TRANSLATIONAL ANDROLOGY AND UROLOGY

Peer Review File

Article Information: Available at http://dx.doi.org/10.21037/tau-20-954

Review Comments:

This review is an informative piece that fills a gaping hole in the current practice of oncology. This is important work that will hopefully make progress in increasing rates of cancer screening in transgender and gender diverse patient populations. Your discussion of specific cancers and their guidelines is very helpful, especially the discussion of socioeconomic and psychological factors that discourage screening in these populations. Please see my below comments:

1. In the abstract you state that "Cross-sex hormone therapy does not pose any additional oncologic risk or eliminate natal sex organ oncologic risk for transgender individuals." This is not in line with the current literature and should be removed from the abstract; there is not enough research to conclusively state that there is no additional risk to hormone therapy, and there are many reviews that indicate such therapies do indeed increase the risk of certain cancers. Additionally, your paper does suggest that there may be increased risks associated, but due to lack of research we cannot say for certain. Consider instead replacing with a sentence about the lack of research and uncertainty of cancer risk with gender-affirming hormone therapy.

   Reply: We agree with this critique and suggested change.
   Changes in the text: "Currently, there is not sufficient to evidence to determine the long-term effects of gender-affirming hormone therapy on an individual's cancer risk

2. Consider eliminating the use of "cross-sex" since the genital sex spectrum is not binary, as evidenced by intersex individuals. Instead consider using "gender-affirming hormone therapy." Similarly, consider using "assigned birth sex" rather than "birth-sex."

   Reply: We agree with both suggested changes.
   Changes in the text: Cross-sex hormone therapy has been changed to gender-affirming hormone therapy. All uses of CSHT have been changed to GAHT.

3. Instead of saying "masculine" and "feminine" to describe hormones, consider being consistent and using their medical names (i.e., "testosterone, DHT" and "progesterone, estrogen" to be more specific and reduce unnecessary gendering.

   Reply: We agree that using masculine and feminine to describe hormones can be vague.

However, there are multiple hormone regimens that patients can be on, to avoid leaving out a certain regimens and reduce unnecessary gendering we changed masculine and feminine to masculinizing and feminizing hormones.
Changes in the text: All uses of masculine hormones have been changed to masculinizing hormones. All uses of feminine hormones have been changed to feminizing hormones.

4. Please provide source(s) for this statement: "Transgender and non-binary individuals are poorly captured in these databases making comparisons between the transgender and general populations and identification of high-risk sub-populations within the transgender community very difficult."

   Reply: Thank you for pointing out this missing citation.
   Changes in the text: added citations (WPATH SOC v7, Systematic review and meta-analysis of prevalence studies in transsexualism)

5. Please provide source(s) for this statement: "Gender dysphoria does not affect a patient's cancer risk, but it does decrease a patient's chance of undergoing screening for their birth sex organs."

   Reply: Thank you for pointing out this missing citation.
   Change in the text: added citation (Gender dysphoria in youth: An overview for primary care providers)

6. In line 175 you use the term GAH for the first time. Is this gender-affirming hormone therapy? Please elaborate and define the abbreviation.

   Reply: Thank you for pointing out this error. For consistency we are only using gender-affirming hormone therapy and GAHT.
   Changes in the text: All uses of GAH have been changed to GAHT.

7. The following sentence is not scientifically sound: "These studies would suggest that there isn't an increased cancer risk for patients on gender-affirming hormones but more studies are needed to confirm and validate this." Prior to this sentence you discuss exactly one study from the Netherlands; in no way does that suggest a lack of causal relationship. Please delete.

   Reply: We agree that this is a stretch given the data presented and have removed it.

Changes in the text: Sentence has been removed

8. The following sentence misrepresents the WPATH guidelines entirely. "The WPATH SOCv 7 states that there is no evidence that feminizing hormones increase a patients risk of breast cancer and similarly there is no evidence masculinizing hormones affects a patients risk of breast, cervical, ovarian, or uterine cancer." This is false on many accounts, see the guidelines on page 99. It states, "MtF persons who have taken feminizing hormones do experience breast cancer, but it is unknown how their degree of risk compares to that of persons born with female genitalia. Longer duration of feminizing hormone exposure (i.e., number of years taking estrogen preparations), family history of breast cancer, obesity (BMI >35), and the use of progestins likely influence the level of risk." Similarly, the guidelines state that the evidence for the three cancers you listed for "masculinizing hormones" are inconclusive and may have increased risk. Please correct this misrepresentation.

   Reply: We have adjusted this section to distinguish which for which cancers the evidence of increased risk is lacking and thus considered inconclusive and for which cancers the evidence shows there is no increased risk.
   Changes in the text: The WPATH SOCv 7 states that the current evidence is insufficient to determine if feminizing hormones increase a patients risk of breast cancer but notes that risk of breast cancer in transfemales is not zero[7]. There is no evidence masculinizing hormones increases a patient's risk of breast or cervical, although it may increase the incidence of abnormal pap smears[7]. The current evidence is inconclusive to determine how masculinizing hormones affect the risk of ovarian, or uterine cancer[7].

9. I am puzzled at your conclusions for the ovarian cancer section (as well as others): If you found no strong evidence at all on transmasculine ovarian cancer rates, why do you conclude that screening is not recommended? If there had been strong evidence to suggest no risk, then this conclusion would make sense. However, in cases such as your ovarian cancer section, I would prefer that you recommend further investigation into screening. If you instead recommend "no screening," wouldn't that hinder future research on prevalence rates? Why not simply say "there is no recommendation" as you did in the vulva cancer section? In your table, for ovarian cancer you say "no recommended screening" which makes sense, but this is inconsistent with your in-text claim to not screen at all.

   Reply: Thank you for pointing out the confusing way this information was presented. The USPSTF recommends against routine screening for ovarian cancer and there is no

evidence that transmales should follow different guidelines.

Changes in the text: The USPSTF currently recommends against routine screening of cisgender women for ovarian cancer[57]. A review of the literature found no strong evidence that transmasculine patients are at increased risk of ovarian cancer[36,58]. It is recommended that transmales follow the guidelines for cis-females, routine cancer screening is not recommended and prophylactic oophorectomy without other risk factors is unnecessary[58].

10. Eliminate the use of "cis-gendered" and instead use "cis-gender" (line 354). Eliminate all uses of "transgendered" in favor of "transgender."
    Reply: We agree that these terms should not be used and have removed them.
    Changes in the text: Use of cis-gendered has been changed to cis-gender and uses of transgendered have been changed to transgender.

11. I am unclear of the point you are trying to conclude with in your final paragraph in the "Counseling Patients" section. Please provide concrete instructions for providers on how to apply the Biopsychosocial model. Please specify what you mean by "removing these artificial boundaries" and "consider the health domain they focus on" as these sentences are currently too broad and not helpful for providers as they are.

    Reply: Thank you for pointing out the confusion in our final paragraph. We were not clear or specific in our discussion of the biopsychosocial model. We have reworked and expanded that section to fully explain how the biopsychosocial model can be applied to the care of transgendered patients.
    Changes:
    The Biopsychosocial Model and transgender healthcare
    When counseling patients, physicians often rely on the biomedical model, which has been the dominant model for Western medicine since the 19th century. The biomedical model focuses on health status, and achieving freedom from compromised health. By focusing on decreasing chronic conditions, it creates a common language and understanding between the physician and patient. Such commonality of focus and language is harder for many transgender patients because of the fact that many patients have very personalized transition goals, and, due to the lack of information regarding long-term outcomes in transgender patients. Other important factors that limit the utility of the biomedical model for transgender care is because some care providers lack of understanding about not only what it is to be transgender, but also, how being transgender can affect- and be affected by, different aspects of the patient's social world and health. The disconnect that results can for many patients foster distrust towards

the healthcare system.

We propose a new model for transgender healthcare, which is rooted in the Biopsychosocial Model first proposed by George L. Engel and Jon Romano in 1977. Engel and Romano's model focuses on the development of illness from the complex interactions across and within biological, psychological and social systems (Figure 1) [75,76]. Engel emphasized that the biomedical approach is flawed because the body is not the only contributor to illness, or wellness [76,77]. Instead, an individual's own psychological (mood, personality, behavior, etc.) and social (cultural, familial, socioeconomic, etc.) domains also significantly impact underlying biological (genetic, biochemical, etc.) factors, to determine how illness and health are caused and treated [75]. Engel also emphasized the need for two-way dialogue between the patient and doctor in order to find the most effective treatments [76].

We note that the process of gender transition affects (and is affected by) both biological and social continua. For example, gender affirming hormone therapy and surgery are a part of gender transition for many transgender/gender non-conforming people, as is a significant change in an individual's gender and social roles. A common theme in the World Professional Association for Transgender Health (WPATH) Standards of Care (SOC) Guidelines is that a cornerstone of care for the transgender patient is to facilitate and adapt to positive change in mental health, social domains, and for some, physical/body related domains. [7]

What is perhaps less obvious from the biopsychosocial model is that for people undergoing gender transition, certain subdomains of the biological and social continua change significantly, and often over a relatively short period of time. It is useful for healthcare providers to consider how changes in sex hormones, body appearance, dress, personal pronouns, partner, family and professional relations can occur during gender transition, and that such changes affect health and illness. In essence, a provider can consider how each subdomain of Engel's biopsychosocial model is affected by the nature, and stage ,of gender transition.

We propose a model for healthcare of the transgender and gender non-conforming individual that accounts for the complex interplay between the individual's gender transition, biological and social systems. (Figure 2A)

In the context of cancer screening, the model we propose reminds us that cancer risk at any given time is influenced by the multiple levels of organization that Engel describes in the biopsychosocial model [78],, and, other factors. (Figure 2B) For example, the age at which an individual commenced transition with use of GAHT, and what stages of transition they have completed (Figure 2B, column a.), influence factors in column b., which are predictors of cancer screening needs and cancer risk (column c.)

When we consider transgender health from the perspective of the model shown in Figure 2A & 2B, three key points become clear: First, that gender transition constitutes different changes for different people (i.e. it is highly individual); Second, patients can be in

different states of transition across different domains at any given time; and Third, an individual's present state of gender transition independently influences- and is influenced by, each of the concentric levels of organization within the biological, psychological and social continua.

12. The following sentence in the opening line of your conclusion once again misrepresents the current literature and the WPATH. "CSHT does not pose any additional oncologic risk for transgender individuals." Instead, state that it is not known whether gender affirming hormone therapy poses additional oncologic risk, or that there is a lack of evidence to show an increased risk. You make it clear in the text that this lack of evidence is due to lack of research, so please do not misrepresent your claim.

Reply: We agree that this statement did not accurately summarize our findings.
Changes in the text: The current available evidence does not show GAHT increases oncologic risk for transgender individuals. The available evidence is limited and further research into the effects of long-term GAHT is needed. However, GAHT does not eliminate the potential for malignancy of the patient's natal sex organs and transgender individuals should undergoing cancer screening for all organs present regardless of transition status