ANNUAL REVIEWS

Annual Review of Medicine

Gender-Affirming Care of Transgender and Gender-Diverse Youth: Current Concepts

Janet Y. Lee[1,2,3] and Stephen M. Rosenthal[1]

[1]Division of Pediatric Endocrinology, Department of Pediatrics, University of California, San Francisco, California, USA; email: Janet.lee@ucsf.edu, Stephen.rosenthal@ucsf.edu

[2]Division of Endocrinology & Metabolism, Department of Medicine, University of California, San Francisco, California, USA

[3]Endocrine and Metabolism Section, San Francisco Veterans Affairs Health Care System, San Francisco, California, USA

Annu. Rev. Med. 2023. 74:107–116

First published as a Review in Advance on October 19, 2022

The *Annual Review of Medicine* is online at med.annualreviews.org

https://doi.org/10.1146/annurev-med-043021-032007

Keywords

transgender, gender-diverse youth, pubertal blockers, gonadotropin-releasing hormone agonists, gender-affirming hormone treatment

Abstract

Increasing numbers of transgender and gender-diverse (TGD) youth, from early puberty through late adolescence, are seeking medical services to bring their physical sex characteristics into alignment with their gender identity—their inner sense of self as male or female or elsewhere on the gender spectrum. Numerous studies, primarily of short- and medium-term duration (up to 6 years), demonstrate the clearly beneficial—even lifesaving—mental health impact of gender-affirming medical care in TGD youth. However, there are significant gaps in knowledge and challenges to such care. Long-term safety and efficacy studies are needed to optimize medical care for TGD youth.

INTRODUCTION

Increasing numbers of transgender and gender-diverse (TGD) youth, from early puberty through late adolescence, are seeking medical services to bring their physical sex characteristics into alignment with their gender identity—their inner sense of self as male or female or elsewhere on the gender spectrum. While gender-affirming care for TGD youth is a relatively new field, close to 25 years of published research support current models of care. This review focuses on current concepts of TGD youth, the impact of gender-affirming care, gaps in knowledge, challenges to care, and priorities for research.

UPDATE ON PREVALENCE AND TERMINOLOGY

The size of the TGD youth population is difficult to accurately discern. Survey-based studies estimate that the percentage of teenagers in the United States who identify as TGD ranges from 0.7% to 2.7% (1–3). Clinics worldwide have reported on the growing number of TGD youth presenting for gender-affirming hormone treatment (GAHT) (4, 5). Terminology in this field is constantly evolving, with sex and gender as distinct entities. Sex is typically designated at birth, based on physical or chromosomal features, and may be male, female, or intersex. Gender identity exists separately on a spectrum that can be binary male or female, nonbinary, gender fluid, agender, or other genders (6).

OVERVIEW OF CURRENT CLINICAL PRACTICE GUIDELINES FOR THE GENDER-AFFIRMING MODEL OF CARE

In recent years, a new model of care for TGD youth has emerged: the gender-affirming model. The basic premise is that every individual is entitled to live in the gender that is most authentic to them (7). Professional societies have published evidence-based guidelines encompassing care of TGD youth since 1998. The World Professional Association for Transgender Health (WPATH) has updated its Standards of Care (SOC) in 2022, now referred to as SOC8 (8), and the Endocrine Society last updated its Clinical Practice Guideline in 2017 (9).

Following a thorough assessment by a mental health gender specialist, TGD youth may be eligible for gender-affirming medical care after they have reached Tanner Stage 2 of puberty (6). Such treatment may include a reversible gonadotropin-releasing hormone agonist (GnRHa), or pubertal blocker, to pause puberty, prevent otherwise permanent development of secondary sex characteristics that are not aligned with a person's affirmed gender identity, and allow time for further gender exploration. In adolescents >14 years of age, there are currently no data to indicate whether pubertal blockers can be used as a monotherapy without potentially compromising bone mineral density (BMD). Older adolescents may request phenotypic transition with GAHT, either estradiol (in combination with an antiandrogen) or testosterone. While current clinical practice guidelines recommend initiation of GAHT in eligible adolescents once they have reached 16 years of age, the guidelines also recognize that there may be compelling reasons to initiate such treatment before age 16 in some adolescents, on a case-by-case basis (9). Like pubertal blockers, GAHT should be initiated only after a thorough assessment by a qualified mental health gender specialist. Detailed protocols for use of pubertal blockers (including alternatives to GnRHa) as well as for pubertal induction with GAHT, including guidelines for physical examination and laboratory surveillance, have been described (9).

Menstrual suppression is often desired by transmasculine and nonbinary youth designated female at birth. Treatment options may include oral, injectable, intradermal, or intrauterine progestins and continuous combined oral contraceptives (10). For those TGD youth initiating

testosterone, this treatment is generally effective in induction and maintenance of amenorrhea, although it should be noted that testosterone is not a form of contraception (10).

OUTCOMES OF CURRENT MODELS OF CARE

Mental Health

TGD youth have an increased prevalence of autism spectrum disorder and are also at increased risk for mood disorders, anxiety, depression, suicidal ideation, and suicide attempts (11–19). Based on survey data from transgender youth, the frequency of internalizing disorders appears to be impacted by degree of family support: TGD youth with "very supportive" parents reported a greater degree of positive self-esteem and life satisfaction and a decreased frequency of depression and suicide attempts in comparison to those youth whose parents were "somewhat to not at all supportive" (20). Such findings underscore the concept that many of the mental health challenges faced by TGD youth are not intrinsic to their gender identity but rather likely reflect lack of societal acceptance. Notably, TGD youth presenting for gender-affirming medical care at earlier pubertal stages demonstrated better mental health and sense of well-being at baseline in comparison to older adolescents presenting at later pubertal stages, suggesting the potential benefits of gender-affirming medical treatment earlier in life (21, 22).

Only limited mental health outcomes data are available to support current clinical practice guidelines and standards of care for TGD youth. However, in recent years, a medium-term study (up to 6 years) and several shorter-term studies have demonstrated the positive and potentially lifesaving impact of gender-affirming medical care for TGD youth (23–29). A prospective 2-year study of 70 gender-dysphoric adolescents in the Netherlands observed that treatment with a GnRHa/pubertal blocker was associated with a decrease in depression and an improvement in general mental health functioning (29). None of the 70 patients withdrew from this study, and all went on to GAHT (29). After treatment with pubertal blockers, a 6-year follow-up study of 55 individuals from this original cohort reported on mental health outcomes after subsequent GAHT and genital reassignment surgery (23). At the conclusion of this observation period, gender dysphoria was reported to have resolved, general psychological function improved, and, remarkably, sense of well-being was equivalent or superior to that seen in age-matched controls from the general population (23).

Subsequent reports have confirmed the positive mental health impact of gender-affirming medical care for TGD adolescents and young adults. In particular, a cross-sectional survey of more than 20,000 transgender adults (aged 18–36 years) found significantly lower odds of lifetime suicidal ideation ($p = 0.001$) in those who had been treated with pubertal blockers during adolescence in comparison to those who wanted such treatment but did not receive it (24). Several shorter-term longitudinal studies have demonstrated that gender-affirming medical care was associated with improved body image, decreases in body dissatisfaction, and improved psychological functioning (25–28).

A 2020 survey of 11,914 transgender or nonbinary youth, aged 13–24 years, of whom 14% were receiving GAHT, demonstrated that such treatment was associated with lower odds of recent depression and serious consideration of suicide compared to those who wanted such care but did not receive it (30). A separate survey study demonstrated that patients with access to GAHT during adolescence had lower odds of past-year suicidal ideation ($p = 0.0007$) than those who accessed such care during adulthood (31).

Physiological Considerations

The goal of gender-affirming medical care is to bring a person's physical characteristics into alignment with their gender identity, and to do so in a way that minimizes adverse physiological

outcomes. The use of pubertal blockers and/or GAHT may have adverse impacts on a variety of physiological/metabolic processes, as described below.

Bone. Since 2015, when the first study examining the effects of GAHT on bone health in TGD adolescents showed low pretreatment BMD by dual-energy X-ray absorptiometry (DXA) and impaired bone mass accrual in transgender women who initiated GnRHa in late puberty and were treated with more than 5 years of estradiol (32), additional studies have focused on the skeletal effects of gender-affirming medical therapy in TGD youth (32–35). These groups have shown lower BMD in transfeminine youth, with less concerning data in transmasculine youth (33–36). Because the studies were retrospective, no specific determinants of bone health were implicated for potential interventions.

A prospective study of early pubertal TGD individuals in the United States about to begin GnRHa treatment demonstrated a greater prevalence of low baseline BMD in both those designated male and those designated female at birth, although the percentage of those with low BMD was higher in those designated male at birth (37). Prospective collection of dietary calcium intake, serum 25-hydroxyvitamin D, and physical activity assessments revealed that calcium intake was globally low and that low physical activity was predictive of low BMD (37). Another recent study showed that TGD individuals have bone geometry trajectories matching gender curves if GnRHa was initiated in early puberty (38), suggesting that TGD individuals initiating treatment in early puberty have skeletal trajectories distinct from those initiating treatment in late puberty or adulthood.

All studies to date have analyzed BMD Z-scores using sex designated at birth reference standards, and the International Society for Clinical Densitometry (ISCD) has not produced specific guidance on how to interpret DXA in TGD youth. A recent study has described how interpretation of BMD Z-scores may be impacted by skeletal age, which reflects pubertal timing, and by the sex reference standard used (39), and proposes that guidance on interpretation of DXA in TGD youth be considered at the next ISCD Pediatric Position Development Conference.

Growth. Early studies investigating height velocity, growth potential, and adult height attainment in TGD youth are still emerging, although variation in genetic height potential and pubertal stages at initiation of GAHT produces significant challenges to data interpretation (40). A study investigating growth in TGD youth during the first year of GnRHa treatment showed height velocity similar to prepubertal children except when GnRHa was initiated in later puberty (Tanner Stage 4), in which case height velocity was significantly below the height velocity seen in prepubertal youth (41).

Cardiometabolic parameters and lipids. Investigations on the effects of puberty suppression and GAHT on cardiometabolic parameters such as blood pressure, body composition, body mass index (BMI), and lipids in TGD youth are underway. In 36 transgender girls and 41 transgender boys at a median Tanner Stage 4 of pubertal development, one year of GnRHa increased fat percentage, decreased lean body mass percentage, and increased BMI (42). A small study compared nine transgender boys and eight transgender girls with age-, sex designated at birth-, and BMI-matched cisgender controls and found lower estimated insulin sensitivity and higher glycemic markers and body fat in TGD youth on GnRHa, but the study was of relatively short duration (43).

A cross-sectional study of older TGD adolescents (both designated males at birth and designated females at birth) on GAHT showed significant body composition differences from cisgender controls and higher insulin resistance in transfeminine youth than in cisgender male controls (44). A retrospective study of late pubertal transgender boys compared with BMI-matched cisgender girls revealed increased BMI and decreased high-density lipoprotein (HDL) in the transgender

boys a relatively short time after starting testosterone therapy (<12 months) (45). Examination of a cohort of TGD individuals aged 22 years (71 trans women and 121 trans men) treated with GnRHa and GAHT showed increased BMI as well as obesity prevalence of 9.9% in trans women and 6.6% in trans men, compared with 2.2% in cis women and 3.0% in cis men (46). Another study demonstrated pretreatment HDL in TGD youth to be slightly lower when compared with age-matched controls but otherwise similar to an age-matched National Health and Nutritional Examination Survey (NHANES) comparison group for BMI, blood pressure, and baseline laboratory measurements (47). Following treatment with GAHT, transgender girls have been shown to have increases in HDL and transgender boys to have decreases in HDL (48–50), with differences influenced by the presence of obesity (51).

Brain. Limited studies have evaluated the impact of gender-affirming medical care on neurocognitive development in TGD youth (for a review, see 6). A small study from the Netherlands demonstrated no apparent adverse impact of GnRHa on the acquisition of executive functioning, a developmental milestone typically achieved during puberty (52). A single case report demonstrated lack of expected white matter fractional anisotropy and a nine-point drop in operational memory after approximately 2 years of GnRHa treatment (53).

Other. A retrospective study of 611 TGD adolescents who were 13–24 years old at initiation of GAHT and remained on the therapy for a median duration of 574 days showed no incidental occurrence of arterial or venous thrombosis associated with GAHT (54). The expected increases in hemoglobin and hematocrit with testosterone therapy have been shown in TGD youth, with no significant adverse effects reported (34, 48, 50).

Fertility

A discussion about fertility preservation is an essential part of the evaluation of every TGD youth prior to initiation of either pubertal blockers or gender-affirming sex hormones. While late pubertal/postpubertal adolescents are likely able to provide a sperm sample or undergo egg cryopreservation, TGD youth treated with GnRHa during early puberty are at increased risk for compromised fertility if they then undertake transition with GAHT (6). An important advance in fertility preservation has been the demonstration of in vivo oocyte maturation in a gender-dysphoric designated female at birth with a male gender identity. This patient was treated with GnRHa at Tanner Stage 2, resulting in pubertal suppression, and concurrently underwent a short course of ovarian stimulation with follitropin-alpha and human chorionic gonadotropin (55). In vivo maturation of sperm in a gender-dysphoric designated male at birth with a female gender identity who was treated with GnRHa at Tanner Stage 2 has not yet been reported.

Surgical Care

In earlier years, gender-affirming surgeries had not been considered in TGD individuals younger than the age of majority. Current clinical practice guidelines recommend delaying gender-affirming genital surgery until the patient is at least 18 years old or the legal age of majority in his or her country, though the WPATH SOC8 does not give specific age guidelines (8, 9). In accordance with clinical practice guidelines, gender-affirming surgeons have performed chest masculinization surgeries at younger ages; timing is based on the physical and mental health status of the individual patient (8, 9, 56). A larger study of 68 transmasculine youth undergoing chest reconstruction surgery included patients 13–24 years of age, 33 of whom were <18 years at the time of surgery (16 of whom were ≤15 years), compared with 68 transmasculine youth who did not

undergo surgery. This study showed a significant improvement in chest dysphoria in the postsurgical group (57). A smaller study of 14 TGD youth ranging in age from 13.4 to 19.7 years who pursued chest reconstructive surgery reported high satisfaction rates with no regret and minor surgical complications of keloid, seroma, and hematoma in five individuals (58). More recently, surgeons have performed vaginoplasty surgeries on TGD youth under 18 years of age, on an individualized basis, adjusting the surgical approach for those who initiated GnRHa in early puberty (59).

GAPS IN KNOWLEDGE AND CHALLENGES TO CARE

In addition to the need for long-term safety and efficacy studies to evaluate current clinical practice guidelines and standards of care, significant gaps in knowledge remain with respect to optimal management of TGD youth. For example, increasing numbers of youth identifying as gender nonbinary are presenting for care, for whom no formal guidance existed until a "nonbinary" chapter was included in the SOC8 (8, 60–66). In addition, a putative condition termed rapid-onset gender dysphoria (ROGD) has been proposed to describe adolescents who first experience gender dysphoria either in the later stages of puberty or after puberty has been completed (67). However, significant methodological concerns have been raised calling into question the existence of ROGD; for example, only parents and none of the adolescents with gender dysphoria participated in the study, and the parents were recruited from websites not thought to be supportive of transgender youth (68). Additional gaps in knowledge exist, in particular, with respect to the long-term impact of GnRHa/pubertal blockers on fertility, skeletal health, and neurocognitive development, as recently described (6).

In addition to the above-noted gaps in knowledge, there are significant challenges to care of TGD youth. All hormonal interventions for TGD youth are considered "off-label" and are often denied coverage by insurance companies. Furthermore, lack of formalized training limits access to optimal care (69). Another notable challenge to care pertains to sexual anatomy: Designated males at birth treated with GnRHa in early puberty who subsequently transition with estrogen and request vaginoplasty will likely require a more complex surgical procedure than that typically required for designated males at birth who request vaginoplasty after completing endogenous, testosterone-mediated puberty (70). Most notably, there are unprecedented challenges to the care of TGD youth, both in the United States and abroad, with policies and in some cases state-based legislation banning gender-affirming medical care to TGD minors and criminalizing medical providers of such care (6). As noted in recent position statements sponsored by the Endocrine Society, Pediatric Endocrine Society, and United States Professional Association for Transgender Health, these legislative efforts are thought to "lack scientific merit and in some cases misinterpret or distort available data" (71, p. 1; see also 72).

SUMMARY

Key advances in the care of TGD youth include the recognition that being transgender or gender diverse is not rare, and that being TGD is no longer considered a mental illness, but rather represents an example of human diversity (6). Numerous studies, primarily of short- and medium-term duration (up to 6 years), demonstrate the clearly beneficial—even lifesaving—mental health impact of gender-affirming medical care in TGD youth. Long-term safety and efficacy studies are needed to optimize medical care for TGD youth.

DISCLOSURE STATEMENT

S.M.R. is a Board Member-at-Large of the World Professional Association for Transgender Health.

ACKNOWLEDGMENTS

We are grateful for and inspired by our patients who strive to live authentic lives and to their families who support them. We are grateful to our colleagues with whom we work in an interdisciplinary model of care.

LITERATURE CITED

1. Herman JL, Flores AR, Brown TNT, et al. 2017. *Age of individuals who identify as transgender in the United States*. Rep., Williams Institute, UCLA School of Law, Los Angeles, CA. **https://williamsinstitute.law.ucla.edu/wp-content/uploads/Age-Trans-Individuals-Jan-2017.pdf**
2. Johns MM, Lowry R, Andrzejewski J, et al. 2019. Transgender identity and experiences of violence victimization, substance use, suicide risk, and sexual risk behaviors among high school students—19 states and large urban school districts, 2017. *Morb. Mortal. Wkly. Rep.* 68:67–71
3. Rider GN, McMorris BJ, Gower AL, et al. 2018. Health and care utilization of transgender and gender nonconforming youth: a population-based study. *Pediatrics* 141:e20171683
4. Wiepjes CM, Nota NM, de Blok CJM, et al. 2018. The Amsterdam Cohort of Gender Dysphoria Study (1972–2015): trends in prevalence, treatment, and regrets. *J. Sex. Med.* 15:582–90
5. Arnoldussen M, Steensma TD, Popma A, et al. 2020. Re-evaluation of the Dutch approach: Are recently referred transgender youth different compared to earlier referrals? *Eur. Child Adolesc. Psychiatry* 29:803–11
6. Rosenthal SM. 2021. Challenges in the care of transgender and gender-diverse youth: an endocrinologist's view. *Nat. Rev. Endocrinol.* 17:581–91
7. Ehrensaft D. 2016. *The Gender Creative Child*. New York: The Experiment. 304 pp.
8. Coleman E, Radix AE, Bouman WP, et al. 2022. Standards of care for the health of transgender and gender diverse people, version 8. *Int. J. Transgend. Health* 23:S1–S259
9. Hembree WC, Cohen-Kettenis PT, Gooren L, et al. 2017. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. *J. Clin. Endocrinol. Metab.* 102:3869–903
10. Carswell JM, Roberts SA. 2017. Induction and maintenance of amenorrhea in transmasculine and nonbinary adolescents. *Transgend. Health* 2:195–201
11. Reisner SL, Vetters R, Leclerc M, et al. 2015. Mental health of transgender youth in care at an adolescent urban community health center: a matched retrospective cohort study. *J. Adolesc. Health* 56:274–79
12. Kuper LE, Mathews S, Lau M. 2019. Baseline mental health and psychosocial functioning of transgender adolescents seeking gender-affirming hormone therapy. *J. Dev. Behav. Pediatr.* 40:589–96
13. de Vries AL, Cohen-Kettenis PT. 2012. Clinical management of gender dysphoria in children and adolescents: the Dutch approach. *J. Homosex.* 59:301–20
14. Spack NP, Edwards-Leeper L, Feldman HA, et al. 2012. Children and adolescents with gender identity disorder referred to a pediatric medical center. *Pediatrics* 129:418–25
15. Olson J, Schrager SM, Belzer M, et al. 2015. Baseline physiologic and psychosocial characteristics of transgender youth seeking care for gender dysphoria. *J. Adolesc. Health* 57:374–80
16. Davey A, Arcelus J, Meyer C, Bouman WP. 2016. Self-injury among trans individuals and matched controls: prevalence and associated factors. *Health Soc. Care Community* 24:485–94
17. Veale JF, Watson RJ, Peter T, Saewyc EM. 2017. Mental health disparities among Canadian transgender youth. *J. Adolesc. Health* 60:44–49
18. Bauer GR, Pacaud D, Couch R, et al. 2021. Transgender youth referred to clinics for gender-affirming medical care in Canada. *Pediatrics* 148:e2020047266
19. Nunes-Moreno M, Buchanan C, Cole FS, et al. 2022. Behavioral health diagnoses in youth with gender dysphoria compared with controls: a PEDSnet study. *J. Pediatr.* 241:147–53.e1
20. Travers RB, Bauer G, Pyne J, et al. 2012. *Impacts of strong parental support for trans youth: a report prepared for Children's Aid Society of Toronto and Delisle Youth Services*. Rep., Trans PULSE, Ont., Can.
21. Sorbara JC, Chiniara LN, Thompson S, Palmert MR. 2020. Mental health and timing of gender-affirming care. *Pediatrics* 146:e20193600

22. Chen D, Abrams M, Clark L, et al. 2021. Psychosocial characteristics of transgender youth seeking gender-affirming medical treatment: baseline findings from the Trans Youth Care Study. *J. Adolesc. Health* 68:1104–11
23. de Vries AL, McGuire JK, Steensma TD, et al. 2014. Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics* 134:696–704
24. Turban JL, King D, Carswell JM, Keuroghlian AS. 2020. Pubertal suppression for transgender youth and risk of suicidal ideation. *Pediatrics* 145:e20191725
25. Costa R, Dunsford M, Skagerberg E, et al. 2015. Psychological support, puberty suppression, and psychosocial functioning in adolescents with gender dysphoria. *J. Sex. Med.* 12:2206–14
26. Becker I, Auer M, Barkmann C, et al. 2018. A cross-sectional multicenter study of multidimensional body image in adolescents and adults with gender dysphoria before and after transition-related medical interventions. *Arch. Sex. Behav.* 47:2335–47
27. Achille C, Taggart T, Eaton NR, et al. 2020. Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: preliminary results. *Int. J. Pediatr. Endocrinol.* 2020:8
28. Kuper LE, Stewart S, Preston S, et al. 2020. Body dissatisfaction and mental health outcomes of youth on gender-affirming hormone therapy. *Pediatrics* 145:e20193006
29. de Vries AL, Steensma TD, Doreleijers TA, Cohen-Kettenis PT. 2011. Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. *J. Sex. Med.* 8:2276–83
30. Green AE, DeChants JP, Price MN, Davis CK. 2022. Association of gender-affirming hormone therapy with depression, thoughts of suicide, and attempted suicide among transgender and nonbinary youth. *J. Adolesc. Health* 70:643–49
31. Turban JL, King D, Kobe J, et al. 2022. Access to gender-affirming hormones during adolescence and mental health outcomes among transgender adults. *PLOS ONE* 17:e0261039
32. Klink D, Caris M, Heijboer A, et al. 2015. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. *J. Clin. Endocrinol. Metab.* 100:E270–75
33. Vlot MC, Klink DT, den Heijer M, et al. 2017. Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. *Bone* 95:11–19
34. Stoffers IE, de Vries MC, Hannema SE. 2019. Physical changes, laboratory parameters, and bone mineral density during testosterone treatment in adolescents with gender dysphoria. *J. Sex. Med.* 16:1459–68
35. Schagen SEE, Wouters FM, Cohen-Kettenis PT, et al. 2020. Bone development in transgender adolescents treated with GnRH analogues and subsequent gender-affirming hormones. *J. Clin. Endocrinol. Metab.* 105:e4252–63
36. Navabi B, Tang K, Khatchadourian K, Lawson ML. 2021. Pubertal suppression, bone mass, and body composition in youth with gender dysphoria. *Pediatrics* 148:e2020039339
37. Lee JY, Finlayson C, Olson-Kennedy J, et al. 2020. Low bone mineral density in early pubertal transgender/gender diverse youth: findings from the Trans Youth Care Study. *J. Endocr. Soc.* 4:bvaa065
38. van der Loos MA, Hellinga I, Vlot MC, et al. 2021. Development of hip bone geometry during gender-affirming hormone therapy in transgender adolescents resembles that of the experienced gender when pubertal suspension is started in early puberty. *J. Bone Miner. Res.* 36:931–41
39. Lee JY, Fan B, Montenegro G, et al. 2022. Interpretation of bone mineral density Z-scores by dual-energy X-ray absorptiometry in transgender and gender diverse youth prior to gender-affirming medical therapy. *J. Clin. Densitom.* 25:559–68
40. Roberts SA, Carswell JM. 2021. Growth, growth potential, and influences on adult height in the transgender and gender-diverse population. *Andrology* 9:1679–88
41. Schulmeister C, Millington K, Kaufman M, et al. 2022. Growth in transgender/gender-diverse youth in the first year of treatment with gonadotropin-releasing hormone agonists. *J. Adolesc. Health* 70:108–13
42. Schagen SE, Cohen-Kettenis PT, Delemarre-van de Waal HA, Hannema SE. 2016. Efficacy and safety of gonadotropin-releasing hormone agonist treatment to suppress puberty in gender dysphoric adolescents. *J. Sex. Med.* 13:1125–32

43. Nokoff NJ, Scarbro SL, Moreau KL, et al. 2021. Body composition and markers of cardiometabolic health in transgender youth on gonadotropin-releasing hormone agonists. *Transgend. Health* 6:111–19
44. Nokoff NJ, Scarbro SL, Moreau KL, et al. 2020. Body composition and markers of cardiometabolic health in transgender youth compared with cisgender youth. *J. Clin. Endocrinol. Metab.* 105:e704–14
45. Valentine A, Nokoff N, Bonny A, et al. 2021. Cardiometabolic parameters among transgender adolescent males on testosterone therapy and body mass index-matched cisgender females. *Transgend. Health* 6:369–73
46. Klaver M, de Mutsert R, van der Loos M, et al. 2020. Hormonal treatment and cardiovascular risk profile in transgender adolescents. *Pediatrics* 145:e20190741
47. Millington K, Schulmeister C, Finlayson C, et al. 2020. Physiological and metabolic characteristics of a cohort of transgender and gender-diverse youth in the United States. *J. Adolesc. Health* 67:376–83
48. Olson-Kennedy J, Okonta V, Clark LF, Belzer M. 2018. Physiologic response to gender-affirming hormones among transgender youth. *J. Adolesc. Health* 62:397–401
49. Millington K, Finlayson C, Olson-Kennedy J, et al. 2021. Association of high-density lipoprotein cholesterol with sex steroid treatment in transgender and gender-diverse youth. *JAMA Pediatr.* 175:520–21
50. Jarin J, Pine-Twaddell E, Trotman G, et al. 2017. Cross-sex hormones and metabolic parameters in adolescents with gender dysphoria. *Pediatrics* 139:e20163173
51. Millington K, Chan YM. 2021. Lipoprotein subtypes after testosterone therapy in transmasculine adolescents. *J. Clin. Lipidol.* 15:840–44
52. Staphorsius AS, Kreukels BP, Cohen-Kettenis PT, et al. 2015. Puberty suppression and executive functioning: an fMRI-study in adolescents with gender dysphoria. *Psychoneuroendocrinology* 56:190–99
53. Schneider MA, Spritzer PM, Soll BMB, et al. 2017. Brain maturation, cognition and voice pattern in a gender dysphoria case under pubertal suppression. *Front. Hum. Neurosci.* 11:528
54. Mullins ES, Geer R, Metcalf M, et al. 2021. Thrombosis risk in transgender adolescents receiving gender-affirming hormone therapy. *Pediatrics* 147:e2020023549
55. Rothenberg SS, Witchel SF, Menke MN. 2019. Oocyte cryopreservation in a transgender male adolescent. *N. Engl. J. Med.* 380:886–87
56. Telfer MM, Tollit MA, Pace CC, Pang KC. 2018. Australian standards of care and treatment guidelines for transgender and gender diverse children and adolescents. *Med. J. Aust.* 209:132–36
57. Olson-Kennedy J, Warus J, Okonta V, et al. 2018. Chest reconstruction and chest dysphoria in transmasculine minors and young adults: comparisons of nonsurgical and postsurgical cohorts. *JAMA Pediatr.* 172:431–36
58. Marinkovic M, Newfield RS. 2017. Chest reconstructive surgeries in transmasculine youth: experience from one pediatric center. *Int. J. Transgend.* 18:376–81
59. Milrod C, Karasic DH. 2017. Age is just a number: WPATH-affiliated surgeons' experiences and attitudes toward vaginoplasty in transgender females under 18 years of age in the United States. *J. Sex. Med.* 14:624–34
60. Richards C, Bouman WP, Seal L, et al. 2016. Non-binary or genderqueer genders. *Int. Rev. Psychiatry* 28:95–102
61. Todd K, Peitzmeier SM, Kattari SK, et al. 2019. Demographic and behavioral profiles of nonbinary and binary transgender youth. *Transgend. Health* 4:254–61
62. Twist J, de Graaf NM. 2019. Gender diversity and non-binary presentations in young people attending the United Kingdom's National Gender Identity Development Service. *Clin. Child Psychol. Psychiatry* 24:277–90
63. Chew D, Tollit MA, Poulakis Z, et al. 2020. Youths with a non-binary gender identity: a review of their sociodemographic and clinical profile. *Lancet Child Adolesc. Health* 4:322–30
64. Cheung AS, Leemaqz SY, Wong JWP, et al. 2020. Non-binary and binary gender identity in Australian trans and gender diverse individuals. *Arch. Sex. Behav.* 49:2673–81
65. Hastings J, Bobb C, Wolfe M, et al. 2021. Medical care for nonbinary youth: individualized gender care beyond a binary framework. *Pediatr. Ann.* 50:e384–90
66. T'Sjoen G, Arcelus J, Gooren L, et al. 2019. Endocrinology of transgender medicine. *Endocr. Rev.* 40:97–117

67. Littman L. 2018. Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria. *PLOS ONE* 13:e0202330
68. Wadman M. 2018. "Rapid onset" of transgender identity ignites storm. *Science* 361:958–59
69. Vance SR Jr., Halpern-Felsher BL, Rosenthal SM. 2015. Health care providers' comfort with and barriers to care of transgender youth. *J. Adolesc. Health* 56:251–53
70. van de Grift TC, van Gelder ZJ, Mullender MG, et al. 2020. Timing of puberty suppression and surgical options for transgender youth. *Pediatrics* 146:e20193653
71. USPATH. 2022. *USPATH position statement on legislative and executive actions regarding the medical care of transgender youth*. Position statement, Apr. 22, US Prof. Assoc. Transgender Health
72. Walch A, Davidge-Pitts C, Safer JD, et al. 2021. Proper care of transgender and gender diverse persons in the setting of proposed discrimination: a policy perspective. *J. Clin. Endocrinol. Metab.* 106:305–8