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Cancer Care for Transgender and Gender Diverse (TGD) People:

Practical, Literature-Driven Recommendations from the Multinational Association of Supportive Care in Cancer (MASCC)

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Introduction

In the United States, over two million individuals openly identify with a gender that differs from their sex assigned at birth, and this number of transgender or gender diverse (TGD) people is increasing for reasons that are not entirely clear.[1] This review defines gender as a spectrum of identities that incorporates the behavioral, psychological, social, and cultural traits that are critical to an individual's identity as a man, woman, or non-binary person, among others (as there are many gender identities that individuals find affirming). Sex refers to an individual's biologic and anatomic features that define their assignment to male or female, or intersex, at birth. While gender and sex are often conflated, they are not interchangeable, as is the case for the TGD community, who may utilize differing terms of self-description. A list of preferred terms for gender and TGD individuals are included in Table 1 (informed by expert consensus and the Gay and Lesbian Alliance Against Defamation, "GLAAD").[3, 4] TGD individuals may pursue gender affirming surgeries, including chest masculinization or breast augmentation and/or gonadectomy, and/or gender affirming hormonal therapy (e.g., estrogen or testosterone), with the goal to align their gender identity and gender expression.

A cancer diagnosis is physically and psychologically taxing – and, in some, traumatic -- but for TGD people, many of whom have experienced discrimination in a myriad of healthcare settings, the challenges may be even greater. While it is presumed that TGD patients have experienced healthcare trauma, robust studies that have examined population differences are lacking.[5-11] Furthermore, TGD people appear to be under-screened for cancer, at high risk for some cancers, and often fraught with late-stage cancer diagnoses and early mortality.[12-18] Indeed, inequities in cancer care seem to abound among TGD patients, but such inequities are also likely under-reported.

These recommendations focus on how best to deliver quality cancer care to transgender men (individuals who identify as men but were assigned female sex at birth), transgender women (individuals who identify as women but were assigned male sex at birth), and people who identify somewhere beyond this gender spectrum, as non-binary, or utilizing other terms (Table 1), based on the available, albeit sparse, literature. This paper broaches: 1) the epidemiology of cancer in TGD individuals, including the incidence of cancer, and cancer-related mortality, 2) cancer center practices that are welcoming and affirming to TGD patients, 3) the need for

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awareness and intentionality in the spaces of diagnosis and treatment for cancer, 4) the inevitable conclusion that gender differences exist but much more needs to be learned about the impact of gender affirming therapy (GAT), consisting of gender affirming surgeries and gender affirming hormonal therapy (GAHT), on cancer therapy, and 5) efficacy and perceived safety of antineoplastic therapy and GAHT.

Finally, these recommendations often refer to the binomial, gendered reference ranges, for ease, as this is conventional. However, the authors encourage healthcare practitioners, researchers, and all readers to consider gender as a spectrum, rather than a construct of two binary variables. Many TGD individuals do not identify with one, binary gender: in one recently published study from the Kaiser Family Foundation, 40% of TGD individuals identified as non-binary and 22% as gender non-conforming; 22% identified as transgender women, and 12% as transgender men.[2] Not only will shifting towards recognizing the full spectrum of gender aid in mitigating the stigma and discrimination surrounding gender diverse individuals, but it will allow for the provision of higher quality patient-centric cancer care.

Literature Review Methods

The authors searched PubMed for the terms "trans," "transgender," "gender diverse," "gender minority," "gender non-conforming," "transwomen," "transmen," in addition to subject-specific terms, such as "malignancy," "cancer," or "chemotherapy," among others (“renal function”), (without restricting the date range). This comprehensive search was conducted from April through July 2024. Non-peer-reviewed papers and reviews of the literature were excluded. These database searches were supplemented with hand searches of the references within key articles. Studies were included based on their impact and methods with a focus on the highest level of evidence available.

Epidemiology of Cancer in TGD individuals

Few studies have been able to ascertain the incidence and mortality of cancer among TGD individuals due to insufficient data collection on sex assigned at birth and gender identity. As recently as 2023, fewer than two-thirds of National Cancer Institute Community Oncology Research Program sites in the United States reported that they collect gender identity information.[18] Tumor registries, medical records, and national surveys contain

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high rates of misclassification of sex assigned at birth and gender identity; and few such data compendiums collect granular details on receipt of gender affirming therapies.[19-21] Thus, numbers might be viewed as inaccurate and likely underrepresentative of TGD patients with cancer.

Cancer incidence appears to vary between transgender and cisgender populations. Two primary explanations for these purported differences are as follows: gender affirming therapies (GAT, including both gender-affirming surgery and GAHT) and minority stress. First, GAHT can be critical to the livelihood of TGD individuals; such therapies improve quality of life and reduce depression and suicidality.[22-26] Gender affirming surgeries and hormonal therapies can conceivably modify cancer risk. For instance, one cohort study found that breast cancer risk in transgender men was lower than risk in cisgender women, with a standardized incidence ratio (SIR) of 0.2 (95% Confidence Interval (CI) 0.1-0.5).[27] Breast cancer risk in transgender women was lower than that of cisgender women (SIR 0.3, 95% CI 0.2-0.4).[27] All transgender individuals included in this study had been on GAHT with estradiol and/or anti-androgens, or testosterone. The lower breast cancer risk in transgender men may be explained in part by chest masculinization surgery, which leads to a significant reduction in breast tissue and hence a reduction of its malignant transformation, but this information was not reported in this study. This study suggests that transgender women may be at higher risk for breast cancer than cisgender men after estrogen supplementation, but when the referent group is cisgender women (who have a higher risk of breast cancer compared to cisgender men as well), the risk is low. Given the paucity of population-level data, however, more data on GAHT and cancer risk are needed. In other studies, TGD individuals overall appear to have a lower incidence of breast cancer than cisgender women, but details on gender identity and GAHT are lacking.[20, 21, 28] Similarly, transgender women on GAHT appear to be at lower risk for prostate cancer than cisgender men; however, more robust studies are needed to confirm the findings.[28-30] A National Cancer Database study did not show higher rates of endocrine-associated cancers in transgender individuals.[12]

In addition to gender affirming therapies, minority stress may increase the risk for some cancers in TGD individuals. The minority stress model upholds the concept that individuals who face stigma and discrimination are more likely to engage in risk-taking behaviors, which, in turn, increase their risk for adverse health

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outcomes, such as the development of cancer. Multiple Behavioral Risk Factor Surveillance Survey (BRFSS) studies have reported that TGD individuals are at higher risk for tobacco use disorder, alcohol use disorder, and sexually transmitted infections,[8, 21, 31, 32] although a few studies report contradictory findings.[33, 34] Indeed, TGD individuals are at higher risk for viral infections and smoking-related cancers.[20, 28, 35] One cohort study of insured TGD individuals found a higher incidence of viral infection-related cancers in transgender men (Hazard Ratio (HR) 2.7, 95% CI 1.1-6.7) and transgender women (HR 2.0, 95% CI 1.0-3.9). Higher rates of smoking-related cancers in transgender men (HR 2.7, 95% CI 1.3, 5.6), as compared to a matched population of cisgender men and women, were also reported.

This concept of minority stress might have other implications, including those that negatively impact cancer outcomes. Among TGD patients who are diagnosed with cancer in the United States, cancer mortality appears to be higher compared to cisgender individuals. Although explanatory data are sparse, these poorer outcomes appear to be shown most saliently in TGD patients with non-Hodgkin lymphoma, prostate cancer, and bladder cancer.[12] It is clear that many TGD individuals suffer poorer social determinants of health, such as poorer access to quality health insurance, which is a direct result of multi-level discrimination and stigma, and which exacerbates poorer health outcomes.[2, 36]

Gender Affirmation in a Cancer Setting

Kerr and others conducted in-depth interviews of TGD individuals with cancer and their interactions with healthcare.[37] Using rigorous methods, these investigators identified themes, many of which were negative and indicative of the alienating aspects of cancer healthcare among these underserved individuals. These negative themes focused on clinicians' heavy reliance on gender stereotypes and assumptions, clinicians' negation of individuals' actual gender identity, clinicians' seemingly quick dismissal of patients' concerns, a perception among TGD patients that they are invisible in a healthcare setting, these patients' sense of feeling alienated in waiting rooms and support groups, and a TGD patient's anxiety that arises because of their uniquely gendered bodies.

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Importantly, amid all these negative themes, these researchers also identified one positive one: gender-affirming healthcare experiences enable TGD patients to feel connected and recognized, thus making the cancer healthcare experience more favorable. A glimpse into such a positive healthcare experience is perhaps conveyed in the following patient quotation, “[My doctor] did not bat an eyelid to the fact that I was trans, she just said to me, ‘I will ask you this question because it’s part of collective trans health,’ she said, ‘do you engage with your previous gender-identified preventative screening,’ like Pap smears. So the way she worded it was so sensitive…” In this context, the comments and recommendations below, and those provided in Figure 1, are aimed at trying to help TGD patients with cancer feel affirmed when they interact with clinicians and healthcare systems.

Gender-affirming care starts before the first clinic visit. Even before TGD patients appear within the walls of a cancer center, they should be sent non-gendered forms with visual representation and verbiage that are gender neutral. This initial paperwork should not address the TGD patient by their older legal name (dead name) but rather use their current (affirmed) name. In keeping with the foregoing, cancer centers should broaden their intake questionnaires to include information on whether a patient’s current name differs from an earlier one and to capture gender identity, sex assigned at birth, sex marker in legal documents, and sexual orientation. These changes appear to create a more inclusive environment and minimize the stress of having to repeat who they are, especially when TGD patients are navigating multiple healthcare systems. For TGD patients, and all patients, completion of an organ inventory, for organs that are applicable in the provision of appropriate care, will allow for tailored recommendations for cancer screening and can inform treatment options. As an example, a transman who has undergone hysterectomy (including removal of the cervix) will not require pap smears as part of their routine screening.

All staff members should avoid gender assumptions and preconceptions; for example, staff members should refrain from even overly positive remarks about a patient’s appearance. A welcoming approach can build trust. For example, the person who performs the initial in person intake might introduce themselves with, "Hello, my name is [name] and my pronouns are [pronouns]. What is your name, and what are your pronouns?"

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Once in the waiting room, an all-inclusive environment can be achieved with welcoming imagery and language (e.g. “All are welcome here” on posters with pictorial depictions of diversity). Clinics can also consider use of colors without a strong binary gender association. The optimal situation is for bathrooms to be single person and gender neutral. The latter will congruently present the idea of a safe space for TGD individuals who may feel uncomfortable in a gendered space.

All clinic staff, including receptionists, front desk staff, medical assistants, phlebotomists, nurses, and other clinicians, should use inclusive and neutral language. They should complete training modules on how the team works together to promote an affirming space for TGD individuals. They should also be aware of implicit biases that might impact the care of the TGD patient. Such bias testing for clinic staff is available online (www.implicit.harvard.edu) and should be offered or mandated regularly. "They/them" should be used when a patients’ pronouns are unknown, with avoidance of "ma'am" and "sir" when meeting patients for the first time. Gender neutral prefixes such as "Mx" or the affirmed name should be used. When questioning about interpersonal relationships, historically used "wife" or "husband" terms should be avoided and instead more gender-neutral terms such as "partner", "spouse", or "lover" should be adopted.[38]

Once a patient is in an examination room with a clinician, clinicians should avoid making TGD individuals feel responsible for teaching clinic staff about appropriate verbiage or related matters. If important for and relevant to the provision of quality cancer care, clinicians should review the organ inventory. Opinions or assumptions regarding approval or effectiveness of gender-affirming hormone therapy or classifying sex reassignment surgery as anything other than “gender-affirming” should be avoided. When explaining cancer pathophysiology and potential side effects of treatment, especially within a gendered site of disease, clinicians should refrain from using gendered terms such as "women diagnosed with breast/gynecological cancers" or "women treated with this cytotoxic drug usually experience the following side effects".

Additionally, healthcare institutions should maintain an up-to-date and shareable list of trusted referrals for cosmetic resources or emotional support groups during cancer therapy. Some cis-gender patients may welcome gendered titles, such as “women’s breast cancer survivors’ group,” but such wording might be viewed

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as non-inclusive to TGD patients. A more gender-neutral title, such as a "breast cancer survivor group" may create a safer space for TGD patients while still being acceptable to cis-gender persons.

Can such a welcoming environment be designed and adapted in a space where it had not previously existed? Furness and others have demonstrated that it can.[39] In a non-oncology setting, these investigators implemented a quality improvement intervention aimed at creating inclusive environments, acquiring data from patients on sexual orientation and gender identity, taking comprehensive sexual histories, and pursuing the appropriate screening for sexually transmitted diseases. This large-scale study also acquired pre- and post-outcome data, which showed, for example, that the clinic staff were 43% more successful than earlier in collecting patient pronouns. These investigators also observed that the documentation of sexual orientation and gender identity increased by 276.3%. Although this study did not specifically examine patient satisfaction, the fact that patients were willing to disclose the above information attests to the success of such gender affirmation interventions and underscores the possibility that clinicians' willingness and desire to serve TGD people can result in success in doing so. In essence, these data foster hope.

TGD Patients with Cancer: A Need for More Data

Relevant to any discussion of TGD patients is that fact that pathophysiologic differences exist based on an individual's chromosomes, anatomy, hormonal milieu, and experiences, noting that data collection has historically been collected using the male/female binary. Table 2 reports the pharmacodynamic and pharmacokinetic properties of certain drugs that may differ between males and females. There are also gender-based differences in how adverse events are reported.[40-42] These pathophysiologic differences have resulted in numerous studies that have shown women commonly experience more severe adverse events from systemic therapy (chemotherapy, targeted therapy, and immunotherapy) than men.[43, 44 45] Furthermore, these worse gender-related toxicity profiles in women have downstream consequences, including more unscheduled outpatient visits in women.[46]

However, a compelling multifaceted, unanswered question that emerges from these data is as follows: How should these well-established, well-described physiological differences among cisgender individuals influence

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the management of TGD patients, for whom far fewer clinical experiences and far less informed data are available, especially in the setting of cancer? This question prompts the need for more research in this area, including the potential utility of patient registries to inform clinicians, management decisions, and the conduct of prospective trials.

Clinical Data: Understanding Reference Ranges

A growing body of literature examines the impact of GAHT on medical care, and specifically on how it might affect laboratory values.[47-54] Cheung et al. suggest that affirmative practices for TGD people who are receiving GAHT calls for the use of laboratory reference ranges that coincide with the patient's affirmed gender rather than with sex at birth due to the impact of GAHT on fat and muscle distribution.[47] This is particularly applicable for red blood cell indices; hemoglobin typically increases to the male reference range in TGD individuals on testosterone, and decreases to the female reference range in TGD individuals on estradiol.[47, 49, 50] Exceptions should be noted, including prostate specific antigen (PSA) and troponin, both of which are primarily based on organ size,[47] and, hence, normal reference ranges for TGD patients on GAHT have been put forth (Table 3). Importantly, good clinical judgment should always temper clinicians' need to test and to react to abnormal laboratory values, particularly in TGD patients (Table 3a).

The literature notes that GAHT exerts a variable impact according to the specific test. In one study of 126 transgender women and 91 transgender men, all of whom had initiated GAHT, Allen and others found that red blood cell indices stabilized within six months of the initiation of GAHT.[48] Alternatively, for transgender women, HDL and platelet values significantly increased beyond the first year of hormone therapy; for transgender men, LDL and ALT significantly increased beyond one year while HDL showed significant decline in values. Following discontinuation of hormone therapy, however, values returned to baseline within three months.

Humble and colleagues also looked at the impact of gender-affirming estradiol (n=93) or testosterone (n=82) when taken for at least 12 months.[51] These investigators reported no impact on electrolyte levels, urea nitrogen, hemoglobin A1c, or C-reactive protein. However, liver enzyme measurements (alkaline phosphatase, ALK; alanine aminotransferase, ALT; aspartate aminotransferase, AST; gamma-glutamyltransferase, GGT)

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shifted towards the affirmed gender.[50] Of incidental note, these pre-clinical models bolster these clinical observations; the addition of estrogen or testosterone to in vitro cell cultures exerts epigenetic changes (including DNA acetylation and methylation on cell behavior) which appear to cause sex differences in human physiology and consequently on the mechanism of drug action,[52] presumably even in hepatic cells. With respect to kidney function, two large studies of medical records of TGD individuals on estradiol and testosterone report that creatinine also shifts toward the reference range of affirmed gender.[49, 50] However, in the study by Humble and colleagues, creatinine overlaid the reference range for cisgender men in both transgender men and women; no shift was seen for TGD individuals using estradiol.[51] These data show that changes in lab values are dynamic and depend on whether or not one is on GAHT at the time labs are checked, and the duration of treatment or discontinuation.

In a separate editorial in the *Journal of Applied Laboratory Medicine*, Marzinke and Radix argue that reference values for TGD individuals should not be expected to conform to those used for cisgender people.[53] Instead, they called for the empiric study of labs in TGD people so that such data could more accurately be used in patient care. The complicating factor is that GAHT is not uniformly dosed and/or administered; this factor can conceivably impact absorption and the lab value itself. One area that may need further scrutiny is the impact of GAHT on therapeutic drug monitoring, based on studies of TGD people who used preexposure prophylaxis (PrEP) against HIV showing GAHT seemed to reduce the concentrations of tenofovir and emtricitabine,[53, 55, 56] which could be due to the metabolism-based interaction but also could be due to the change of physiological function in TGD people. To our knowledge, similar data on how GAHT might affect tumor markers or antineoplastic therapy have not been sought.

Extrapolating from the observations in HIV patients, laboratory values should be interpreted in the context of GAHT in TGD individuals. Duration of GAHT, dose, and the route of administration should be recorded. For those on GAHT for more than one year, in general, many labs should be interpreted based on their affirmed gender (Table 3).[49] For those who are newly initiated on hormone therapy for less than one year, it is important to understand the values may change over time. For those who have stopped GAHT, within 3 months, lab values typically reflect their sex assigned at birth.

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With respect to renal function, as noted, GAHT can result in alterations in body mass index, muscle mass, and fat mass. These changes may ultimately reflect changes in body composition, volume of distribution, and ultimately, the generation of creatinine. Estimates suggest that a TGD person on testosterone for at least a year manifests a nearly 4 kg increase in lean body mass while TGD person on estradiol has a 2.4 kg decrease.[54] Based on these changes, Turino and colleagues proposed a framework to evaluate kidney function in TGD individuals and advocated for the use of cystatin-C because it is less dependent on both muscle mass and dietary intake and hence its use for eGFR estimation may be less dependent on the sex/gender covariate (male versus female). Because some factors, such as older age, obesity, and cigarette smoking, influence cystatin C, caution should be raised. Of note, cystatin-C is not widely available, and its clinical use has yet to be prospectively evaluated.

If cystatin C is unavailable, recent common practice is to utilize the creatinine reference range and to calculate creatinine clearance based upon one's affirmed gender. This is supported by two recently published studies reporting on laboratory values in large cohorts of individuals on GAHT,[49, 50] . which reported creatinine shifts to the reference range of the affirmed gender in patients on GAHT. The study by Boekhout-Berends and colleagues in the Netherlands included a particularly large cohort and reported on 1178 transgender women on estradiol and 1023 transgender men on testosterone at the time of starting GAHT, and approximately 1 year after initiation. Notably, this is a shift from earlier guidelines that were based on smaller cohorts of patients.[51, 57] Furthermore, data that point to optimal drug dosing or renally cleared drugs in TGD individuals are needed.

For electrolyte monitoring, reference ranges are not sex-specific, but sodium, potassium, and blood urea nitrogen may fluctuate, particularly in individuals receiving spironolactone as a part of gender affirming therapy.[57]

With respect to pulmonary function, a paucity of data guides the interpretation of spirometry in TGD patients on GAHT. Roth suggests spirometry results be accompanied by reference ranges for both cisgender men and women to provide for flexibility in how results should be interpreted.[58] Doing so would address the potential

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risks for mischaracterizing disease severity, misdiagnosis, and inappropriate treatment, including the risk of withholding antineoplastic drugs that carry the risk for pulmonary complications (e.g. bleomycin, checkpoint inhibitors, trastuzumab deruxtecan). Hence, the current American Thoracic Society (ATS) spirometry guidelines[59] specify that, regardless of gender identity, patients should "be informed" that "birth sex" is a determinant of predicted lung size. However, all clinicians should exert caution in interpreting results, particularly when GAHT is introduced pre-pubertally or after the development of pulmonary disease.[60, 61] Furthermore, clinicians inconsistently select the appropriate sex reference ranges for TGD individuals.[62]

Clinicians should also be aware that TGD patients may wear chest binders as a gender-affirming intervention to achieve a more masculine appearance and alleviate chest dysphoria in the absence of top surgery. One study of 20 transgender men who habitually used chest binders showed changes to baseline lung function with higher median FEV1/FVC with a binder compared to without a binder; both the standard residual of forced spirometric values and peak expiratory flow were significantly lower than predicted with a significant reduction in vital capacity.[63] For those who wear a chest binder, clinicians should explore the option of pulmonary function tests and/or spirometry with and without the binder in place with patients, respecting their decisions in a patient-centric fashion.

GAHT can affect even the heart. In one study,[64] a statistically significant prolongation of the mean QTc interval was observed among patients who received long-term GAHT; it appears that the QTc interval may be mediated by tissue-level androgen activity which is suppressed in individuals receiving feminizing hormone therapies. These findings support the use of the female reference range for interpretation of the QTc interval in people taking feminizing hormone therapy. As stated above, an exception to monitoring laboratory results is cardiac troponin, where the size of the heart influences reference values. Although one cohort study suggests that applying sex-specific thresholds may not significantly affect outcomes of acute cardiac events in transgender patients, current recommendations suggest that the reference range for sex at birth should be applied.[65]

Prostate specific antigen (PSA) interpretations are also influenced by GAHT. PSA is primarily dependent on prostatic volume, which can be influenced by anti-androgens (including 5-alpha reductase inhibitors) and

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estrogens used as a part of GAHT. One study of a cohort of 320 transgender women revealed lower prostatic volumes and PSA values compared with non-transgender (cisgender) men.[66] One suggestion is to lower the PSA upper limit of normal for transgender women with low testosterone to 1.0 ng/mL.[66-68]

Cancer Treatment Decisions in TGD Individuals

Dosing of many chemotherapy agents is based on ideal body weight and creatinine clearance, two values that utilize gender to inform accurate calculations. GAHT influences an individual's serum creatinine and lean body mass, such that values more closely correspond with gender identity (rather than sex assigned at birth).[69] Therefore, some pharmacists have advocated dosing medications based on gender identity, in individuals who have been on GAHT for 6 months or more.[69] For chemotherapy agents that rely on calculations of body weight for appropriate dosing, we would suggest that clinicians calculate both "male" and "female" doses, and then, choose the most appropriate dose, based upon clinician expertise.

A TGD individual's anatomy and gender identity may influence cancer treatment in other ways, as well. Understanding an individual's anatomy and experiences of gender dysphoria are particularly important after diagnoses of hormonally-driven cancers and in situations where there is equipose or near-equipose among standard cancer treatment options, as explained below.

Firstly, an individual's anatomy may factor into decisions regarding both local and systemic cancer therapies. As gender affirming surgical care differs among TGD individuals with no single approach for all, discussions and decisions should be individualized. For instance, a transgender man who has undergone a chest masculinizing "top surgery" often retains some breast tissue, including the nipple-alveolar complex. The volume of breast tissue remaining after top surgery is variable, based upon patient preferences for chest contouring and surgical decision-making. Imaging, particularly breast Magnetic Resonance Imaging (MRI), can help elucidate the volume of residual breast tissue, as this information is critical for surgical and radiation therapy decision-making.[70] In individuals who have significant breast tissue remaining after top surgery, a full mastectomy might be considered and might yield similarly low risks for recurrence, as compared with a lumpectomy with radiation.

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An individual's anatomy may also influence their decision to pursue certain systemic therapies. This decision is particularly salient for TGD individuals diagnosed with reproductive or hormonally-driven cancers. For instance, a transgender man may undergo gonadectomy (bilateral oophorectomy) as a part of gender affirming surgery. This individual would not require goserelin or leuprolide as a part of endocrine therapy for estrogen-dependent breast cancer. Similarly, a transgender woman with prostate cancer who has undergone a gender-affirming gonadectomy (orchiectomy) would not need a systemic therapy plan that includes a gonadotropin-releasing hormone (GnRH) agonist or antagonist. On the other hand, a transgender woman who has undergone breast augmentation may retain her gonads and prostate, and, therefore, the hormonal therapy recommendations for her prostate cancer may be analogous to that of a cisgender man.

Such examples reveal that, as mentioned earlier, clinicians should ensure that an accurate anatomy/organ inventory, as relevant to an individual's care, is documented as part of the medical record of TGD – and all patients - to ensure that care teams understand local and systemic therapy options. For some patients, the primary oncology clinician might need to talk directly to the surgeon who provided the patient's gender affirming care to ensure that the extent of prior surgery is well understood, and so that the multidisciplinary care team understands what options might exist. In the case of a transgender men with breast cancer after chest masculinization surgery, both the surgery and radiation oncology specialists should review the patient's breast imaging with a trained breast radiologist to better understand how much breast tissue is present, the location of the remaining tissue, and possible associated cancer risk.[70]

Secondly, a TGD individual's experiences of gender dysphoria may impact cancer treatment. Some TGD individuals might find surgical procedures affirming or, alternatively, compromising their gender identities.[71, 72] For instance, a transgender man diagnosed with early-stage breast cancer might elect to undergo a bilateral mastectomy without reconstruction, as compared with a lumpectomy with radiation, in view that the more invasive procedure might better align with their gender embodiment goals.[71] In a separate example, a transgender woman may opt for a gonadectomy (orchiectomy) rather than a GnRH agonist or antagonist, as residual testes may exacerbate dysphoria. Furthermore, hormonal therapies such as leuprolide may be a

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component of an individual's gender affirming therapy and a recommended part of prostate cancer therapy. It is worth noting that gender dysphoria is also experienced by some cisgender individuals undergoing cancer treatments, such as mastectomy or gonadectomy; although these experiences are labeled differently.[73] Overall, clinicians must learn about each TGD individual's goals and perceptions, share evidence-based recommendations, and participate in a patient-centric risk-benefit discussion of options for cancer-directed therapy.

Finally, there are strongly held concerns among oncologists and TGD patients that GAHT may influence the progression of hormonally driven cancers and the efficacy of endocrine therapy. Importantly, we must recognize that there are no prospective clinical data to inform or estimate the risk of GAHT on the progression of a hormone-sensitive cancer.

Nevertheless, TGD individuals who are on hormonal therapy and diagnosed with hormonal-sensitive malignancies face treatment dilemmas. Some TGD individuals may not feel GAHT is needed for their gender expression. For others, however, GAHT remains lifesaving.[74] Gender affirming therapy may improve gender dysphoria and quality of life; it may also lessen depression, anxiety, and suicidality.[75] TGD individuals may wish to continue the exogenous hormones and acknowledge and accept these risks, regardless of the possibility of a worse cancer outcome. One study surveyed TGD individuals about whether they would theoretically consider continuing their hormone therapy if diagnosed with a new hormonally dependent cancer.[76] As many as 35% said they would continue despite such a diagnosis. Hence, all patients' unique experiences and goals must be considered in these challenging discussions. These goals must be weighed against what is known about GAHT and about hormone sensitive cancers. Studies conducted with cisgender women on hormone replacement therapy suggest that exogenous estradiol can promote estrogen-dependent breast cancer recurrence.[77] Associations between exogenous testosterone and breast cancer development and progression are conflicting.[78-81] Early pre-clinical studies suggest exogenous testosterone in high concentrations may increase the risk for estrogen-dependent cancer progression, as testosterone is aromatized to estrogen.[78, 82] Androgen receptor activation by exogenous testosterone may promote breast cancer growth, according to other pre-clinical studies.[78, 83, 84] However, recent data from Cedars Sinai, in which

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the investigators genomically profiled breast tissues in transgender men following androgen therapy, suggest that androgen receptor activation may prevent or even reduce hormonally driven breast cancers.[83] But in the absence of clinically relevant outcome data, a tailored conversation around whether to continue GAHT should be informed by the patient, their choices should be respected and paternalism in medicine should be avoided.

Prospective data on the efficacy of antineoplastic endocrine therapy in the setting of GAHT are also lacking. Implanted testosterone pellets, when given to help with vasomotor or sexual symptoms, may be combined with aromatase inhibitors, and have not been shown to increase cancer risk; however, the doses of testosterone in these preparations are much lower than the doses utilized in GAHT.[85, 86] Therefore, it is not clear whether breast cancer endocrine therapy, such as tamoxifen or aromatase inhibitors, may block the effects of testosterone (in the doses used for GAHT) and of its aromatization to estrogen and thereby stymie cancer cell proliferation, particularly in the setting of gender affirming hormonal therapy. Translational trials that examine cancer-directed hormonal therapy in TGD patients on gender-affirming therapy are challenging to mount but remain critical to advance our understanding of how best to treat TGD patients.

Comments on Symptom Control, Surveillance, and Survivorship

From diagnosis through treatment, surveillance, and survivorship, TGD individuals should be counseled about potential risks from cancer and cancer therapy. While TGD individuals may suffer from similar side effects as their cisgender peers, adverse events such as loss of fertility and sexual effects are less frequently discussed.[69] Clinicians should discuss these crucial pre-therapy decisions with all patients, regardless of gender identity. Furthermore, TGD individuals may experience adverse effects, such as chemotherapy-induced alopecia, that threaten their gender identity and precipitate worsening dysphoria. Clinicians should proactively monitor distress and assess and help to control adverse events in TGD individuals. Many Patient Reported Outcome Measures (PROMs) may be directly applied TGD individuals, but some assessments, including many existing sexual health questionnaires, require modifications to enable them to be acceptable to TGD patients. Many such validated questionnaires need to include gender neutral language prior to their use in a TGD cancer clinic. Recommendations for cancer surveillance and screening for other cancers must consider an individual's existing organs, based on an anatomy inventory. Understanding that many of these strategies

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involve sensitive exams that may trigger gender dysphoria, clinicians should be prepared to share the risks and benefits of surveillance and screening in detail. As discussed above, healthcare systems should ensure that surveillance and screening programs are welcoming to people of all gender identities. Finally, following cancer treatment, many individuals may transfer their care back to their primary care clinician and other sub-specialty clinicians (such as an endocrinologist). In such cases, communication among teams is critical to ensure care plans are understood and harmonized.

Clinicians must share the available data and theoretical risks posed by the continuation of exogenous hormones after a diagnosis of a hormone-sensitive cancer with their TGD patients. However, clinicians should also consider the importance of gender affirming hormone therapies to patients when discussing these risks and benefits.

Conclusions

““We are all unique. Don’t judge, understand instead.” – Roy T. Bennett

This review attempts to bring together data and perspectives with the goal of providing inclusive, high-quality cancer care to TGD patients (see Table 4 for a summary of recommendations). It also points out prior inequities in cancer care and charts a forward course that emphasizes affirmation of patients’ gender identity with patient/clinician partnerships that enhance decision-making. A notable theme is the absence of data on some aspects of cancer care in TGD patients and a call for better patient self-reporting of gender identity, improved record keeping of gender identity in cancer clinics, and more research on how best to treat cancer in TGD patients.

But perhaps the most salient lesson of all that emerges from this review is the uniqueness of each patient with cancer, the need to tailor cancer care on a patient-by-patient basis for all patients but especially for TGD patients, and the importance of clinicians’ seeking to understand patients’ goals with the overarching goal of providing the best care possible to each TGD patient with cancer.

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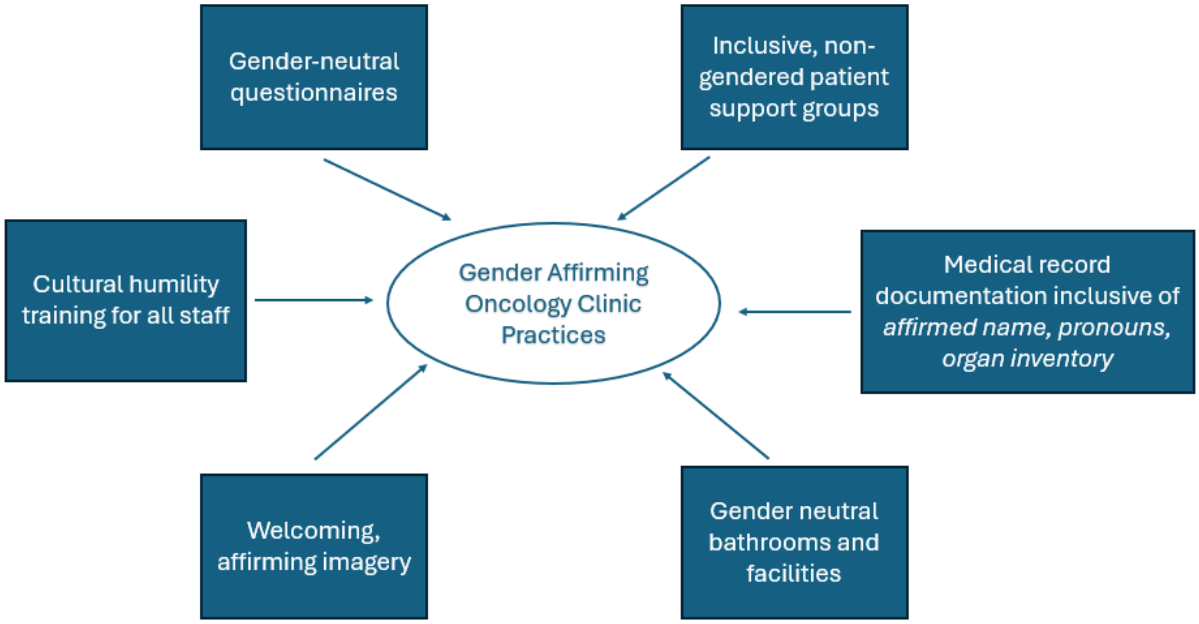
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Figure 1. Practices that point to affirming oncology clinic for TGD individuals.



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Table 1. Frequently used terms, when discussing gender among TGD individuals.

Term	Description
Gender identity	A person's internal sense of their gender. This may or may not align with a person's sex assigned at birth or one of the two binary genders (man and woman). This may or may not be outwardly visible to others.
Gender expression	The external representation of a person's gender, which may include one's behavior, name, pronouns, hairstyle, and voice, among others.
Gender incongruence	This is the term utilized in the International Classification of Diseases (ICD)-11 medical diagnosis code to denote care for an individual who identifies with a gender identity that is not identical to their sex assigned at birth: "characterized by a marked and persistent incongruence between an individual's experienced gender and the assigned sex, which often leads to a desire to transition, in order to live and be accepted as a person of the experienced gender…". Gender incongruence overlaps with, but is not identical, to the mental health diagnosis of gender dysporia which is used in The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Gender dysphoria refers specifically to the presence of psychological distress associated with gender incongruence, an experience that is not universally present in transgender and gender diverse people. The older ICD-10 nomenclature of "gender identity disorder" has fallen out of favor, even though ICD-10 is still in use in the United States and other countries.
Transgender or Trans Gender diverse	An adjective that describes an individual who has a gender identity that differs from the sex they were assigned at birth.
Transgender woman Trans woman	A woman who was assigned male sex as birth
Transgender Man Trans man	A man who was assigned female sex as birth
Gender non-conforming	An adjective that describes a person whose gender expression is different than the traditional expectation of a man and a woman.
Cisgender or Cis	An adjective that describes an individual who has a gender identity that is consistent with the sex that they were assigned at birth
Nonbinary (or non-binary)	An adjective for an individual who feels that their gender identity falls outside of the binary categories of "man" and "woman."

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Other terms may include: agender, bigender, demigender, pangender	These other terms may describe other, non-cisgender identities. For instance, “agender” typically refers to a person who does not identity as any gender.
Intersex	An adjective to describe people with sex characteristics, including anatomical features, chromosomes, or hormones, that do not fit the binary categories of man or woman.
Queer Genderqueer	An adjective describing a person whose gender identity or sexual orientation does not fall within the category of cisgender or heterosexual/straight. While this may be viewed as an offensive term for some, some individuals in the sexual and gender diverse community find this term to be affirming. Genderqueer specifies an individual whose gender identity does not align with their sex assigned at birth.
Sexual orientation	This is separate from gender identity and refers to a person’s sexual attraction.

Many cultures around the world utilize different adjectives to describe individuals with incongruence between their gender identity and sex assigned at birth. These terms often carry specific meanings within each culture and therefore the terms listed above may not accurately reflect such an individual’s identity.

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Table 2. Drug pharmacodynamics and pharmacokinetics that may differ, based upon female vs. male chromosomal makeup, anatomy, hormonal milieu, and other factors.

Pharmacokinetics	**Difference by gender, in females (compared with males)**	**Example Drugs**	**Potential effect**
Distribution	Decrease in the distribution of hydrophilic medications	Carboplatin Cisplatin 5-fluorouracil Gemcitabine	Lower efficacy
	Increase in the distribution of lipophilic drugs	Docetaxel Doxorubicin Irinotecan Paclitaxel	Higher toxicity
Metabolism	Higher activity of CYP3A4	Docetaxel Etoposide Irinotecan Vinca alkaloids	Lower efficacy
	Lower activity with Phase II enzymes	6-mercaptupurine	Higher toxicity
Elimination	Lower drug elimination/clearance	Bevacizumab Cetuximab Doxorubicin 5-fluorouracil Gemcitabine Imatinib Ofatumumab Paclitaxel Rituximab Temozolomide Topotecan Sunitinib	Higher toxicity

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Table 3. Interpretation of clinical data for TGD individuals on GAHT.

Value	**Is value significantly influenced by gender affirming therapy?***	**Recommendation**
Red blood cell indices	Yes; influenced by GAHT	If on GAHT for < 12 months, put in context of type, dose, and duration of GAHT; value may change over time If individual has been on GAHT for 12+ months, interpret within reference range for affirmed gender If GAHT has been stopped for 3+ months, interpret with reference range for sex assigned at birth
Liver enzymes	Yes, mildly influenced by GAHT	Reference range is not sex-specific. However, values shift towards affirmed gender.
Electrolytes BUN	Yes, fluctuations may occur secondary to spironolactone	Reference range is not sex-specific.
Creatinine Creatinine Clearance Cystatin C	Yes, creatinine and creatinine clearance influenced by GAHT	If available, suggest use of Cystatin C. If cystatin C is unavailable, suggest using the reference range for affirmed gender if an individual has been on GAHT for 12+ months. If GAHT has been stopped for 3+ months, interpret with reference range for sex assigned at birth
Hemoglobin A1c	No (according to current literature)	Reference range is not sex-specific.
Troponin	No (according to current literature)	Suggest use of reference range from sex assigned at birth.
QTc	Yes; influenced by GAHT	If on GAHT for < 12 months, put in context of type, dose, and duration of GAHT; value may change over time If individual has been on GAHT for 12+ months, interpret within reference range for affirmed gender If GAHT has been stopped for 3+ months, interpret with reference range for sex assigned at birth
PFTs	Yes; influenced by chest binding. GAHT may influence mildly, depending on timing of initiation.	If patient uses a chest binder, suggest completing PFTs with and without chest binder in place. Suggest use of reference ranges from sex assigned at birth.
PSA	Yes; influenced by GAHT (and surgery, including gonadectomy, prostatectomy)	Suggest lowering upper limit of normal to 1.0 ng/mL for individuals with low testosterone

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GAHT = gender affirming hormone therapy; estradiol, testosterone; PFTs=pulmonary function tests

*If pursued, gonadectomy also induces hormonal changes and, while lesser studied, likely also influences many of the values of those tests which are affected by GAHT.

Note: These suggestions are based on current evidence and consensus guidelines, understanding that large, prospective studies are needed.

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Table 3 A: Noteworthy Points Relevant to Table 3

- The categorial nature of reference ranges for gender diverse patients should not undermine the non-binomial nature of gender itself.
- GAHT dosing is not standardized, and different dosing might also influence reference ranges.
- Timing of initiation of GAHT (either pre-pubertally or late in life) may also influence clinical data.
- Discontinuation of GAHT or modifications in dosing over time would likely also influence reference ranges.
- In determining how to interpret and act upon a laboratory value that falls outside the reference range, clinical judgment, the implications of a potentially aberrant value, the possibility of monitoring this laboratory value over time, and, of course, the need to serve the best interests of the patient -- should all be considered.

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Table 4. Overall Recommendations

Issue	Recommendation(s)
Poor sexual orientation and gender identity data collection	- Create affirming environments where patient safety and confidentiality are assured - Craft sexual orientation and gender identity questions that are acceptable to TGD individuals - Document sexual orientation and gender identity data in appropriate parts of the electronic record to allow for future research.
Lower rates of cancer screening	- Completion of an organ inventory, as relevant to cancer screenings - Creation of welcoming spaces for all genders in cancer screening facilities - Careful discussion of risks vs benefits of screenings, particularly for screenings of organs that contribute to dysphoria
Lack of gender affirming practices in oncology clinics	- Staff should not make assumptions about gender identity or sexual orientation - Documentation and discussions should utilize a patient's affirmed name and pronouns - Gender-neutral terms should be adopted to describe an individual's relationships - TGD-focused cultural sensitivity training of staff - Gender neutral bathrooms and facilities - Use of colors without a strong binary gender association - Welcoming imagery and language - TGD-specific support groups and other resources should be offered
Unclear interpretation of gendered lab values	- Develop prospective studies of lab values in TGD individuals - Utilize reference ranges corresponding to an individual's gender identity, in individuals who have been on gender affirming hormone therapy for 12 months or more for the following: red blood cell indices, QTc - In transgender women with low testosterone, lower the Prostate Specific Antigen reference range upper limit of normal to 1.0 ng/mL - Interpret troponin the reference range for sex assigned at birth - To evaluate kidney function, it's ideal to use cystatin C.
Unclear interpretation of pulmonary function tests	- Interpret spirometry using sex assigned at birth reference ranges - Ask individuals who wear chest binders to complete spirometry with and without the binder
Unclear dosing of chemotherapy agents	- In individuals who have been on GAHT for 6+ months, use gender identity in ideal body weight calculations - For doses that require calculations of body weight, calculate "male" and "female" doses, and then, choose the most appropriate dose, based upon clinician expertise.
Unaddressed side effects of cancer therapy	- Proactively discuss future fertility, risks for sexual side effects to therapy - Help to monitor for worsening gender dysphoria and offer supports early - Use non-gendered Patient Reported Outcome Measures (PROMs) to track symptoms so that they may be addressed early
Poor data quality to inform cancer care in TGD individuals	- Clinical trials should be developed focusing on the needs of TGD Individuals

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