Primary Care

Introduction

Primary care is the broadest of health care disciplines, defined by the "provision of integrated, accessible health care services by clinicians who are accountable for addressing a large majority of personal health care needs, developing a sustained partnership with patients, and practicing in the context of family and community." (Institute of Medicine, 1996).

Primary care providers (PCPs) encompass a wide range of health care professionals who deliver this care, including general and family medical practitioners, nurse practitioners, advanced practice nurses, physician associates/assistants and internists.

PCPs cross a variety of education, training, and specialties. Given degree and specialty, the scope of practice varies, and not all providers may be trained or qualified to directly provide the full breadth of trans health care, such as mental health, genital/pelvic care, or post-operative care following gender confirming procedures. Physicians and other providers receive little education in transgender health at any time during their training (Dubin, et al., 2018; see SOC8 education section), thus most skills are currently acquired out in practice, either informally or through brief continuing education opportunities (Jaffee et al., 2016), see SOC8 education section. However, if providers are competent to deliver similar care for cisgender patients, they should develop competency with TGD patients. Competencies outlined below are all to be understood as applying within the provider's scope of licensure and practice. However, all PCPs should be able to manage the comprehensive health of transgender patients either directly or by appropriate referral to other health care providers, including other specialists, for evaluation and treatment. There is no evidence that competency in caring for TGD patients can only be achieved through a formal or certification process. In explicitly stating recommended competencies, however, PCP's and TGD persons across all settings can share a standard set of expectations of the knowledge, skills and cultural competence required in the care of TGD persons.

Due the singular medical, surgical and social conditions faced by TGD people, primary care providers (PCPs) need distinct competencies in the care of transgender persons, apart from what is expected of all PCP's who may otherwise care for diverse population, including ethnic, racial, or sexual minorities. Professional bodies from a range of generalist disciplines have issued position statements and guidelines specific to the care of TGD people, including the American College Obstetrics and Gynecology (ACOG), the Italian Society of Gender, Identity and Health (SIGIS), the Italian Society of Andrology and Sexual Medicine (SIAMS) and the Italian Society of Endocrinology (SIE), the Polish Sexological Society and Southern African HIV Clinicians' Society, 2021. (ACOG, 2021; Fisher et al., 2021; Grabski et al., 2021; Tomson et al., 2021) Reisner et al. (2015) state that "For the most part, the general health and wellbeing of transgender people should be attended to within the primary care setting, without differentiation from services offered to cisgender (non-transgender) people for physical, psychological, and sexual health issues. Specific care for gender transition is also possible in primary care." There are many examples of these services being provided safely and effectively outside of specialist care in diverse cities such as Toronto and Vancouver in Canada, New York and Boston, USA, and Sydney, Australia. (Radix & Eisfeld, 2014; Reisner, 2016)

Hormone Therapy

Whether transgender patients receive HT from a specialist, e.g., an endocrinologist, or a primary care provider (PCP) may depend on the availability of knowledgeable and welcoming providers and country-level factors such as healthcare regulations and health services funding. In much of the world, specialty services for TGD people are partly or wholly unavailable, which reinforces the need for all health providers to undertake training in provision of gender affirming care. In some countries, primary care providers may be required to refer TGD patients to specialist services (e.g., gender identity clinics) resulting in unacceptable delays to access HT. (Royal College of General Practitioners, 2019).

Hormone-related therapy encompasses a range of interventions, such as puberty suppression and hormone initiation or hormone maintenance. With training, gender affirming hormone therapy can be managed by most PCPs. Regardless of whether or not serving as the primary hormone prescriber, all PCPs should be familiar with the medications, suggested monitoring, and potential side effects for hormone therapy as noted in the Standards of Care 8 (see hormone therapy section). PCPs should be able to make appropriate referral to appropriate providers for all transition related services they do not themselves provide.

This chapter supports the argument that hormone therapy (HT) can be prescribed by PCPs or other non-specialists - “Considering barriers to health care access and the importance of HT to this population, it is imperative that PCPs are able and willing to provide HT for transgender patients (Shires, 2017).

Primary Care Providers are commonly called upon to provide care for a broad range of conditions and needs, including those with which they may have had limited or no prior experience. Often this care involves accessing commonly used and readily available reference sources, such as professional society guidelines, or subscription online knowledge bases. PCPs are advised to use a similar approach when asked to provide basic hormone therapy care, by using these Standards of Care as well as other readily accessed resources (Oliphant et al., 2018, Cheung et al., 2019, T’Sjoen et al., 2020, Hembree et al., 2017) It should be noted that most of the commonly used medications in gender affirming regimens are familiar to everyday primary care practice, including but not limited to: Testosterone, estradiol, progesterone and other progestagens, and spironolactone.

Mental Health

Primary care providers should be able and willing to provide mental health support for transgender people and gender-affirming hormone treatments that can alleviate gender dysphoria and allow gender expression. At the very least, they should be aware of these needs and consult additional specialty support if needed.
Wylie et al state that “Primary health-care providers assessing for hormone and surgery eligibility should be competent in assessing basic mental health issues and should recognize that referral to a mental health professional may be necessary—for example, where there is evidence of depression or gender minority stress.” (Wylie et al., 2016)

Preventive Care

General practitioners are versed in providing comprehensive primary and secondary cancer prevention as a part of routine primary care. Evidence based cancer prevention guidelines vary globally, due to differences in national guidelines and levels of access to screening modalities at the local level. To date, research on the long-term impact of gender affirming hormone therapy on cancer risk is limited (Blondeel et al., 2016; Braun et al., 2017). We have insufficient evidence to estimate prevalence of cancers in breast or reproductive organs among transgender populations (Joint et al., 2018). However, cancer screening should commence, in general, according to local guidelines. Several modifications are discussed in detail, below, depending on type and duration of hormone use and/or surgical intervention. The primary care provider should maintain an updated record of which organs are present for transgender patients (an organ inventory), that is updated based on surgical history or development from gender affirming hormones, and then offer routine screening as appropriate.

Not all PCP's provide care across the lifespan. However, if providers routinely care for children, adolescents or elder cisgender persons, they should develop competency in trans care applicable to these age groups. Otherwise, PCPs should be able to make appropriate referral to other health care providers caring for these populations.de.

Summary of Recommendations

Statement 1: We recommend that clinicians obtain detailed medical history for trans and gender diverse people, including past and present use of hormones and gonadal surgeries, and presence of traditional cardiovascular and cerebrovascular risk factors, in order to provide regular cardiovascular risk assessment according to established, locally used guidelines.

Statement 2: We recommend that clinicians should assess and manage cardiovascular health in trans and gender diverse people using tailored risk factor assessment and cardiovascular/cerebrovascular management methods.

Statement 3: We recommend that clinicians tailor sex-based risk calculators used for assessment of medical conditions to the needs of trans and gender diverse people, taking into consideration length of hormone use, dosing and levels, current age, and age at initiation of hormones.

Statement 4: We recommend that clinicians counsel trans and gender diverse patients about their tobacco use and advise tobacco/nicotine abstinence prior to gender affirming surgery.

Statement 5: We recommend that clinicians discuss and address aging-related psychological, medical, and social concerns with trans and gender diverse patients.

Statement 6: We recommend that clinicians follow local breast cancer screening guidelines developed for cisgender women for transfeminine individuals who have received estrogens, taking into consideration length of hormone use, dosing, current age, and age at initiation of hormones.

Statement 7: We recommend that clinicians follow local breast cancer screening guidelines developed for cisgender women in transmasculine individuals who have not had chest

masculinization surgery.

Statement 8: We recommend that clinicians should follow local screening guidelines developed for cisgender women of average and elevated risk respectively including recommendation not to screen) for transmasculine individuals of average and elevated risk for ovarian or endometrial cancer.

Statement 9: We recommend against routine oophorectomy or hysterectomy in transmasculine individuals on testosterone treatment with otherwise average risk solely for the purpose of preventing ovarian or uterine cancer.

Statement 10: We recommend that clinicians should offer cervical cancer screening to transmasculine individuals with a cervix, or a history of having a cervix, following local guidelines for cisgender women.

Statement 11: We recommend that clinicians counsel trans and gender diverse people that the use of antiretroviral medications is not a contraindication for gender-affirming hormone therapy.

Statement 12: We advise that clinicians obtain a detailed medical history on trans and gender diverse people including past and present use of hormones and gonadal surgeries, and presence of traditional osteoporosis risk factors, to assess optimal age and necessity for osteoporosis screening.

Statement 13: We advise that clinicians discuss bone health with transgender individuals including the need for active weight bearing exercise, healthy diet, calcium and vitamin D supplementation and fall prevention strategies.

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Cardiovascular disease (CVD) and stroke are the leading causes of mortality worldwide (World Health Organization, 2017). Extensive data among racial, ethnic and sexual minorities in multiple settings demonstrate significant disparities in prevalence of CVD and its risk factors, as well as outcomes to medical interventions. Structural factors such as access to care, socioeconomic status, and allostatic load related to minority stress contribute to these disparities (Flentje et al., 2019; Havranek et al., 2015). TGD people often experience social, economic and discriminatory conditions similar to other minority populations with known increased cardiovascular risk (James et al., 2016, Reisner et al., 2016; Carpenter et al., 2020). Transgender and gender diverse persons of racial, ethnic and sexual minorities would experience increased impact related to intersectional stress. Conversely, access to gender affirming care, including hormone therapy, may buffer against the elevation of CVD risk due to improving quality of life, and reducing gender dysphoria and incongruence (Martinez C et al., 2018; Defreyne, J et al., 2019). Primary care providers can significantly improve transgender health through screening and prevention of CVD and its associated risk conditions—tobacco use, diabetes mellitus, hypertension, dyslipidemia, and obesity.

The few, primarily U.S based, studies of the prevalence of CVD, stroke or CVD risk in transgender and gender diverse persons independent of hormone therapy indicate elevated CV risk, including high rates of undiagnosed and untreated CV risk factors with inadequate CV prevention compared to cisgender populations (Denby et al., 2021; Nokoff et al., 2018, Malhotra, A et al., 2020). In one population based study, transgender people had greater odds of discrimination, psychological distress, and adverse childhood experience, and these were associated with increased odds of a having cardiovascular condition (Poteat et al., 2021).

In U.S studies based on the data from the Behavioral Risk Factor Surveillance System, both transgender men and transgender women show higher prevalence of myocardial infarction (MI), stroke, or any CVD compared to cisgender men and/or cisgender women. Results vary based on the adjustment of data for additional variables, including race, income or cardiovascular risk factors. (Nokoff et al., 2018; Caceres et al., 2020, Alzahrani et al., 2019). Gender nonbinary persons also had higher odds of CVD (Downing & Przedworski, 2018). Data on hormone use was not collected in these studies, and the studies are limited by the use of self-reported health histories. In the U.S., transgender and gender diverse individuals presenting for hormone therapy may have higher rates of undiagnosed and untreated CVD risk factors compared to the cisgender population (Denby et al., 2021), although may not be applicable globally.

A large 2018 case control study from several US centers which used 10:1 cisgender matched controls found no statistically significant difference in rates of MI or stroke between transgender women and cisgender men, and rates of MI, stroke, or VTE between transgender men and cisgender men or women. There was a statistically significant hazard ratio of 1.9 for venous thromboembolism among transgender women in comparison to cisgender men. A sub-cohort of transgender women who initiated hormone therapy during (as opposed to prior to) the 6-year study window did show an increased risk of stroke. Increases in rates of VTE in the overall cohort of transgender women and stoke in the initiation sub-cohort of transgender women demonstrated calculated numbers-needed-to-harm (not reported in the paper) between 71-123. (Getahun et al, 2018) Other studies have demonstrated no increase in CV events or stroke among transgender men on testosterone therapy, though studies are limited by small sample size, relatively short follow up, and younger age of sample population. (Nota et al., 2019; Martinez et al., 2020).

European and US studies in transgender women who have accessed feminizing hormone therapy increasingly indicate higher risk of CVD and/or stroke, compared to cisgender women

and in some studies, cisgender men (Wierckx et al., 2013; Nota et al., 2019; Getahun et al., 2018). Many of these studies had significant limitations: variably adjusting for CV related risk factors, small sample sizes especially of older transgender women, and variable duration and types of hormone therapy (Connelly et al., 2019; Defreyne et al., 2019, Connelly et al., 2019 Martinez et al., 2020). The overall increased risk was small. The majority of transgender women who experienced cardiac events or stroke in many of these studies were over 50 years old, had one or more CVD risk factors, and were on a variety of hormone regimens, including but not limited to ethinyl estradiol, which is a synthetic estrogen that confers significant elevations in thrombotic risk and is not recommended for use in feminizing regimens. (Martinez et al., 2020; Gooren et al., 2014). Current limited evidence suggests that estrogen-based hormone therapy is associated with an increased risk of myocardial infarction and stroke, but whether this small risk is a result of hormone therapy or an effect of pre-existing CV risk in unclear. There are no known studies specifically addressing CVD and related conditions in non-binary individuals, those who use sub-physiologic doses of gender affirming hormones, or in adults previously treated with puberty suppression.

Primary care providers can best address CVD risk during hormone therapy by assessing transgender and gender diverse people for CVD and modifiable CVD risk factors: diabetes mellitus, hypertension, hyperlipidemia, obesity, and smoking, as well as address minority stress contributing to cardiovascular risk. In addition, primary care providers can mitigate transgender cardiovascular health disparities with timely diagnosis and treatment of risk conditions, and tailored management supportive of ongoing gender affirming interventions.

Risk assessment guidelines vary, based on the national or international context and scientific affiliation of guideline developers. CVD prevention guidelines vary regarding the nature and frequency of risk assessment for otherwise healthy adults under age 40 (WHO, 2007; Arnett et al., 2019; Authors/Task Force members et al., 2016; Precoma et al., 2019) Over age 40, when cardiovascular risk increases, guidelines clearly recommend scheduled risk assessment using a calculated prediction of ten-year total CVD risk, based on risk prediction equations from large population samples. Examples of risk calculators include SCORE (recommend by European Guidelines on CVD Prevention), Pooled Cohort Studies Equations (2013 AHA ACC Guideline on the assessment of CVD risk), Framingham risk scores, and the World Health Organization (WHO) Risk Prediction Charts. The WHO charts were developed based on information on the countries in each WHO subregion. In many low resource settings, facilities are not available to measure cholesterol or serum glucose, and alternative predication charts are available based without these measures.

However, all current cardiovascular risk calculators are gendered, using sex as a significant risk variable. There is currently insufficient data on cardiovascular risk interventions across the lifespan in transgender and gender diverse persons with medical and surgical interventions to adjust these predictive equations. Nonetheless, it is clear that both sex-assigned at birth and medical transition can affect the parameters used to calculate cardiovascular risk (Maraka et al., 2017; Martinez et al., 2020; Defreyne et al., 2019; Connelly et al., 2019). Providers can take a variety of approaches to the use of cardiovascular risk calculators in transgender and gender diverse persons, including using the risk calculator for the sex assigned at birth, affirmed gender, or a weighted average of the two, taking into consideration total lifetime exposure to hormone therapy. Though data are lacking, it is likely most appropriate to use the affirmed gender for transgender adults with a history of pubertal-age hormone therapy initiation. Patients with a history of sub-maximal hormone therapy use, or prolonged periods of time post-gonadectomy without hormone replacement before roughly age 50 may require an even more nuanced approach. Providers should be aware of the characteristics and limitations of the risk

calculator in use. Providers should engage patients in shared decision making regarding these specific considerations.

There are currently no studies comparing the prevalence of dyslipidemia between transgender and cisgender samples, controlled for hormone use. As noted previously, data in other populations demonstrates that psychosocial stress during childhood and remote adulthood favor adiposity and abnormal lipid metabolism (Grebreab et al., 2018). Both testosterone and estrogen-based hormone therapy affect lipid metabolism, although evidence is limited by the variety of hormone regimens and additional variables (Maraka et al., 2017; Martinez et al., 2020; Defreyne et al., 2019 Connelly et al., 2019; Deutsch et al., 2013). On balance, estrogen tends to raise in high-density lipoprotein (HDL) cholesterol and triglycerides, with variable effects on low density lipoprotein (LDL) cholesterol, while testosterone variably affects triglycerides, decreases HDL cholesterol and increase LDL cholesterol. The method of administration may affect this pattern, particularly related to oral versus transdermal estrogen and triglycerides (Maraka et al., 2017). In general, the effect sizes of these differences are minimal, and the overall impact on cardio- and cerebrovascular outcomes are unclear. There are no studies examining hormone effects on transgender and gender diverse people with pre-existing dyslipidemia, with hormone use starting over age 50 or effects beyond 2-5 years of therapy.

There are currently no studies comparing the prevalence of hypertension between transgender and cisgender samples, controlled for hormone use. Data in other populations demonstrates that chronic and acute psychosocial stress, including experiences of discrimination, can mediate hypertension (Spruill, 2010; Din-Dzietham et al., 2004). There were no differences in reported hypertension between transgender men or women compared to cisgender samples in studies from U.S. the Behavioral Risk Factor Surveillance System, a large national US health survey. (Nokoff et al., 2018; Alzahrani et al., 2019).

Studies of testosterone and estrogen-based hormone therapy have shown inconsistent effects on systolic and diastolic blood pressure, and a systematic review concluded that given the limited quality of the studies, there is insufficient data to reach conclusions on the effects of gender affirming hormone therapy on blood pressure (Connelly et al., 2021). Spironolactone, often used as an androgen blocker in feminizing hormone therapy, is a potassium sparing diuretic, and may increase potassium when use conjunction with ACE inhibitors or angiotension receptor blocker medications, as well as salt substitutes. There are no studies examining hormone effects on transgender and gender diverse people with pre-existing hypertension, with hormone use starting over age 50 or effects beyond 2-5 years of therapy. Transgender persons on hormone therapy should undergo any additional blood pressure screening or monitoring as indicated by WPATH guidelines for hormone therapy.

There are currently no studies comparing the prevalence of diabetes mellitus between transgender and cisgender samples, independent of hormone use. Data in other populations, including sexual minorities, indicates that chronic and acute psychosocial stress can mediate the development and control of type 2 diabetes (Kelly and Mubarak, 2015; Beach et al., 2018).

No differences in reported diabetes were found between transgender men, transgender women or nonbinary persons compared to cisgender samples in studies from the U.S. Behavioral Risk Factor Surveillance System (Nokoff et al., 2018; Alzahrani et al., 2019; Caceres et al., 2020). Several small studies have shown a higher-than-expected prevalence of polycystic ovarian syndrome or hyperandrogenemia among transgender men (Feldman, J 2016), conditions associated with insulin resistance and diabetes risk. While studies of both testosterone and estrogen-based hormone therapy show varying effects on weight/body fat, glucose metabolism

and insulin resistance (Defreyne et al., 2019), most do not demonstrate any increase in prediabetes or diabetes (Connelley et al., 2019; Chan et al., 2018). There are no studies examining hormone effects on transgender and gender diverse people with pre-existing diabetes, with hormone use starting over age 50 or effects beyond 2-5 years of therapy. There are currently no studies specifically addressing diabetes in adults previously treated with puberty suppression.

Statement 4:
We recommend that clinicians counsel trans and gender diverse patients about their tobacco use and advise tobacco/nicotine abstinence prior to gender affirming surgery.

Tobacco use is a leading contributor to cardiovascular disease, pulmonary disease and cancer worldwide (World Health Organization, 2020, May 27). TGD persons have a higher prevalence of tobacco use compared to cisgender individuals, varying across the gender spectrum (Buchting et al., 2017; Azagba et al.,2019), a pattern consistent with other populations experiencing minority stress (Gordon et al., 2020). Primary care providers can promote protective factors against tobacco use, including reducing exposure to personal or structural discrimination, having gender affirming identification, and having health insurance (Shires & Jafee, 2016; Kidd et al., 2018).

The health risks of tobacco use affect trans and gender diverse persons disproportionately, primarily due to decreased access to culturally competent, affordable screening and treatment of tobacco related disease (Shires & Jafee, 2016; Alzahrani et al., 2020). Smoking may further increase cardiovascular and venous thromboembolic risk for trans and gender diverse individuals on feminizing gender affirming hormone therapy (Alzahrani et al., 2020; Hontscharuk et al., 2021). Smoking doubles or triples the risk of general surgery complications, such as wound healing, scarring, and infection (Yoong et al., 2020), increasing the risk for those accessing gender affirming surgeries. Quitting smoking prior to surgery and maintaining abstinence for six weeks after significantly reduces complications (Yoong et al., 2020)

There are currently few studies of smoking cessation programs specifically focused on trans and gender diverse persons (Berger & Mooney-Somers, 2017). Limited evidence suggests, however, that primary care providers can enhance smoking cessation efforts by addressing the effects of minority stress (Gamarel et al., 2015), and incorporating gender affirming interventions such as hormone therapy (Myers & Safer, 2016).

Statement 5:
We recommend that clinicians discuss and address aging-related psychological, medical, and social concerns with trans and gender diverse patients.

Aging presents specific social, physical, and mental health challenges for trans and gender diverse persons. While the literature on aging and trans elders is limited, many older trans and gender diverse adults have experienced a lifetime of stigma, discrimination, and repression of identified gender (Witten, et al.,2017; Fabbre, V. D., & Gaveras, E. 2020). This experience affects trans and gender diverse elders' interactions with health care (Fredriksen-Goldsen et al., 2014; Kattari & Hasche, 2016; Walker et al., 2017). Trans elders are more likely than cisgender LGB peers to report poor physical health, even when controlled for socio demographic factors. (Fredriksen-Goldsen et al., 2011; Fredriksen-Goldsen et al., 2014). Reduced access to culturally competent care and sequelae of minority stress often result in delayed care, potentially

exacerbating chronic conditions common with aging (Fredriksen-Goldsen et al., 2014; Bakko & Kattari, 2021.

Although there are few studies on gender affirming medical interventions among trans and gender diverse elders, evidence suggests that older adults experience significantly higher quality of life with medical transition even compared to younger trans and gender diverse adults (Cai, X et al., 2019). Age itself is not an absolute contraindication or limitation to gender affirming medical or surgical interventions, however trans and gender diverse elders may not be aware of the current range of social, medical or surgical options available to meet their individual needs (Hardacker et al., 2019; Houlberg, 2019).

While studies on mental health among trans and gender diverse elders are limited, those over age fifty experience significantly higher rates of depressive symptoms and perceived stress compared to cisgender LGB and heterosexual older adults. (Fredriksen-Goldsen et al., 2011, Fredriksen-Goldsen et al., 2014). Risk factors specific to trans and gender diverse elders include gender and age-related discrimination, general stress, identity concealment, victimization, and internalized stigma, while social support, and community belonging appear protective (Fredriksen-Goldsen et al., 2014; Hoy-Ellis& Fredriksen-Goldsen, 2017; White Hughto & Reisner, 2018). PCPs may assist patients by encouraging spirituality, self-acceptance and self-advocacy, and an active healthy lifestyle which are associated with resilience and successful aging (McFadden et al., 2013; Witten, 2014).

TGD elders often face social isolation and loss of support systems, including close friends and children (Fredriksen-Goldsen et al., 2011; Witten, 2017). The most common aging concerns among trans and gender diverse persons are losing the ability to care for themselves followed by having to go into a nursing home or assisted living facility (Henry et al., 2020). Long term care settings present the potential for physical or emotional abuse, denial of hormones, denial of routine care, being “outed,” and being prevented to live and dress according to ones affirmed gender Services and Advocacy for GLBT Elders (SAGE) and National Center for Transgender Equality (NCTE), 2012; Porter et al., 2016; Pang et al., 2019). TGD elders identify senior housing, transportation, social events, support groups as being most needed services (SAGE) and National Center for Transgender Equality (NCTE), 2012; Witten, 2014).

Despite barriers, most trans and gender diverse persons engage in successful aging, strengthened with clear areas of resilience (Fredriksen-Goldsen et al., 2011; Witten, 2014). Primary care providers should address core health issues facing trans and gender diverse elders, including mental health, gender affirming medical interventions, social support, and end of life/long term care.

Beyond the independent impact of factors such as minority stress and social determinants on health in later years, data are lacking on specific health issues for transgender people using hormone therapy later in life, including those who began hormone therapy at a younger age, and those seeking to continue or begin hormone therapy in their sixth, seventh, eighth, or later decades. With an increasing proportion of transgender people beginning hormone therapy at younger ages, including some who begin at the time of puberty, studies to examine the impact of decades of treatment on long-term health are ever more important.

Statement 6:

We recommend that clinicians follow local breast cancer screening guidelines developed for cisgender women for transfeminine people who have received estrogens, taking into

consideration length of hormone use, dosing, current age, and age at initiation of hormones.

Transfeminine people taking estrogen will develop breasts and therefore warrant consideration for breast cancer screening. Exogenous estrogen may be one of multiple factors that contribute to breast cancer risk in cisgender people. Two cohort studies have been published on breast cancer prevalence among transgender women in the Netherlands (Gooren et al., 2013) and the U.S. (Brown & Jones, 2015). Both were retrospective cohorts of clinical samples using a diagnosis of breast cancer as the outcome of interest, with comparisons made to cisgender controls. Neither study involved prospective screening for breast cancer, and both have significant methodologic limitations. Numerous guidelines have been published (Center of Excellence for Transgender Health & Community Medicine, 2016) recommending some combination of age + length of estrogen exposure as the determinant of need to commence screening. These recommendations are based on expert consensus only and are evidentiarily weak.

BRCA 1 and 2 mutations increase the risk of breast cancer, including the risk of hormone sensitive tumors. The degree of increase in risk, if any, from gender affirming estrogen therapy is unknown. Patients with a known BRCA1 mutation should be counseled on the unknowns, and shared decision making with informed consent should occur between the patient and provider, recognizing the numerous benefits of hormone therapy.

Other considerations for breast cancer screening among transgender women may include that transgender woman are likely to have more dense breasts on mammography. Dense breasts, history of injecting breasts with fillers such as silicone, and/or breast implants may complicate interpretation of breast imaging via mammography (Sonnenblick et al., 2018); special techniques should be used accordingly. People who have injected particles for breast augmentation such as silicone or other fillers may have complications, including sclersosing lipogranulomas that obscure normal tissue on mammography or ultrasound.

Statement 7:
We recommend that clinicians follow local breast cancer screening guidelines developed for cisgender women in transmasculine people who have not had chest masculinization surgery.

For transgender men, theoretical concerns exist regarding direct exposure to testosterone as well as aromatized estrogen resulting from testosterone therapy as a risk factor for the development of breast cancer. Limited retrospective data has not demonstrated increased risk for breast cancer among transgender men (Gooren et al., 2013; Grynberg et al., 2010), however prospective and comparison data are lacking. Most people who have had chest masculinization surgery will have some breast tissue remaining, and therefore it is important for providers to be aware that breast cancer risk is not zero in this population. The timing and approach to breast cancer screening in transgender men who have had chest surgery is currently not established, and, similar to cisgender men with significant family history or BRCA gene mutation, screening via MRI, or ultrasound may be appropriate. Because the utility and performance of these approaches have not been studied, and because self- and clinician-led chest/breast exams are not recommended in cisgender women due to potential harms of both false-positive results and over-detection (detection of a cancer which would have regressed on its own with no need for intervention), any approach to screening in transgender men who have had chest surgery

should occur in the context of shared decision making between patients and providers regarding the potential harms, benefits, and unknowns of these approaches.

Statement 8:
We recommend that clinicians should follow local screening guidelines developed for cisgender women of average and elevated risk respectively (including recommendation not to screen) for transmasculine people of average and elevated risk for ovarian or endometrial cancer.

Current consensus guidelines do not recommend routine ovarian cancer screening in cisgender women. Case reports of ovarian cancer among transgender men have been reported (Dizon et al., 2006; Hage et al., 2000). No evidence currently exists to suggest that testosterone therapy leads to an increased risk of ovarian cancer, however long-term prospective studies are lacking (Joint et al., 2018).

Statement 9:
We recommend against routine oophorectomy or hysterectomy in transmasculine people **on testosterone treatment with otherwise average risk solely for the purpose of preventing ovarian or uterine cancer.**

Transgender men are often in an oligo- or anovulatory state, or otherwise experience shifts in leuteal phase function and progesterone production. This combined with the possible increased estrogen exposure from aromatization of exogenous testosterone raises the concern for excessive or unopposed endometrial estrogen exposure, although clinical significance is unknown. Histologic studies of the endometrium in transgender men taking testosterone have found atrophy rather than hyperplasia (Grimstad et al., 2018; Grynberg et al., 2010; Perrone et al., 2009). In a large cohort of transmasculine people who had hysterectomy with oophorectomy, benign histopathology in ovaries was noted in all cases (n=85) (Grimstad et al., 2020). While prospective outcome data are lacking, there is insufficient evidence at this time to support a recommendation of routine hysterectomy or oophorectomy solely conducted for prevention of endometrial or ovarian cancer in transgender men. Otherwise, unexplained signs/symptoms of endometrial or ovarian cancer should be evaluated appropriately.

Statement 10:
We recommend that clinicians should offer cervical cancer screening to transmasculine individuals with a cervix, or a history of having a cervix, following local guidelines for cisgender women.

Individuals with a cervix should undergo routine cervical cancer prevention and screening according to age-based regional practices and guidelines. This includes vaccination against the human papilloma virus (HPV) and screening according to local guidelines, including cytologyic, high-HPV co-testing if available. Is important that clinicians are mindful of approaches to the pelvic speculum exams that minimize pain and distress for trans masculine people.

TGD people with a cervix are less likely to have had conventional cervical cancer screening, often because the exam can cause worsening of dysphoria and/or general practitioners and patients are misinformed about the need for this screening (Agenor et al., 2016; Potter et al.,

2015). Testosterone therapy can result in atrophic changes of the genital tract, and length of time on testosterone has been associated with greater likelihood for insufficient sampling on cervical cancer screening cytology (Peitzmeier et al., 2014). Alternatives to speculum exams and/or cervical cytology, such as provider- or self-collected high-risk HPV swabs, may be of particular benefit for screening people with a cervix. Research underway in the U.S. is examining use of self-collected vaginal high-risk HPV testing among trans masculine populations; HPV swabs were found to be highly acceptable among trans men with a sensitivity to high-risk HPV of 71.4% (negative predictive value of X) and specificity of 98.2%, (Reisner et al., 2018). Further study is needed on the harms of HPV primary screening in transgender men with respect to potential increased risk of invasive examinations and colposcopies.

Statement 11:

We recommend that clinicians counsel trans and gender diverse people that the use of antiretroviral medications is not a contraindication for gender-affirming hormone therapy.

PCPs have unique opportunities to contribute crucial education and prevention efforts, especially related to decreasing HIV burden among transgender women. Mistrust of health care providers due to past experiences of discrimination and transphobia impacts HIV prevention and linkage to care efforts (Sevelius et al., 2016; Silva-Santisteban et al., 2016). Stigma, lack of adequate training, and innate power hierarchies within medical establishments all contribute to ambivalence and uncertainty among health care professionals when caring for transgender patients (Poteat et al., 2013). Finally, a lack of inclusive and gender affirming practices in the health care setting may lead to transgender people feeling unsafe discussing sensitive topics such as HIV diagnosis and avoiding care out of fear (Bauer et al., 2014; Gibson et al., 2016; Minor Peters, 2016; Seelman et al., 2017).

Clinicians should be aware of this broader context within which many trans and gender diverse people are seeking care for either gender affirming hormones and/or HIV chemoprophylaxis or treatment. Various misconceptions may exist about the safety of taking gender affirming hormones concurrently with antiretroviral therapy for HIV chemoprophylaxis or treatment.

Direct study of ART/GAHT interactions has been limited. Two studies of the effects of GAHT on tenofovir diphosphate (Grant et al., 2021) and tenofovir diphosphate and emtricitabine (Shieh et al., 2019) have found some signals of statistically significant lowered ART drug levels of unlikely clinical significance. Data on interactions between hormonal contraceptives and anti-retrovirals on the whole are reassuring with respect to the impact of hormones on ART (Nanda et al., 2017). Because estradiol is partially metabolized by cytochrome P450 (CYP) 3A4 and 1A2 enzymes, potential drug interactions with other medications that induce or inhibit these pathways, such as non-nucleoside reverse transcriptase inhibitors (NNRTIs, e.g., efavirenz (EFV) and nevirapine (NVP) may exist. (Badowski, 2021). (DHHS 2021). However, the preferred first-line ART regimens in most countries use integrase inhibitors, which have minimal to no drug interactions with gender-affirming hormones and can be used safely (Badowski, 2021, DHHS 2021).

If concerns exist about potential interactions, clinicians should monitor hormone levels as needed. Therefore, trans and gender diverse people living with HIV and taking antiretroviral medications should be counseled that taking antiretrovirals is safe alongside gender affirming hormone therapy.

Statement 12:
We advise that clinicians obtain a detailed medical history on trans and gender diverse people including past and present use of hormones and gonadal surgeries, and presence of traditional osteoporosis risk factors, to assess optimal age and necessity for osteoporosis screening.

Statement 13:
We advise that clinicians discuss bone health with transgender individuals including the need for active weight bearing exercise, healthy diet, calcium and vitamin D supplementation and fall prevention strategies.

Estrogen and testosterone both impact bone formation and turnover. Testosterone results in greater periosteal apposition and bone mass in individuals assigned male at birth who have a male puberty however peak bone mineral density (BMD) does not vary by sex assigned at birth. (Almeida et al., 2017; Vanderschueren et al., 2004) Declines of sex hormones are associated with development of osteoporosis in older age. (Almeida et al., 2017). The World Health Organization has stated that the osteoporosis prevention and its associated fractures is essential to the maintenance of health and quality of life. (World Health Organization, 2004)

TGD individuals may receive medical and/or surgical interventions that have the potential to influence bone health, such as receipt of sex hormones, androgen blockers, and gonadectomy, therefore a detailed medical history, including past and present use of hormones and gonadal surgeries is necessary to establish the need for osteoporosis screening.

Several observational studies have compared BMD in transgender adults before and after receipt of hormones and in transgender individuals compared to sex-at-birth matched cisgender controls. These studies have had disparate results, including both increases and decreases in BMD after initiating GAHT, likely due to different study designs, hormone regimes and length of follow-up. In recent years, well conducted prospective studies and systematic reviews and metanalyses have advanced knowledge about bone health for TGD persons.

Low bone mineral density may exist before initiation of hormones. One study among transgender women showed lower mean areal BMD at the femoral neck, total hip and spine compared to age-matched cisgender male controls, (Van Caenegem et al., 2013) and another study revealed a high prevalence of low BMD scores among TGD youth before starting puberty blockers. (Lee et al., 2020). The authors for both studies concluded that low rates of physical activity may be an important contributor to these findings.

Acceleration of bone loss can occur after gonadectomy if hormones are stopped, or hormones levels are suboptimal. In one study, thirty percent of transgender women who had undergone gonadectomy had low bone mass, and this correlated with lower 17B estradiol levels and adherence to GAHT. (Motta et al., 2020)

Investigation of the effects of GAHT on BMD have revealed that transgender women receiving estrogen therapy show improvements in BMD. A systematic review and meta-analysis on the impact of sex hormones on bone health of transgender individuals included 9 eligible studies in transgender women (n=392) and 8 eligible studies in transgender men (n=247) published between 2008 and 2015. The meta-analysis revealed that transgender women showed a statistically significant increase in lumbar spine BMD (but not femoral neck BMD) compared with

baseline measures. Among transgender men, there were no statistically significant changes in the lumbar spine, femoral neck, and total hip BMD at 12 and 24 months after starting testosterone compared to baseline. (Singh-Ospina et al., 2017) Since the publication of this study, the European Network for Investigation of Gender Incongruence (ENIGI) study, a multicenter prospective observational study (Belgium, Norway, Italy and the Netherlands) published results on BMD outcomes for 231 transgender women and 199 transgender men one year after initiating hormone therapy. (Wiepjes et al., 2017) Transgender women had an increase in BMD of the lumbar spine, total hip and femoral neck, and increased BMD of the total hip occurred in transgender men. One study has reported no fractures in transgender individuals at 12 months following initiation of hormones (53 transgender men and 53 transgender women. (Wierckx et al., 2014). These studies provide guidance that receipt of GAHT alone is not an indication for enhanced osteoporosis screening.

The recommended screening modality for osteoporosis is dual energy x-ray absorptiometry (DXA) of the lumbar spine, total hip and femoral neck. (Kanis, 1994) However in many low- and middle-income countries BMD tests using DXA are not available, and routine DXA-based screening is conducted in few countries, the USA being an exception. When they exist, recommendations for BMD screening are based on several factors including sex assigned at birth, age and presence of traditional risk factors for osteoporosis, such as prior fracture, high risk medication use, conditions associated with bone loss and low body weight. (International Society for Clinical Densitometry, 2019)

Clinical practice guidelines include recommendations for osteoporosis screening in TGD individuals. (Hembree et al., 2017; Rosen et al., 2019; UCSF Transgender Care, 2016) For TGD people, both the ISCD and The Endocrine Society suggest consideration of baseline BMD screening before initiation of hormones. The ISCD guidelines state that BMD testing is indicated for TGD individuals if they have a history of gonadectomy or therapy that lowers endogenous gonadal steroid levels prior to initiation of hormone therapy, hypogonadism with no plan to take GAHT or known indications for BMD testing.(Rosen et al., 2019)). However, the evidentiary basis for these recommendations is weak, and widespread implementation is not practical and unlikely to result in interventions or changes in management. From the perspective of face validity, there is no reason to suspect that GAHT in the setting of gonadectomy or endogenous hormonal suppression with physiologic add-back until at least the age of 50 would lead to clinically relevant BMD disorders requiring intervention.

PCPs should discuss ways to optimize bone health with TGD clients. In addition, PCPs should provide information about the importance of nutrition and exercise on maintaining bone health. TGD individuals with, or at risk for, osteoporosis should be informed about the benefits of weight bearing exercise and strength and resistance exercises in limiting bone loss. (Benedetti et al., 2018). Good nutrition is integral to bone health as nutritional deficiencies, including insufficient calcium intake and low vitamin D, can result in low bone mineralization. Vitamin D and calcium supplementation have been shown to reduce hip as well as total fracture incidence (Weaver et al., 2016). Although relevant to all populations, this discussion is pertinent as high prevalence of hypovitaminosis D has been seen in TGD populations. (Motta et al., 2020; Van Caenegem et al., 2013).

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