



Transgender patients: considerations for routine gynecologic care and cancer screening

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HIGHLIGHTS

- Gynecologists should be familiar with gender diversity, incorporate gender-neutral language, and be able to treat or refer transgender patients.
- Gender-confirming therapies should be considered for an adequate breast and reproductive cancer screening.
- Long-term prospective studies are imperative to promote healthcare equity incorporating non-traditional genders and sexualities.

ABSTRACT

In the last several years, demand for transgender care from gynecologists has increased significantly. Transgender people comprise a diverse group who do not identify with the sex they were assigned at birth. Worldwide, it is estimated that 25 million people identify as transgender. Some undergo hormonal and/or surgical treatment aiming to feminize or masculinize their bodies. Cross-sex hormone treatment for transgender women—individuals assigned as male at birth who identify themselves as women—includes exogenous estrogen and/or progestin administration in combination with anti-androgens, whereas testosterone is used for transgender men—individuals whose natal sex is women but identify themselves as men. Although it is usually rare, hormone-sensitive malignancies may arise, and long-term effects remain unknown. In addition, reconstructive surgeries may include breast augmentation and vaginoplasty (creation of a vagina) for transgender women, and chest masculinization surgery (bilateral mastectomy) and metoidioplasty (lengthening of the clitoris to create a microphallus) or phalloplasty (creation of a phallus) for transgender men. Evidence relating to breast and reproductive tract cancers in the trans population is limited and insufficient to estimate cancer prevalence, and recommendations for screening and preventive care depend on the patients' hormonal and surgical status. Even less information exists regarding the sub-set of individuals with genetic predisposition for these malignancies. In this review, we aimed to summarize current recommendations for gynecologists and gynecologic oncologists regarding cancer screening and personalized cancer-risk assessment in transgender people.

INTRODUCTION

The American Collage of Obstetrics and Gynecologists (ACOG) and the Royal College of Obstetricians and Gynecologists (RCOG) recommend that gynecologists deal with sexual health in routine clinical practice and encourage not making assumptions or judgments on patients' sexual behavior, including relationships and

sexual practices, aiming to promote sexual health as a right for every person.¹ Gender diversity is an important part of sexual health, and gynecologists should be aware of its variations in order to offer the best screening and preventive strategies. The World Health Organization (WHO) defines sexual health as “a state of physical, emotional, mental, and social well-being in relation to sexuality, which includes sex, gender identities, and roles, sexual orientation, eroticism, pleasure, intimacy, and reproduction”² (Table 1).

TRANSGENER POPULATION

In this manuscript, we will focus on transgender individuals, who are a wide range of people whose sexual identity does not align with the sex they were assigned at birth. A *transfemale* or *transwoman* is a term used to identify someone who was assigned male sex at birth and identifies as a female/woman. On the other hand, *transmale* or *transman* is a person who was assigned female sex at birth and identifies as a male/man. Many transgender people may not self-identify based on binary definitions, or may identify elsewhere along the spectrum of masculine/feminine gender, or their gender identity may vary over time: *gender non-binary*, *gender non-conforming*, *gender fluid*.³ Gender dysphoria is a term used to describe the discomfort or distress that is caused by the discrepancy between their gender identity and sex assigned at birth.

It is estimated that 0.3–0.5% of the world population identifies as transgender, which represents approximately 25 million people. However, the overall world prevalence of transgenderism is difficult to estimate due to discrimination, violence, and social stigma. In the United States, approximately 0.6% of adults or 1.4 million people identify as transgender.⁴ Transgender people are a diverse population affected by a variety of negative health indicators.⁵ Moreover, they often experience discrimination in the

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Table 1 Sexual health definitions

Term	Definition
Sex	Biologic characteristics (sex chromosomes, hormones, reproductive organs, genitalia) used to describe someone as male, female, or variation thereof
Sex assigned at birth	In many cultures, sex is assigned at birth based on the appearance of the neonate's external genitalia. Male: presence of a penis. Female: presence of a vulva. Intersex: sexual anatomy that does not fit typical definitions of male or female
Gender	A social construct, rooted in cultural expectations that drives an individual's outward appearance and behavior
Gender identity	Corresponds to the individual's fundamental and innate sense of being female, male, or identifying with both or neither
Cisgender	Adjective to describe people whose gender identity aligns with sex assigned at birth
Transgender	Adjectives to describe people with gender identity not aligned with sex assigned at birth
Gender expression/roles	Ways in which people communicate gender identity to others.
Gender dysphoria	Mental health term that refers to discomfort or distress caused by the lack of alignment between gender identity and sex assigned at birth
Sexual orientation	Refers to the emotional, physical and erotic attraction that people experience to other people, independent of gender identity.

healthcare setting and lack of access to medical personnel competent in transgender medicine.⁶ The World Professional Association for Transgender Health (WPATH) has published clinical guidelines for professionals who assist transgender individuals, which focus on different, if any, treatment options that include: changes in gender expression, hormone therapy to feminize or masculinize the body, surgical approach to change primary and/or secondary sex characteristics, and/or psychotherapy for purposes such as alleviating internalized transphobia, improving body image, or promoting resilience.⁷ The American Psychological Association, the American Psychiatric Association, and WPATH, among other organizations, have concluded that there is no single explanation for gender-variant behavior, and that gender dysphoria, by itself, does not constitute a mental disorder.⁷⁻⁹

Even though there has been a noticeable growth of research in transgender health in the last decade,¹⁰ screening guidelines regarding gynecologic care for transgender people are scarce in the literature.

TRANSITION OR GENDER AFFIRMATION/CONFIRMATION

Transgender individuals may undergo processes to affirm a gender identity, known as 'transition' or 'gender affirmation/confirmation'. The extent of this transition is highly variable; some people do not transition at all, some change socially, some use techniques such as binding (methods to flatten breast tissue to create a male-appearing chest) or tucking (pushing the testes into the inguinal canal and securing the penis back between the legs), and still others opt for gender-confirming therapies.¹¹

GENDER-CONFIRMING THERAPIES

Some, but not all, transgender people pursue gender-confirming medical interventions, such as cross-sex hormones and/or gender-affirming surgeries and other body modifications (Table 2).

Table 2 Gender-confirming treatment options for transgender patients

Transgender patients	Hormones	Desired effect	Surgery
Transwomen	Estrogens	Decrease in facial and body hair	Facial feminization
	Estradiol	Decrease skin oiliness	Tracheal shave
	Anti-androgens	Increased breast tissue growth	Breast augmentation
	Spironolactone	Redistribution of fat	Body contouring
	Cyproterone acetate GnRH agonists	Reduction of spontaneous erections	Vaginoplasty
Transmen	Testosterone	Deepening of the voice	Chest reconstructive surgery
		Increased facial and body hair	Metoidioplasty
		Increased muscle mass	Phalloplasty
		Clitoromegaly Cessation of uterine bleeding	Testicular implants

GnRH, gonadotropin-releasing hormone.

Cross-sex Hormones

For a *transfemale* or *transwoman*, exogenous estrogen and/or progesterin may be used in conjunction with anti-androgens with the goal of developing female secondary sex characteristics (breast development, redistribution of fat, reduction in body hair) and minimizing male characteristics (softening of skin, slowing of scalp alopecia).¹² For *transmale* or *transman*, exogenous testosterone may be used to develop male secondary sex characteristics (deepening vocal register, development of facial and body hair, increased muscle mass). Also, testosterone can have a positive effect on cessation of genital bleeding, which may be one of *transmale* or *transman* main concerns.

Gender-confirming Surgical Procedures

Surgical interventions for a *transfemale* or *transwoman* may involve breast augmentation, laryngeal surgery, and/or facial feminization, among others. Sex-confirming genital surgery for a *transfemale* or *transwoman* is called vaginoplasty, and consists of the creation of a neovagina, re-positioning of the urethral meatus, and clitoro-labioplasty, while eliminating the male sexual organs (bilateral orchiectomy and penile disassembly). In the inverted penile skin technique, the neovagina is covered with the skin of the penis, the clitoris is constructed with a portion of the glans, labia minora with the prepuce, and labia majora with the skin of the scrotum.^{13 14} Other vaginoplasty techniques include sigmoid flaps to cover the neovagina.

Transmale or *transman* patients may undergo top/chest surgery (bilateral mastectomy and additional reconstructive techniques) and bottom surgery, wherein the female organs are removed and genital reconstruction is achieved through metoidioplasty (lengthening of the clitoris to recreate a microphallus, with no penetrative capacity), or phalloplasty (creation of a phallus using different flaps, with the radial free flap the most used and the one that seems to have better functional and esthetic results).¹⁵

GYNECOLOGIC CONSIDERATIONS

The ACOG recommends that all obstetricians-gynecologists understand gender identity and be able to treat transgender patients or refer them appropriately for medical or surgical therapeutic options.¹⁶ However, medical school and residency curricula are lacking on the care of the transgender patients.¹⁷ In a survey made to nine academic obstetrics/gynecology departments across the United States, 80% of providers answered that they had received no education on the care of transgender patients throughout their medical career or residency.¹⁸ Another national survey showed that only 29% of obstetrician-gynecologists felt comfortable caring for transfemale patients, and 11% were unwilling to perform screening Pap smears on *transmale* or *transman* patients and routine breast examinations on *transfemale* or *transwomen*, respectively.¹⁹

Many transgender people will start their treatment in a specialized center, but over time they often feel the need to merge with the general population, and are no longer within the scope of gender specialists. Therefore, gynecologists in general practice may be increasingly consulted by a *transfemale* or *transwoman* who may be treated with estrogens and progestins, or whose vagina has been surgically created, or by a *transmale* or *transman* who may

Table 3 Suggested gender-neutral gynecologic language

Commonly used	Less-gendered
Period/menstruation	Bleeding
Vulva	External pelvic area
Labia	Outer folds
Vagina	Genital opening
Uterus, ovaries	Internal organs
Breasts	Chest
Pap smear	HPV-related cancer screening
Bra/panties	Underwear

have uterus and ovaries and, consequently, are at risk of pregnancy or gynecologic malignancies.

In this scenario, a gynecologist should be prepared to deal with the following situations with transgender people:

Gynecologic Clinical History

Gynecologists should incorporate gender-neutral language and communicate sensitively, including trans-inclusive options on registration forms, such as gender identity, preferred name, and pronouns. Also, providers should take a respectful and adequate sexual history, making open questions about identity, preferred sexual partners, and present and past sexual practices. Gender identity is independent from sexual orientation. People who are transgender might have sex with men, women, or both, and consider themselves to be heterosexual, gay, lesbian, or bisexual.²⁰ When physical examinations is recommended, patients should be offered a review of what to expect, respecting individual preferences whenever possible. Also, providers are encouraged to use non-gendered terms for anatomical sexual structures and reproductive organs¹⁸ (Table 3).

Gynecologic cancer screening

Evidence relating to breast and reproductive cancers in the trans population is limited and insufficient to estimate cancer prevalence.²¹ Moreover, knowledge about the risks of such cancers in transgender people receiving gender-affirming hormone therapy is scarce in current literature, and even less information exists about the sub-set of individuals with genetic predisposition for these malignancies.²² Following current National Comprehensive Cancer Network (NCCN) Guidelines, personalized cancer risk assessment is recommended in all patients with a strong family history of cancer and/or a known familial gene mutation.²³ For transgender individuals, assessment of cancer risk should ideally be performed during planning stages before gender-affirming therapies are initiated. It should not be used as a barrier to accessing such therapies, but should be intended to complement informed decision-making for those high-risk individuals. However, almost no data exist regarding the impact of gender-affirming hormone therapy on cancer risk for a high-risk transgender patient.²²

Recommendations for routine gynecologic screening are based mainly on observational studies and expert opinion, and there is consensus that it should depend on the patient's hormonal and surgical status. Typically, cancer risk assessment for high-risk individuals relies on estimates derived from risk models for cisgender

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Table 4 Recommendations for breast and reproductive tract cancer screening

Organ	Transwomen	Transmen
Breast/chest	<p>Discuss mammography in transwomen aged >50 years with additional risk factors for breast cancer (body mass index >35 kg/m², estrogen and/or progestin use >5 years, family history)</p> <ul style="list-style-type: none"> ▶ Family history of BRCA mutations: prophylactic mastectomy could be recommended, with consecutive primary reconstruction. 	<p>Patients who have not undergone bilateral mastectomy should follow cisgender women recommendations for breast cancer screening</p> <p>Patients who had undergone chest reconstructive surgery should be offered physical examination and/or chest ultrasound</p>
Cervix	<p>Not recommended (transwomen do not have cervix)</p> <ul style="list-style-type: none"> ▶ Patients should be routinely examined to detect HPV-related lesions. 	<p>Patients with intact cervix should follow the recommendations for cisgender woman</p> <ul style="list-style-type: none"> ▶ Consider self-collected vaginal swabs to test for high-risk HPV DNA ▶ Pathologists should be aware if patient is taking testosterone ▶ Patients who had undergone total hysterectomy and have no history of high-grade cervical pre-cancerous lesion or cervical cancer can discontinue cervical cancer screening
Ovarian	N/A	<p>Do not screen</p> <ul style="list-style-type: none"> ▶ Transmen at increased risk (identified BRCA gene mutation and family history) should be referred for genetic counseling ▶ Consider risk-reduction salpingo-oophorectomy
Endometrial	N/A	<p>Do not screen.</p> <ul style="list-style-type: none"> ▶ Unexplained bleeding (in patients under testosterone who had reached amenorrhea) should be evaluated
Prostate	<p>Monitor following framework for cisgender men.</p> <ul style="list-style-type: none"> ▶ PSA cut-offs may be lower in TM receiving anti-androgens. ▶ Consider transvaginal digital examination and ultrasound. 	N/A

N/A, not applicable; PSA, prostate-specific antigen.

individuals and has not been validated for transgender individuals, and therefore cannot be directly applied to this population.²² A summary of recommendations on breast and reproductive tract cancer screening for transgender people is provided in [Table 4](#).

TRANSWOMEN GYNECOLOGIC SCREENING

Breast Cancer Screening

The overall risk of developing breast cancer in *transfemales* or *transwomen* is lower than in cisgender women.²⁴ However, as prolonged exposure to estrogen and/or progesterone is a well-known risk factor for breast cancer in cisgender women, its use seems to increase lifetime breast cancer risk in transwomen receiving feminizing hormone compared with cisgender men; however, overall lifetime risk of breast cancer remains low in transwomen.²⁵ A retrospective study from a large Dutch cohort showed a 46-fold increase risk of breast cancer development in transwomen receiving hormone treatment compared with Dutch cismen (standardized incidence ratio 46.7, 95% CI 27.2 to 75.4), but a decreased risk compared with Dutch ciswomen (0.3, 0.2–0.4).²⁵

The effect of a feminizing hormone on breast cancer risk in transwomen is not clear, and its effect in breast cancer prognosis and mortality has not been identified. Moreover, recommendations for breast screening have not yet been standardized.²⁶ One should discuss mammography in a *transfemale* or *transwomen* aged >50 years with additional risk factors for breast cancer (estrogen and/or progestin use for >5 years, family history, body mass index >35 kg/m²). If there is a family history of breast cancer for BRCA1 or BRCA2 mutations, a prophylactic mastectomy could be recommended with removal of all sensitive breast tissue, and consecutively, primary reconstruction with either autologous tissue or prosthesis.²⁷ When the decision is made to screen, it should be based on the recommendations for cisgender women.²⁸ Transfemales or transwomen who are not receiving feminizing hormone, regardless of history of breast augmentation, should follow the recommendations for cisgender men.

Cervical/Neovaginal Cancer Screening

Cervical cancer screening is not necessary in *transfemales* or *transwomen* who have undergone vaginoplasty because they do

not have a cervix. The neovagina is typically lined with keratinized penile skin, and evidence suggests that the risk of neoplasia is extremely small.⁶ In cases where a vaginoplasty is performed using a sigmoid segment, long-term follow-up did not show an increased risk of colon cancer in the neovaginal flap.²⁹

While these individuals are not at risk for cervical cancer, they are at risk for HPV and other sexually transmitted infections. Several reports have proved that HPV-related lesions can develop in the genital area after sex-confirming surgeries.^{13 30} This is explained considering that the glans of the penis and its prepuce, which are used to recreate the clitoris and labia minora during vaginoplasty, are the most likely to be HPV-positive in cisgender men.^{31 32} Examination of the neovagina, clitoris, and labia minora after trans feminine sex-confirming surgery should be considered and discussed with patients.

TRANSMEN GYNECOLOGIC SCREENING

The diagnosis of female-organ cancer in *transmen* has important social and psychological impact. What is more, its therapy would probably be under the care of a gynecologist oncologist in offices and treatment areas surrounded by female patients. Moreover, they could face logistic difficulty with insurance authorization because of coding error due to gender assignment. In this setting, despite the rarity of gynecologic malignancies in *transmale* or *transmen* patients, it is recommended that such patients be considered for periodic screening.³³

Chest (Breast) Cancer Screening

The role of testosterone in breast cancer is unclear; however, it does not appear to increase its risk.³⁴ Regardless of testosterone use, the recommendations for screening *transmales* or *transmen* who have not undergone bilateral mastectomy are the same as for non-transgender women.³⁵ The US Preventive Services Task Force recommends biennial screening mammography for women aged 50 to 74 years.³⁶

For those *transmale* or *transmen* patients who have undergone chest reconstructive surgery with bilateral mastectomy, the risk of breast cancer is greatly reduced. However, some degree of breast tissue is left in place after reconstructive top surgery, and cancer has been reported in residual breast tissue.³⁵ In such cases, one should discuss the benefit of annual physical examination and/or chest wall ultrasound.

Cervical Cancer Screening

Currently, no data exist regarding the prevalence of cervical cancer among transgender men. The ACOG and the Canadian Cancer Society recommend that *transmale* or *transmen* patients with intact cervix should follow the recommendations for non-transgender woman.^{37 38} Transmale or transmen patients who have undergone total hysterectomy and have no history of high-grade cervical pre-cancerous lesion or cervical cancer can discontinue cervical cancer screening.³⁹

Screening strategies, including physical examination, should be discussed with patients, using appropriate terms and aiming to preserve a patient's comfort and intimacy. Self-collected vaginal swabs seem to be highly acceptable to *transmales* or *transmen* as a means to test for high-risk HPV DNA, and it represents a reasonable and patient-centered strategy for primary cervical cancer screening in

transmale or *transmen* patients unwilling to undergo provider collection of specimens via speculum examinations. However, longitudinal studies are needed to evaluate its performance.⁴⁰

There is no evidence that testosterone increases or reduces the risk of cervical cancer. However, it might alter Pap smear results. Long-term androgen administration induces vaginal atrophy, which can result in epithelial atrophy that could mimic dysplasia.⁴¹ Pathologists should be informed of the patients' hormonal status.

While transmission of HPV most frequently occur with penetrative sexual intercourse, it can occur following non-penetrative sexual activity. The decision to undergo cervical cancer screening in transmale patients should be based on individual risk and should be encouraged for all patients who have a cervix, regardless of sexual partners or practices.⁴² For patients without any history of sexual activity involving vaginal penetration, gynecologists should discuss the risks of deferring cervical cancer screening, which may vary depending on sexual behaviors.³⁵

Ovarian Cancer Screening

There is no evidence to support screening *transmale* or *transmen* patients for ovarian cancer, and recommendations are identical to those in non-transgender female individuals.³⁵ At present, no routine screening test is available to identify ovarian cancer.⁴³ However, some factors are known to increase its risk, which include an identified BRCA mutation and a family history of cancer. Based on current NCCN guidelines, a cisgender woman with hereditary risk for ovarian cancer is advised to undergo bilateral salpingo-oophorectomy between the ages of 35 and 50 (gene-dependent recommendations).²³ Risk-reduction salpingo-oophorectomy should be offered to transmale patients with BRCA1 or BRCA2 mutations, after discussing their desire for further childbearing.⁴³ Few cases of ovarian cancer are reported in transmen in the literature.^{24 44 45} This could be because many transmen undergo an oophorectomy within 12–18 months of initiation of hormonal treatment.¹²

Endometrial Cancer Screening

There is no evidence to support screening *transmale* or *transmen* patients for endometrial cancer, and recommendations are identical to those in non-transgender female individuals.³⁵ At present, no routine screening test is recommended to identify endometrial cancer.⁴³ The evidence regarding the effects of testosterone on the endometrium in *transmales* or *transmen* is mixed, with evidence of both atrophic and proliferative changes.³⁵ To our knowledge, only one case of endometrial cancer has been reported in a transman receiving testosterone therapy.³³ However, counseling for unexplained uterine bleeding (patients with testosterone-induced amenorrhea who have not missed or changed its dosing) is encouraged in this patient population, and providers should consider evaluation with appropriate modalities.

Urological Counseling

Transfemales or *transwomen*: Transwomen receiving androgen deprivation therapy and estrogens have a substantially lower risk for prostate cancer than the cisgender male population.⁴⁶ Feminizing hormone therapy appears to decrease the risk of prostate cancer, but the degree of reduction is unknown.⁴⁷ However, cases of prostate cancer among transgender women have been reported.⁴⁸ Even transgender women who have had genital surgery will be at some risk because

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the prostate is not removed in feminizing genital surgery. Therefore, some monitoring may be required following the framework for non-transgender men.²⁸ Digital neovaginal examination could be helpful to identify prostate hyperplasia or irregularity. Transvaginal ultrasound of the prostate is technically feasible and well tolerated, and should be considered whenever prostate disease is suspected.⁴⁹ If prostate-specific antigen is checked, it is important to recognize that it may be falsely low in an androgen-deficient setting even in the presence of prostate cancer, and that the prostate-specific antigen cut-off point in transfemale patients is unknown.²⁸

CONCLUSION

Cancer care for transgender individuals is a growing concern. Research into how cancer affects the transgender community, as well screening and preventive strategies in transgender people, is imperative.⁵⁰ Gynecologic oncologists may be increasingly consulted by transgender patients and should be familiar with gender-neutral forms and language, as well as patients' reproductive organs for a correct assessment regarding cancer screening. Moreover, screening for reproductive organ malignancies should be accurate in accordance with the person's hormonal and surgical status. For individuals with familial or hereditary cancer, personalized risk estimation is challenging given the limited information currently available. Long-term multicenter studies are needed in order to promote the best screening and preventive strategies for people with non-traditional genders and sexualities.

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