

## REVIEW ARTICLE

# PRINCIPLES OF TRANSGENDER CARE FOR THE PRIMARY CARE PHYSICIAN

Robert Gotfried, DO, FAAFP<sup>1</sup>

<sup>1</sup>The Ohio State University and Wexler Medical Center

## KEYWORDS:

Gender Affirmation

Gender Dysphoria

Gender Transition

Hormones

Transgender

**ABSTRACT:** The term transgender includes people whose gender identity differs from their sex assigned at birth. People identified as male at birth but possess a female gender identity are called transwomen and people identified as female at birth but experience a male gender identity are called transmen. Transgender individuals may also identify outside the binary norm.

The prevalence of transgender people who seek medical treatment has dramatically increased in recent years. Transgender individuals have a higher prevalence of mental health problems, suicidality and premature mortality risk versus the general population. However, many transgender persons avoid medical care due to perceived stigma, in conjunction with transgender-specific knowledge deficits among health care providers.

Integral to understanding transgender health is the concept of gender dysphoria. This refers to the internal conflict individuals experience due to incongruence between their birth sex and their self-perceived gender. For these individuals, the inconsistency causes significant internal conflict, often to the point that it interferes with functioning.

To address gender dysphoria, many transgender people elect to transition to a gender role that is consistent with their gender identity. These individuals opt for medical and/or surgical interventions to do so. Medical therapy incorporates the use of cross-sex hormones to facilitate the acquisition of secondary sexual characteristics consistent with the individual's internalized identity. Many transgender people choose to undergo gender-confirming surgeries in conjunction with hormonal therapy.

Health care is transgender-affirming when it supports the patient's inherent identity. Educating providers about this population's unique needs can help reduce health disparities and promote respectful transgender care.

## INTRODUCTION

Historically one's gender typically referred to the state of being male or female when considered in reference to societal and cultural norms. Our understanding of this is evolving, in the sense that gender is now seen as a continuum.<sup>1</sup> As described by Heise *et al.*, "Gender is not accurately captured by the traditional male and female dichotomy of sex. Instead, it is a complex social system that structures the life experience of all human beings."<sup>2</sup> Rather than a binary construct, "gender identity includes gradations of masculinity to femininity...as well as identification as neither essentially male nor female."<sup>3</sup> It is not an issue of choice for the individual and

should not be regarded as one. Therefore, one's gender identity is a personal, internalized sense of being male, female or something else. A person's gender identity does not equate to one's sex or sexual orientation. One's sex is typically assigned at birth as either male or female, usually based on the appearance of internal and external genitalia. Sexual identity is equivalent to sexual attraction or sexual preference.

## TRANSGENDER TERMINOLOGY

People who remain in the gender role they were assigned at birth are termed cisgender (CG). Transgender (TG) has been accepted as an umbrella term used to describe people with a wide range of gender identities, which are different from the sex assigned at birth. TG men, or transmen (TM), possess a male gender identity but were identified as females at birth. TG women, or transwomen (TW), have a female gender identity but were identified as males at birth. TG individuals may also identify outside the binary norm. Their identity can exist along a spectrum; they may be both male and female, neither male nor female, or somewhere in between. Appropriate

## CORRESPONDENCE:

Robert Gotfried, DO, FAAFP | gotfried.1@osu.edu

terms for these nonbinary individuals include genderqueer or genderfluid, though TG terminology is evolving as gender diversity becomes more accepted. Being TG implies a gender incongruence and not a sexual preference. TG people can be heterosexual, homosexual or bisexual in their sexual orientation.<sup>4</sup>

## EPIDEMIOLOGY

The estimated incidence worldwide of transgendered persons is 0.5–1.3% of birth-assigned males and 0.4–1.2% of birth-assigned females.<sup>5</sup> A recent review estimates 150,000 youth and 1.4 million adults in the U.S. identify as TG.<sup>6</sup> Other studies place the number closer to approximately 0.6% of the U.S. population or two million persons.<sup>7</sup> However, the true prevalence of TG persons in the U.S. is unknown. Current estimates are extrapolations from state-based surveys; no similar nationwide studies have been performed. Statistically, the percentage of adults who identify as TG doubled from 2011 to 2016.<sup>7</sup> This rise is likely a reflection of changing societal norms; as evidence of social acceptance of the LGBTQ population has increased, more transgender/nonbinary (TNB) people have been willing to question the gender they were assigned at birth.

Based on data from the 2015 U.S. Transgender Survey (USTS), approximately 33% of the nation's TG population identify as TW, 29% identify as TM and 35% describe themselves as TNB.<sup>8</sup> Transgenderism appears to be more common among younger age groups. 42% of respondents to USTS were between the ages of 18–24.<sup>9</sup> Per USTS data, 94% of respondents began to feel gender incongruence by the age of 20.<sup>9</sup>

## HEALTH DISPARITIES

The prevalence of TG people who seek medical treatment has dramatically increased in recent years. Greater visibility and acceptance of TG individuals have likely resulted in more individuals desiring care. However, many physicians find themselves ill-equipped to manage their needs. A nationwide assessment of TG individuals found that while 60% had a primary care provider (PCP), only 43% had informed the PCP they were TG.<sup>10</sup> Among USTS respondents, one-third (33%) of TG persons who had seen a health care provider reported having at least one negative experience including verbal harassment, refusal of treatment or the need to teach the provider about TG people to receive appropriate care.<sup>8</sup> To avoid discrimination, many TG patients prefer not to disclose their gender identity or opt for selective disclosure based on their perception of the provider's attitude, the setting or their medical needs.<sup>11</sup> Not uncommonly, TG individuals are forced to choose between accessing care according to their birth sex or forgoing services entirely.<sup>11</sup> Ultimately, real or perceived stigma in conjunction with knowledge deficits among health providers impacts TG peoples' ability to receive appropriate care.

Numerous factors contribute to the TG population's poor health outcomes. They are more likely to smoke (30%), misuse alcohol and drugs (26%) and be infected with HIV (20% in TG women). Mortality among TG persons is significantly higher than the general population.<sup>12</sup> Suicide, HIV/AIDS, liver failure and cardiovascular disease directly impact this heightened mortality risk.<sup>12</sup> Poorer

health outcomes are partially caused, and further compounded by, socioeconomic inequities, including higher rates of unemployment, poverty, legal discrimination and harassment, when compared with CG people.<sup>13</sup>

## MENTAL ILLNESS

TG patients typically have high rates of mental health diagnoses (depression: 41%, anxiety: 33.2%).<sup>14</sup> Among USTS respondents, 39% had experienced serious psychological distress in the month before completing the survey, compared with only 5% of the U.S. population.<sup>8</sup> 82% of respondents had thought about killing themselves at some point in their lives; 40% had attempted suicide, nearly nine times the U.S. population rate.<sup>8</sup> The data among TG youth is even more striking, with 54% having attempted suicide, the highest rates occurring in TM and nonbinary adolescents.<sup>15</sup> Transgender adolescents may choose to hide their identity due to social or family rejection. However, the propensity towards suicidal behavior in these subgroups is not entirely well understood. It is important to recognize that this prevalence of mental health distress is not inherent to having a TG identity, but rather it is a response to adverse external factors, such as stigma and rejection, alongside discomfort with one's body.<sup>16</sup>

## GENDER DYSPHORIA

Integral to the understanding of TG health is the concept of gender dysphoria (GD). Gender dysphoria refers to the suffering due to incongruence between one's sex assigned at birth and one's self-perceived gender.<sup>17</sup> For GD individuals, inconsistencies between one's biological sex and gender identity cause significant internal conflict, often to the point that it interferes with functioning. Gender dysphoria is manifested in a variety of ways, including strong desires to be treated as the other gender or to be rid of one's sex characteristics, or a strong conviction that one has feelings and reactions typical of the other gender.<sup>18</sup> Feelings of GD most often present before puberty and typically intensify during adolescence with the development of secondary sexual characteristics.

With the release of *The Diagnostic and Statistics Manual of Mental Disorders, Version Five (DSM-5)*, the diagnosis gender dysphoria replaced the diagnosis of gender identity disorder found in prior DSM versions.<sup>19</sup> This change was made to remove the stigma associated with the term "disorder." TG individuals are not inherently disordered. Replacing disorder with dysphoria de-pathologizes the TG identity and focuses instead on dysphoria as the clinical problem. DSM-5 has identified criteria necessary to make a diagnosis of GD. These are listed in Table 1. In keeping with the change in DSM-5, the World Health Organization (WHO) recently adopted new guidelines that no longer describe gender nonconformity as a mental disorder. International Classification of Diseases 11th revision (ICD-11) has redefined gender-identity related health by replacing the prior ICD-10 term of gender identity disorder with gender incongruence and moved the diagnosis from the chapter on Mental and Behavioral Disorders to the one on Conditions Related to Sexual Health.<sup>20</sup>

TABLE 1:

DSM-5 Criteria for gender dysphoria in adolescents and adults from *Diagnostic and Statistical Manual of Mental Disorders*

<b>I. A marked incongruence between one's experienced/expressed gender and natal gender of at least six months in duration, as manifested by at least two of the following:</b>
1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)
2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)
3. A strong desire for the primary and/or secondary sex characteristics of the other gender
4. A strong desire to be of the other gender (or some alternative gender different from one's designated gender)
5. A strong desire to be treated as the other gender (or some alternative gender different from one's designated gender)
6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's designated gender)
<b>II. The condition is associated with clinically significant distress or impairment in social, occupational or other important areas of functioning.</b>

## TRANSITIONING

Because of a pervasive sense of cultural or societal stigmatization, in conjunction with identity-related incongruence, many TG people choose to transition to a gender role that is concordant to their gender identity. Typically, these individuals make a transition from one gender to the binary opposite. The first stage of transition often entails the adoption of gender expression (i.e., physical and behavioral manifestations) that conform to one's preferred identity. Typically, this is accompanied by a social transition to affirm their desired identity. This includes adopting a chosen name, identifying one's preferred gender pronouns and utilizing non-medical approaches to confirm one's gender expression. Often TG individuals in social transition use this time to "come out" to family, friends and coworkers.

TG people may seek any number of non-medical gender-affirming interventions as part of their transition. These include cosmetic approaches such as laser hair removal, gender congruent speech training, and behavioral interventions such as genital tucking or chest binding. It is important to note that not all TG persons choose gender-affirming treatment. This decision does not make them any more or less transgender.

## HORMONAL THERAPY

Many TG individuals opt for medical and/or surgical interventions. The primary medical approach sought by TG people is the use of gender affirming hormone therapy (GAHT).<sup>21</sup> GAHT incorporates the use of feminizing and masculinizing hormones to enable the acquisition of secondary sexual characteristics consistent with an individual's gender identity. GAHT is a medically necessary intervention<sup>22</sup> for many TG individuals with gender dysphoria. Its use is associated with a significantly higher quality of life, greater self-esteem, better mood and reduction in psychological distress.<sup>12</sup> Hormone therapy can be started before an individual's complete social transition and may facilitate the process. It is well-documented that provision of GAHT has been shown to improve (one's) quality of life and reduce mood disorders such as anxiety and depression.<sup>23</sup>

The World Professional Association of Transgender Health (WPATH) is an international, multidisciplinary, professional association that promotes evidence-based safe and effective care for TG individuals. WPATH has established standards of care for individuals wishing to start GAHT. These state that any person wishing to initiate hormone therapy must present with persistent, well-documented gender dysphoria; must demonstrate the capacity to make a fully informed decision and to consent for treatment, and must be the legal age of adulthood in the country of treatment.<sup>4</sup> Additionally, if substantial medical or mental health concerns are present, they must be reasonably well-controlled.<sup>4</sup>

Historically, TG persons wanting to start GAHT required a mental health clearance to do so. The most recent WPATH guidelines (Standards of Care, 7th Version) validate an informed consent model as an alternative.<sup>4</sup> Now, medical providers who feel comfortable making an assessment and diagnosis of gender dysphoria, as well as assessing for the capacity to provide informed consent...are able to initiate gender-affirming hormone therapy.<sup>24</sup> However, medical providers should still consider utilizing health care professionals with training in TG health to assure individuals have the support necessary to transition successfully. Current WPATH guidelines focus primarily on TG individuals with binary identities, i.e., TM and TW. Similar tenets of initiation and management of hormonal therapy apply to people with nonbinary identities, with a focus on prescribing them in an individualized manner, while maintaining accepted safe parameters of use.

## BEFORE TREATMENT: INFORMED CONSENT

Hormone therapy should be provided only to those who are legally able to provide informed consent.<sup>22</sup> Screening for and addressing acute or current mental or physical health concerns that may be exacerbated by GAHT is a required component of the informed consent procedure.<sup>4</sup> Additionally, providers must ensure that patients understand the psychological and physical benefits, risks and potential psychosocial implications associated with GAHT. Patients should be informed that treatment with both feminizing and masculinizing hormones may lead to irreversible changes in gonadal function, leading to subfertility or infertility.<sup>25</sup> Patients interested in biologic parenthood should consider fertility preservation, i.e., egg or sperm banking. The risks associated with masculinizing and feminizing treatments are outlined in Table 2.

**TABLE 2:**  
Risks associated with gender affirming hormone therapy

RISK LEVEL	FEMINIZING HORMONES	MASCULINIZING HORMONES
Likely increase risk	Venous thromboembolic disease Gallstones Elevated liver enzymes Weight gain Hypertriglyceridemia	Polycythemia Weight gain Acne Androgenic alopecia Sleep apnea
Likely increased risk with presence of additional risk factors	Cardiovascular disease	
Possible increased risk	Hypertension Hyperprolactinemia or prolactinoma	Destabilization of certain psychiatric disorders Cardiovascular disease Hypertension
		Type 2 Diabetes
No increased risk or inconclusive	Breast cancer	Loss of bone density Breast cancer Cervical cancer Ovarian cancer Uterine cancer

Coleman E, Bockting W, M B. *Standards of Care For the Health of Transsexual, Transgender, and Gender-Nonconforming People*. [Minneapolis, Minn.]: World Professional Association for Transgender Health; 2012.

**PRIOR TO TREATMENT: HISTORY AND PHYSICAL**

Before initiation of GAHT a detailed medical history must be obtained. This should focus on co-morbidities that may increase the risks identified in Table 2. Patients should be asked about psychiatric diagnoses, current suicidal ideation and psychiatric hospitalizations. Because of the enhanced risk of thromboembolic events and cardiovascular disease, patients should be counseled on tobacco cessation.

A complete physical exam should be performed, with a focus on conditions that might be aggravated with GAHT. However, because of potential prior negative experiences with health care providers, attention should be made to assure patients feel safe and empowered. The need for breast, genital and rectal exams are not required before the initiation of GAHT. They can be performed after rapport and trust have been established.

**FEMINIZING HORMONE THERAPY**

The core tenet of GAHT for TG adults is to establish a hormonal environment that is biologically concordant with the person’s gender identity. This is achieved by suppressing endogenous hormones and/or supplementing exogenous hormones consistent with the individual’s affirmed gender. In TW, feminization is accomplished with the use of estrogens and anti-androgens. Feminizing hormone regimens promote breast growth, softening of the skin, reduction

of androgenic hair loss, fat redistribution from the abdomen to the hips, a change in sweat and odor patterns, and reduced prostate and testicular size.<sup>21,23</sup> Additional effects include a reduction in erectile function, changes in libido, and reductions in sperm count and volume of ejaculatory fluid.<sup>21</sup> Most changes start within the first months of treatment; maximum benefit usually occurs after approximately three years of treatment. Feminizing regimens do not affect facial hair growth and do not change the voice.<sup>23</sup>

Estrogen therapy usually involves the use of 17 β-estradiol administered either by oral, transdermal or intramuscular routes.<sup>23</sup> 17 β-estradiol is recommended rather than conjugated estrogens or ethinyl estradiol because it can be accurately measured in plasma and has a lower risk for thromboembolic disease.<sup>23,26,27</sup> Absolute contraindications to the use of estrogenic therapy include previous venous thrombotic events related to an underlying hypercoagulable condition, history of estrogen-sensitive neoplasm and end-stage chronic liver disease.<sup>4</sup>

The anti-androgen used most frequently in the U.S. is the mineralocorticoid-receptor antagonist spironolactone. Spironolactone is a potassium-sparing diuretic, which in higher doses has direct anti-androgen receptor activity as well as a suppressive effect on testosterone synthesis.<sup>28</sup> The 5-α reductase inhibitors finasteride and dutasteride are an option for patients unable to tolerate, or with contraindications to the use of spironolactone. 5-α reductase inhibitors may also be an option for those patients who continue to exhibit virilized features or hair loss after complete androgen blockade.<sup>21</sup>

Progestagens such as micronized progesterone and medroxyprogesterone acetate are less frequently used feminizing agents. They have some anti-androgen effects via the central blockage of gonadotropins. The rationale for their use is anecdotal only. Some TW report improved breast and/or areolar development, mood and libido with these agents.<sup>29</sup> Table 3 lists feminizing hormone options and dosages.

TABLE 3:

Feminizing hormone regimens

HORMONE	INITIAL DOSE	MAXIMAL DOSE	COMMENTS
<b>Estrogen</b>			
Estradiol oral	2-4 mg/day	8 mg/day	If > 2 mg is necessary use BID dosing
Estradiol Transdermal	100 mcg	100-400 mcg	Max single patch availability is 100 mcg. Frequency of application is product dependent.
Estradiol Valerate IM	20 mg IM q 2 wk	40 mg IM q 2 wk	May divide to weekly dosing at patient preference due to cyclic symptoms
Estradiol Cypionate IM	2 mg IM q 2 wk	5 mg IM q 2 wk	May divide to weekly dosing at patient preference due to cyclic symptoms
<b>Anti-androgens</b>			
Spironolactone	50 mg/day - BID	200 mg BID	
Finasteride	1 mg/day	5 mg/day	
Dutasteride		0.5 mg/day	
<b>Progestagens</b>			
Medroxyprogesterone acetate (Provera)	2.5 mg qhs	5-20 mg qhs	

Deutsch M. Guidelines for The Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People. San Francisco, CA: UCSF; 2016.

## FEMINIZING HORMONE MONITORING

TW being treated with GAHT should be seen one month after initiation of therapy, then every three months for the first year. Subsequently, they can be seen every 6–12 months, assuming they are stable and have had no complications from treatment. Estrogen and testosterone levels should be measured at each visit, with the goal to achieve a serum estradiol level between 100–200 pg/ml and a testosterone level < 50 ng/ml.<sup>26</sup>

Prolactin elevations related to the growth of pituitary adenomas have been reported with estrogen therapy. Therefore, some authorities suggest periodic monitoring of serum prolactin levels.<sup>1</sup> This is based on the case reports of prolactinomas in patients using older estrogen-cyproterone regimens. Findings from a recent study in patients treated with an estrogen-spironolactone regimen did not demonstrate prolactin elevations.<sup>30</sup> A consensus has not been reached on whether prolactin monitoring is necessary. However, it is currently recommended that prolactin levels be checked only in cases of visual disturbances, excessive galactorrhea and new-onset headaches.<sup>12</sup>

## MASCULINIZING HORMONE THERAPY

In TM, masculinization is accomplished with testosterone supplementation. Testosterone is most frequently administered via either intramuscular or subcutaneous injection, though transdermal (via patch or gel) and nasal options exist. The effects of testosterone include changes in fat distribution, growth of facial hair, an increase in muscle mass and strength, deepening of the voice and cessation of menstruation.<sup>17,23</sup> Additional effects include clitoromegaly, oily skin, acne, vaginal dryness, increased libido and androgenic hair loss.<sup>17,23</sup> As with TW, changes typically begin within the first months of use and are maximized after several years of treatment. Table 4 lists testosterone prescription options and dosages.

**TABLE 4:**

Testosterone therapy

ANDROGEN	INITIAL	MAXIMUM	COMMENTS
Testosterone Cypionate	50 mg/wk IM/SC	100 mg/wk IM/SC	Q2wk dosing at double weekly dose
Testosterone Enanthate	50 mg/wk IM/SC	100 mg/wk IM/SC	Q2wk dosing at double weekly dose
Testosterone 1% topical gel	50 mg q am	100 mg q am	Available in either pump or packet
Testosterone 1.62% topical gel	40.5–60.75 mg q am	103.25 q am	Available in either pump or packet
Testosterone patch	4 mg q pm	8 mg q pm	Patches come in 2 mg, 4 mg sizes
Testosterone cream	50 mg	100 mg	
Testosterone 2% axillary gel	60 mg q am	90–120 mg q am	One pump = 30 mg

Deutsch M. *Guidelines for The Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People*. San Francisco, CA: UCSF; 2016.

### MASCULINIZING HORMONE MONITORING

In TM, the goal is to achieve a testosterone level in the usual male range of 400–700 ng/dl.<sup>1</sup> The frequency of lab monitoring is the same as per TW. However, serum hemoglobin and hematocrit (H&H) levels should also be measured regularly, as exogenous androgens may be associated with erythrocytosis.<sup>21</sup> TM with physiologic male testosterone levels who are amenorrhoeic would be expected to have H&H values in the male normal range. TM with true polycythemia may require a reduction in their testosterone dose.<sup>21</sup>

### CONTRACEPTION

While testosterone typically induces amenorrhea, it is not an effective means of contraception.<sup>23</sup> In one recent study, 20% of TM respondents who experienced pregnancy were amenorrhoeic on testosterone at the time of conception.<sup>31</sup> Therefore, TM on testosterone needs counseling about contraception. Because testosterone is not a known contraindication to any form of contraception, transmen on testosterone should be offered all options<sup>32</sup> including subdermal etonogestrel implants, depo medroxyprogesterone, and both hormonal and nonhormonal intrauterine devices.

### GENDER CONFIRMING SURGERY

For many TG adults, gender-confirming surgery (GCS) is an essential and necessary step to alleviate their gender dysphoria and fully transition to their desired gender role.<sup>1,22</sup> Accordingly, TG people often choose to undergo GCS in conjunction with hormonal therapy. Among USTS respondents, 25% reported having undergone some form of GCS.<sup>8</sup>

Generally, GCS falls into two main categories: those that directly affect fertility and those that do not.<sup>1</sup> GCS for TW that affect fertility include gonadectomy, penectomy and creation of a neovagina.<sup>1</sup> Surgeries that affect fertility in TM include oophorectomy, vaginectomy and complete hysterectomy.<sup>1</sup>

TM may have external genital surgery as a component of GCS. Often this involves the creation of a neopenis, typically derived from a radial forearm flap.<sup>1,21</sup> As an alternative, some TM choose a

less invasive procedure, metaoidioplasty, that creates a neophallus from the hormonally enlarged clitoris.<sup>1,21</sup> In actuality, most TM opt against external genital surgery. This is related to the expense of the procedures, limited access to experienced surgeons and the potential for complications.<sup>1</sup>

Breast surgery represents the most common GCS that does not affect fertility.<sup>1</sup> For TM, the most important masculinizing surgery is mastectomy.<sup>1</sup> As breast size only partially regresses with androgen therapy, mastectomy is often necessary to create a male appearing chest. Similarly, augmentation mammoplasty is often desired by TW to achieve a feminine identity fully.<sup>1</sup> Other nongonadal GCS include numerous facial procedures to promote either masculinization or feminization.

Most guidelines recommend the use of GAHT for at least 12 months before surgical conformation to allow TG individuals to experience and socially adjust to their desired gender. Longer periods may be preferred to allow target tissues to respond to sex hormone stimulation fully. Because surgery that affects fertility is irreversible, gonadal surgery should be reserved for TG individuals who have had an acceptable social transition, are satisfied with their response to GAHT and desire definitive physical changes.<sup>1,22</sup> Detailed information regarding surgical approaches to TG care is available via the *Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People*.<sup>21</sup>

### CANCER SURVEILLANCE

TW and TM remain susceptible to cancers specific to their biological sex. TG individuals may choose to opt out of cancer screenings because of physical or emotional distress associated with inherent gender dysphoria. It is incumbent on treating physicians to advocate for organ-based routine cancer screenings for all TG patients following current standards.<sup>21</sup>

### PROSTATE CANCER

Recent literature suggests that prostate cancer is very rare among TW.<sup>17</sup> While the risk is low, underdiagnosis is possible due to a lack of close monitoring. Therefore, screening should be in concordance with the United States Preventive Services Task Force (USPSTF) guidelines, via a shared decision-making model.<sup>33</sup> Of note, when

prostate-specific antigen (PSA) testing is performed in TW with low testosterone levels, it may be appropriate to reduce the upper limit of normal to 1.0 ng/ml.<sup>21</sup>

## CERVICAL CANCER

Cervical cancer screening guidelines for TM who have not undergone hysterectomy are no different than for ciswomen. Unfortunately, papanicolaou testing (PAP) from TM has a 10-fold higher rate of uninterpretable or unacceptable samples vs. CW.<sup>34</sup> This directly correlates with an individual's duration of testosterone treatment. It is important to recognize that the speculum and bimanual exam in TM receiving GAHT may be painful due to testosterone-induced vaginal atrophy. Many TM, particularly those with gender dysphoria, may never have had vaginal penetration. Consequently, having a gynecologic exam may be distressing to the point of being unacceptable. Self-collected vaginal sampling for high-risk human papillomavirus (HPV) has been suggested as an alternative to PAP testing for TM. Self-collected PAPs have been shown to yield test results with a very high positive predictive value and may be a consideration for TM.<sup>35</sup>

## BREAST CANCER

Breast cancer screening is more individualized in TG populations; TW who have received feminizing hormone therapy or TM who have breast tissue present should be screened. TW who use estrogen supplementation in conjunction with androgen antagonists have a risk of breast cancer that is greater than for cismen (CM) but lower than for CW.<sup>12</sup> TW with feminized breast tissue and TM who have not undergone complete mastectomy should receive screening mammography as per guidelines established for CG persons. Breast imaging is typically not recommended for TW who have not received GAHT. In keeping with guidelines for CW, clinical breast examination is not recommended for either TM or TW. Mammography is not recommended for TM after a bilateral mastectomy, as mastectomy reduces the risk of breast cancer similar to CW. However, as some breast tissue may remain after surgery, an annual clinical examination of the chest wall and axilla is recommended. For TM who have not undergone a mastectomy, typical screening mammography recommendations apply.<sup>36</sup>

## HORMONE REPLACEMENT AND CARDIOVASCULAR RISK

The effects of cross-sex hormones on cardiovascular (CV) disease risk is the principal concern regarding GAHT safety. Testosterone administration in TM has been associated with reductions in high-density lipoprotein (HDL), increases in total cholesterol, triglycerides and inflammatory markers. However, no studies have demonstrated an increase in CV events among TM using testosterone.<sup>12</sup>

TW using GAHT have an increase in stroke incidence (80%) and venous thromboembolic disease (355%) when compared with CM.<sup>17</sup> This enhanced risk may be related to the hypercoagulable effect of feminizing hormones. Consequently, transdermal estradiol may be preferred in TW aged 45 or older, when there is a

history of thromboembolic or CV disease and in smokers.<sup>23</sup> There is no evidence of increased coronary events in TW using GAHT.<sup>12</sup>

Because CV disease is a prominent cause of morbidity and mortality in both men and women, modifiable CV risk factors, including lipid levels, serum glucose and blood pressure, should be regularly monitored in TG persons and addressed in accordance with guidelines for CG persons.

## CONCLUSION

As TG individuals integrate more into mainstream society, there will be an increasing demand for physicians well-versed in TG care. PCPs have a unique opportunity to address the TG population's specific health care needs in a caring and inclusive manner. PCPs must be willing to improve the skills, knowledge and awareness<sup>37</sup> necessary to integrate a more comprehensive approach to gender-affirmative care. To best accomplish this, they need to have an understanding of culturally competent TG terminology and a recognition of diversity within the TG culture. Equally important is for physicians to create a safe and welcoming environment for TG patients consciously.

The majority of medical issues affecting TG people are no different from those of the CG population. Hence, PCPs are ideally positioned to assist TG patients in making reasonable, informed choices about their health care needs. This includes decisions regarding physical health, mental health and preventive services. Providers must consider the unique impact that gender dysphoria imparts on TG patients' clinical interactions, including the history, physical examination and diagnostic testing. Special attention should be given to the impact of GAHT and GCS on biologic-based preventive screenings.

The PCP may choose to adopt an active role in hormonal management, via the informed consent model. The resources available through WPATH<sup>22</sup>, the University of California, San Francisco Center of Excellence for Transgender Health<sup>21</sup> and the American Association of Clinical Endocrinologists<sup>1</sup> are highly suggested for the PCP interested in doing so. Alternatively, the PCP can be an advocate and provide routine primary care while coordinating referrals for psychiatric, endocrinologic and/or surgical care.

## AUTHOR DISCLOSURES:

No relevant financial affiliations or conflicts of interest.

## REFERENCES:

1. Hembree W, Cohen-Kettenis P, Gooren L *et al*. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. *Endocrine Practice*. 2017;23(12):1437-1437. doi:10.4158/1934-2403-23.12.1437
2. Heise L, Greene M, Opper N *et al*. Gender inequality and restrictive gender norms: framing the challenges to health. *The Lancet*. 2019;393(10189):2440-2454. doi:10.1016/s0140-6736(19)30652-x
3. Fausto-Sterling A. *Sexing the Body*. New York: Basic Books; 2008.
4. *The Health of Lesbian, Gay, Bisexual, and Transgender People*. Washington, D.C.: The National Academies Press; 2011.

5. Winter S, Diamond M, Green J *et al*. Transgender people: health at the margins of society. *The Lancet*. 2016;388(10042):390-400. doi:10.1016/s0140-6736(16)00683-8
6. Klein DA, Paradise SL, Goodwin ET, *et al*. Caring for transgender and gender-diverse persons: what clinicians should know. *Am Fam Physician*. 2018;98(11):645-653.
7. Flores AR, Herman JI, Gates GJ, *et al*. How many adults identify as transgender in the United States? Williams Institute. <https://williamsinstitute.law.ucla.edu/> Published 2016. Accessed February 6, 2020.
8. James S, Herman J, Rankin S, Keisling M, Mottet L, Anafi M. *The Report of the 2015 U.S. Transgender Survey*. Washington, DC: National Center for Transgender Equality [NCTE]; 2016.
9. Nolan I, Kuhner C, Dy G. Demographic and temporal trends in transgender identities and gender-confirming surgery. *Transl Androl Urol*. 2019;8(3):184-190. doi:10.21037/tau.2019.04.09
10. Abeln B, Love R. Considerations for the Care of Transgender Individuals. *Nursing Clinics of North America*. 2019;54(4):551-559. doi:10.1016/j.cnur.2019.07.005
11. Kcomt L. Profound health care discrimination experienced by transgender people: rapid systematic review. *Soc Work Health Care*. 2018;58(2):201-219. doi:10.1080/00981389.2018.1532941
12. Aitken S. The primary health care of transgender adults. *Sex Health*. 2017;14(5):477. doi:10.1071/sh17048
13. Dubin SN, Nolan IT, Jr CGS, Greene RE, Radix AE, Morrison SD. Transgender health care: improving medical students' and residents' training and awareness. *Advances in Medical Education and Practice*. 2018;Volume 9:377-391. doi:10.2147/amep.s147183
14. The Lancet Diabetes & Endocrinology. Transgender health: access to care under threat. *The Lancet Diabetes & Endocrinology*. 2018;6(6):427. doi:10.1016/s2213-8587(18)30144-x
15. Committee Opinion No. 512. *Obstetrics & Gynecology*. 2011;118(6):1454-1458. doi:10.1097/aog.0b013e31823ed1c1
16. Wagner J, Sackett-Taylor A, Hodax J, Forcier M, Rafferty J. Psychosocial overview of gender-affirmative care. *J Pediatr Adolesc Gynecol*. 2019;32(6):567-573. doi:10.1016/j.jpag.2019.05.004
17. Nota NM, den Heijer M, Gooren LJ, ed. Evaluation and treatment of gender-dysphoric/gender incongruent adults. MDText.com, Inc. <https://www.endotext.org/chapter/?p=10715>. Updated July 21, 2019. Accessed February 12, 2020.
18. Hales R, Yudofsky S, Roberts L. Gender dysphoria, *The American Psychiatric Publishing Textbook of Psychiatry*, Seventh Edition.
19. *Diagnostic and Statistical Manual of Mental Disorders*. Arlington, VA: American Psychiatric Association; 2017.
20. WHO/Europe brief - transgender health in the context of ICD-11. euro.who.int. <http://www.euro.who.int/en/health-topics/health-determinants/gender/gender-definitions/whoeurope-brief-transgender-health-in-the-context-of-icd-11>. Accessed January 28, 2020.
21. Deutsch M. *Guidelines for The Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People*. San Francisco, CA: UCSF; 2016.
22. Coleman E, Bockting W, M B. *Standards of Care For the Health of Transsexual, Transgender, and Gender-Nonconforming People*. [Minneapolis, Minn.]: World Professional Association for Transgender Health; 2012.
23. Radix A. Hormone therapy for transgender adults. *Urologic Clinics of North America*. 2019;46(4):467-473. doi:10.1016/j.ucl.2019.07.001
24. Deutsch MB, Feldman JL. Updated recommendation from the world professional association for transgender health standards of care. *Am Fam Physician*, 2013;87(2):89-93.
25. Hembree W, Cohen-Kettenis P, Delemarre-van de Waal H *et al*. Endocrine Treatment of Transsexual Persons: an Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*. 2009;94(9):3132-3154. doi:10.1210/jc.2009-0345
26. Safer J, Tangpricha V. Care of transgender persons. *New England Journal of Medicine*. 2019;381(25):2451-2460. doi:10.1056/nejmcp1903650
27. Wylie K, Knudson G, Khan S, Bonierbale M, Watanyusakul S, Baral S. Serving transgender people: clinical care considerations and service delivery models in transgender health. *The Lancet*. 2016;388(10042):401-411. doi:10.1016/s0140-6736(16)00682-6
28. Prior J, Vigna Y, Watson D. Spironolactone with physiological female steroids for presurgical therapy of male-to-female transsexualism. *Arch Sex Behav*. 1989;18(1):49-57. doi:10.1007/bf01579291
29. Wierckx K, Gooren L, T'Sjoen G. Clinical review: breast development in trans women receiving cross-sex hormones. *J Sex Med*. 2014;11(5):1240-1247. doi:10.1111/jsm.12487
30. Bisson J, Chan K, Safer J. Prolactin levels do not rise among transgender women treated with estradiol and spironolactone. *Endocrine Practice*. 2018;24(7):646-651. doi:10.4158/ep-2018-0101
31. Abern L, Maguire K. Contraception knowledge in transgender individuals. *Obstetrics & Gynecology*. 2018;131:65S. doi:10.1097/01.aog.0000533319.47797.7e
32. Krempasky C, Harris M, Abern L, Grimstad F. Contraception across the transmasculine spectrum. *Am J Obstet Gynecol*. 2019. doi:10.1016/j.ajog.2019.07.043
33. Final Recommendation Statement: Prostate Cancer Screening. U.S. Preventive Services Task Force. October 2018. <https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/prostate-cancer-screening1>. Accessed January 28, 2020.
34. Peitzmeier S, Reisner S, Harigopal P, Potter J. Female-to-male patients have high prevalence of unsatisfactory paps (PAP) compared to non-transgender females: implications for cervical cancer screening. *J Gen Intern Med*. 2014;29(5):778-784. doi:10.1007/s11606-013-2753-1
35. Mangold B. Self-Collected Samples in Cervical Cancer Screening: Results of HPV and Pap Self-Collected Samples Compared to Physician-Obtained Specimens. *Acta Cytol*. 2019;63(5):379-384. doi:10.1159/000499373
36. Phillips J, Fein-Zachary V, Mehta T, Littlehale N, Venkataraman S, Slanetz P. Breast imaging in the transgender patient. *American Journal of Roentgenology*. 2014;202(5):1149-1156. doi:10.2214/ajr.13.10810
37. Fraser L, Knudson G. Education needs of providers of transgender population. *Endocrinol Metab Clin North Am*. 2019;48(2):465-477. doi:10.1016/j.ecl.2019.02.008