schoenfeld residuals in the multivariable model and was not met for sex assigned at birth. Therefore, we stratified the analyses by sex assigned at birth. To check for collinearity, we calculated the variance inflation factor (VIF) for each variable. A VIF greater than 10 was regarded as significant collinearity. Collinearity was found between duration of GnRHa monotreatment, and age at start of GnRHa treatment and age at start of gender-affirming hormone treatment. Duration of GnRHa monotherapy was therefore removed from the model. In the multivariable model without duration of GnRHa monotherapy, all VIF were below 10.

Except for age, which was modelled as a continuous variable, independent variables were dichotomous or categorical. Puberty stage at start of GnRHa treatment was divided into early or late puberty. For people assigned male at birth, a maximum testicular volume of 9 mL was considered early puberty, and a testicular volume above

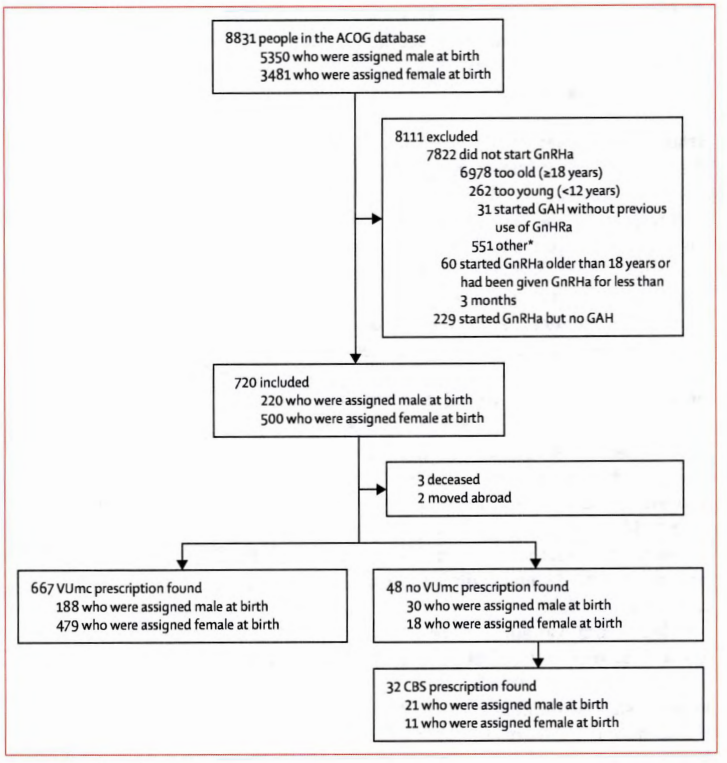


**Figure 1: Flowchart of participants**
ACOG=Amsterdam Cohort of Gender dysphoria. CBS=Centraal Bureau voor de Statistiek (Statistics Netherlands). GAH=gender-affirming hormones. GnRHa=gonadotropin-releasing hormone agonist. VUmc=Vrije Universiteit Medical Center prescription registry. *These people could still be in the diagnostic phase or were not diagnosed with gender dysphoria.

9 mL was considered late puberty. For people assigned female at birth, a Tanner breast stage II was considered early puberty, and stage III or greater was considered late puberty.

To investigate whether there was a difference in continuation of gender-affirming hormones between earlier and more recent years, year of start of gender-affirming hormones was divided in two categories (<2012 or ≥2012). We chose 2012 as the cutoff point because previous research has shown that the sharp increase in referrals of people assigned female at birth occurred around that time.[12]

Our gender identity clinic also provided care to youth who had already started medical treatment elsewhere. The initial dates of start of GnRHa and gender-affirming hormone treatment (taken from the referral letter) were registered for these people and used in the analyses. To avoid bias, these people were excluded when analysing age at first visit in our centre.

Use of CBS data is bound by strict rules to ensure anonymity. Due to low numbers, anonymity could not be guaranteed when stratifying people for both gonadectomy and sex assigned at birth. Therefore, this analysis was only done for the overall study population. We used STATA (15.1) for all data analyses.

Before initiation of the study, the local Medical Ethics Committee confirmed that the Medical Research Involving Human Subjects Act (WMO) did not apply to this study due to the retrospective design, and absence of interventions. The collaboration between the Amsterdam UMC, location Vrije Universiteit Medical Center, and Statistics Netherlands has been approved by the privacy officer of the Amsterdam UMC, location Vrije Universiteit Medical Center, and a lawyer from Statistics Netherlands. All data were reviewed by Statistics Netherlands to verify that the results did not contain any identifiable data.

### Role of the funding source
There was no funding source for this study.

## Results
In total, 720 people (529 [96%] White; 171 had missing ethnicity data) were included in this study (figure 1), of whom 220 (31%) were assigned male at birth and 500 (69%) were assigned female at birth. Their baseline characteristics are shown in table 1. Median duration of gender-affirming hormone treatment by the time of study analysis was 3·5 (IQR 1·5–7·6; range 0·1–20·0) years for people assigned male at birth, and 2·3 (1·2–4·8; range 0·0–15·5) years for those assigned female at birth. Median age at end of data collection was 20·2 (17·9–24·8) years for people assigned male at birth and 19·2 (17·8–22·0) years for those assigned female at birth. Overall, 282 (59%) of all 480 eligible (ie, minimum age of 18 years and at least 1 year of gender-affirming hormone treatment) participants had gonadectomy.

Of all participants, three died and two had moved abroad during the study. For 667 (93%) of the remaining 715 individuals, we found a prescription for gender-affirming hormones consistent with the affirmed gender in the hospital's 2018 prescription registry. For an additional 32 (4%), we found a prescription in the CBS-linked database. There were 16 (2%) people for whom no prescription was found. Of these, nine were assigned male at birth (4% of all 220 people assigned male at birth) and seven were assigned female at birth (1% of all 500 those assigned female at birth). Figure 2 shows a Kaplan-Meier curve for the proportion of people prescribed gender-affirming hormones and duration of gender-affirming treatment. Of the 16 people for whom no prescription was found, 12 (75%) had undergone gonadectomy. For these individuals, no prescriptions were found for sex hormones of the sex assigned at birth either.

In the multivariable model, none of the assessed variables were correlated with finding a prescription or not. Year of start of gender-affirming hormone treatment (<2012 or ≥2012) could not be assessed because the event rate was too low in the groups starting medical treatment

in 2012 or after. All people assigned female at birth for whom a prescription was not found were in late puberty at start of GnRHa treatment. Therefore, we could not assess the association between puberty stage and finding a prescription or not finding a prescription in people assigned female at birth.

Because more people could be included in the univariable models than in multivariate models (ie, the people who had been externally referred and had already started medical treatment elsewhere were excluded from the multivariable model to avoid bias based on the year of first visit), the overall group could be assessed in the univariable models. In the univariable models, age at first visit, at start of GnRHa, and at start of gender-affirming hormone treatment were not associated with us finding a prescription or not, nor were puberty stage at start of GnRHa treatment, whether or not gonadectomy was done, year in which people first visited, or year in which gender-affirming hormone treatment was started (table 2).

## Discussion

In this cohort study, we show that most people who had started medical transition with puberty suppression in adolescence followed with gender-affirming hormone treatment, continued using gender-affirming hormones in adulthood. Ongoing gender-affirming hormones use was not associated with age at first visit, nor was age at start of GnRHa treatment, age at start of gender-affirming hormone treatment, puberty stage at start of GnRHa treatment, nor gonadectomy.

In recent years, a surge of referrals of predominantly people assigned female at birth has been seen at our gender identity clinic.[12] Some people have raised concerns about gender-affirming treatment for adolescents because of poor diagnostic certainty of gender dysphoria, especially in light of the increasing demand for this treatment.[19] However, Arnoldussen and colleagues[12] have already shown that the proportion of adolescents diagnosed with gender incongruence has not changed between 2000 and 2016 at the gender identity clinic of the Amsterdam UMC, location Vrije Universiteit Medical Center, suggesting that current referrals are similar with regard to gender dysphoria to those from earlier years. We have now shown that there is no difference in continuation of treatment between people who started gender-affirming hormones before 2012 and those who started treatment after 2012 in the Netherlands, corroborating Arnoldussen and colleagues'[12] statement. When assessing the association between not finding a prescription and age at first visit, at start of GnRHa treatment, and at start of gender-affirming hormone treatment, the chance of discontinuing treatment seemed to increase with older age at all these timepoints in people assigned female at birth in this Article. However, these were not statistically significant.

We were unable to find a prescription for only 2% of people in our cohort. These people might have stopped using gender-affirming hormones. There are several plausible reasons for discontinuation of treatment. There might be a lack of knowledge on the importance of continued hormone treatment after gonadectomy, or the side-effects of medication could have led to stopping of medication. Any participants with a non-binary gender identity might require only short-term medical treatment. No prescriptions for any kind of sex hormones (ie, neither for the sex assigned at birth or the experienced gender) were found, suggesting that people might not have stopped treatment because of regret of transition or change of gender identity; if people who had gonadectomy

| | Overall | | No prescription found | |
|---|---|---|---|---|
| | People assigned male at birth (n=220) | People assigned female at birth (n=500) | People assigned male at birth (n=9) | People assigned female at birth (n=7) |
| Age at start of GnRHa treatment, years | 14·1 (13·0–16·3) | 16·0 (14·1–16·9) | 14·6 (13·3–15·2) | 16·6 (16·5–16·9) |
| Early puberty at start of GnRHa treatment, | 64 (30%)* | 16 (3%)* | 3 (33%) | 0 |
| Testicular volume at start of GnRHa treatment, mL | 15 (8–20)† | NA | 20 (6–22)† | NA |
| Menarche before GnRHa initiation | NA | 335 (81%)† | NA | 7 (100%)† |
| Monotherapy with GnRHa, years | 1·7 (0·7–2·6) | 0·8 (0·5–1·9) | 2·4 (1·1–2·7) | 0·7 (0·5–1·0) |
| Age at start of gender-affirming hormone treatment, years | 16·0 (15·5–17·1) | 16·7 (16·0–17·5) | 16·0 (16·0–16·6) | 17·6 (17·0–17·7) |
| Age at end of data collection, years | 20·2 (17·9–24·8) | 19·2 (17·8–22·0) | 29·3 (27·8–31·2) | 25·3 (19·6–26·5) |
| Age at last found prescription, years | NA | NA | 24·6 (22·8–25·9) | 20·7 (17·7–23·1) |

Data are median (IQR) or n (%). Early puberty in people assigned male at birth was considered as testicular volume ≤9 mL and in people assigned female at birth considered as Tanner breast stage II. GAH=gender-affirming hormones. GnRHa=gonadotropin-releasing hormone agonist. NA=not applicable. *Data on puberty stage at start of GnRHa was missing for three people who were assigned male at birth and seven people who were assigned female at birth. †For eight people who were assigned male at birth, including two without a prescription at the end of follow-up, testicular volume was missing; for 85 people who were assigned female at birth, including one without a prescription at the end of follow-up, data on menarche were missing.

*Table 1:* **Characteristics of all participants**

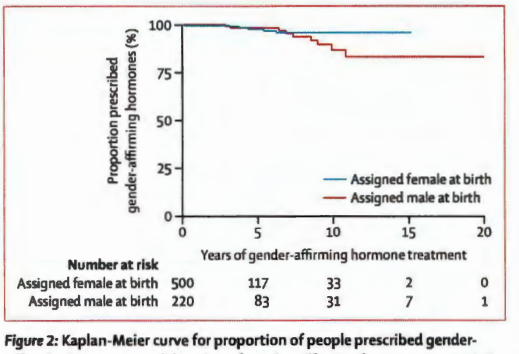


*Figure 2:* **Kaplan-Meier curve for proportion of people prescribed gender-affirming hormones and duration of gender-affirming hormone treatment, stratified by sex assigned at birth**

| | Univariable model, overall | Univariable model, people assigned male at birth | Multivariable model*, people assigned male at birth | Univariable model*, people assigned female at birth | Multivariable model, people assigned female at birth |
|---|---|---|---|---|---|
| Age at first visit* | 1·21 (0·95–1·54) | 1·04 (0·76–1·41) | 1·09 (0·62–1·92) | 1·69 (0·97–2·93) | 0·89 (0·31–2·53) |
| Age at start of GnRHa treatment | 1·21 (0·91–1·59) | 0·99 (0·67–1·45) | 0·62 (0·23–1·69) | 1·86 (0·97–3·56) | 2·60 (0·37–18·4) |
| Age at start of gender-affirming hormone treatment | 1·37 (0·85–2·20) | 1·20 (0·67–2·16) | 2·47 (0·60–10·1) | 1·94 (0·89–4·26) | 0·70 (0·08–6·20) |
| Puberty stage at start of GnRHa treatment | | | | | |
| Early puberty | Reference | Reference | Reference | Reference | Reference |
| Late puberty | 0·62 (0·18–2·18) | 0·62 (0·15–2·48) | 0·56 (0·08–3·71) | Omitted† | Omitted† |
| Year of first visit* | 1·03 (0·89–1·19) | 0·85 (0·67–1·08) | 0·83 (0·63–1·09) | 1·24 (0·95–1·64) | 1·09 (0·80–1·49) |
| Year of start of gender-affirming hormone treatment | | | | | |
| <2012 | Reference | Reference | Reference | Reference | Reference |
| ≥2012 | 0·68 (0·17–2·76) | 0·90 (0·07–11·43) | Omitted‡ | 0·53 (0·10–2·85) | Omitted‡ |
| Gonadectomy§ | | | | | |
| No | Reference | .. | .. | .. | .. |
| Yes | 0·43 (0·11–1·63) | .. | .. | .. | .. |

Data are in hazard ratio (95% CI). Early puberty in people assigned male at birth was considered as testicular volume ≤9 mL and in people assigned female at birth was considered as Tanner breast stage II. GnRHa=gonadotropin-releasing hormone agonist. NA=not applicable. *External referrals excluded. †Analyses not possible because all people assigned female at birth for whom a prescription was not found were in late puberty at start of GnRHa treatment. ‡Analyses not possible because the event rate was too low in the group starting gender-affirming hormones after 2012. §Not stratified by sex assigned at birth to ensure anonymity.

*Table 2:* **Association between independent variables and the outcome of no prescription found**

regretted their transition they might have started treatment with sex hormones of their sex assigned at birth. A survey study by Turban and colleagues[20] found that, even among adult participants with a history of detransitioning, very few reported internal factors, including uncertainty about gender identity, as the reason for detransitioning. Alternatively a non-supportive, or even disapproving, attitude towards transitioning from an individual's environment, could have compelled participants to discontinue treatment due to social rejection.[21]

Roberts and colleagues[22] reported that, 4 years after hormone initiation, 74·4% of individuals who had started gender-affirming hormones before age 18 years continued treatment. However, it is unclear how many of these adolescents used puberty suppressing treatment before gender-affirming hormone treatment, and to what extent they underwent diagnostic evaluation before initiation of medical treatment. At our gender identity clinic, adolescents go through a meticulous diagnostic process before the start of GnRHa and gender-affirming hormone treatment. Perhaps differences in diagnostic evaluation and criteria to start treatment contribute to the discrepancy in continuation rates found between studies. In a small study from Germany,[23] the main objective of which was to assess satisfaction with transition-related care, three (9%) of 32 adolescents discontinued gender-affirming hormone treatment, none due to regret of transition. The higher proportion than in our study of discontinuation found by these authors[23] might be explained by their select and small study population. Whereas we were able to include the complete adolescent population seen at our centre, Nieder and colleagues[23] only included people who actively participated in their follow-up study. In a UK-based gender identity clinic, nine (5·1%) of 175 participants who had started gender-affirming hormones when at least age 17 years, discontinued this treatment.[24] However, this population started gender-affirming hormone treatment at a later age than our participants, without previous GnRHa treatment, and were discharged from their gender identity clinic.

Of all people for whom a prescription was not found at follow-up, 12 (75%) of 16 underwent gonadectomy and appeared to not use any sex hormones. This particular fact is troublesome as these individuals are at increased risk of complications such as osteoporosis. The proportion of people undergoing gonadectomy might be higher compared with in other countries because, in the Netherlands, gonadectomy was obligatory (until July 1, 2014) for transgender people to change their legal sex. Our findings underline the importance of careful counselling of young adults considering gonadectomy about the need for ongoing hormone treatment after gonadectomy.

To our knowledge, this study is the first to assess continuation of gender-affirming hormones in a large group of transgender individuals who started medical treatment with puberty suppression in adolescence. A valuable asset to our study is the link with a national prescription registry, yielding information on hormone use of all people who were treated at our centre. A limitation of our study is that gender-affirming hormones being prescribed does not necessarily mean that people are using the medication, possibly overestimating the number of people still using gender-affirming hormones. The results over the most recent years should be regarded with caution, as duration of follow-up is of course limited by time. This limitation by time is represented by the gradually decreasing number of people at risk with an increasing duration of gender-affirming hormone treatment in the Kaplan-Meier curve. Unfortunately, due to data limitations, we could only speculate about reasons why people might have stopped using gender-affirming hormones. Another limitation is that we were unable to do a power and sample size calculation in advance of the study because we could not find a study providing an estimation on the number of expected events in this population. Because the event rate in our study was very low, the regression analyses regarding determinants of stopping gender-affirming hormone

treatment might have been underpowered. Lastly, prescriptions might have been not recorded for people obtaining treatment outside of the regular health system. However, this would mean we overestimated the number of people stopping use of gender-affirming hormones, and would not alter the key message that the vast majority of this particular group continued using gender-affirming hormones.

Overall, 98% of people who had started gender-affirming medical treatment with puberty suppression in adolescence in this study continued gender-affirming hormones. This proportion is reassuring considering the public concern regarding regret of transition when started in adolescence. Factors associated with possibly stopping treatment were not identified; future research should identify reasons why young adults stop taking gender-affirming hormones. In the meantime, educating all young people who undergo gender-affirming treatment on the need for continued hormone treatment and on the health risks of discontinuing treatment should be a priority.

#### Contributors

MATCvdL contributed to conceptualisation, data curation, formal analysis, investigation, methodology, data visualisation, and writing of the Article. SEH contributed to conceptualisation, supervision, and writing of the Article. DTK contributed to conceptualisation, supervision, and writing of the Article. MdH contributed to conceptualisation, methodology, project administration, supervision, and writing of the Article. CMW contributed to conceptualisation, data curation, methodology, project administration, supervision, validation, data visualisation, and writing of the Article.

#### Declaration of interests

We declare no competing interests.

#### Data sharing

Individual participant data will not be made available as this is prohibited by Statistics Netherlands to guarantee the anonymity of the people in its databases.

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