Contemporary Clinical Trials Communications 19 (2020) 100597

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: http://www.elsevier.com/locate/conctc

Inclusion of transgender and gender diverse health data in cancer biorepositories

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ARTICLE INFO

Keywords:
Transgender persons
LGBT
SGM
Biospecimens

ABSTRACT

Biobanks have the potential to be robust resource for understanding potential cancer risks associated with gender-affirming interventions. In this narrative review, we synthesized the current published literature regarding the inclusion of TGD health data in cancer biorepositories and cancer research conducted on biospecimens. Of the 6986 initial results, 153 (2.2%) assessed the biological effects of gender-affirming interventions on TGD tissues. Within that category, only one paper examined transgender tissues in relation to cancer biobanks. Strategies are offered to address the inequities in TGD tissue-based research and diversify the field of biobanking as a whole.

1. Introduction

Emerging evidence suggests cancer in the lesbian, gay, bisexual, transgender, and queer/questioning (LGBTQ) population is a growing epidemic whereby this population experiences increased risk and poorer outcomes for some cancers. The National Institutes of Health recently designated cancer in LGBTQ populations as a priority research area as they are a medically underserved and disparate population [1]. Each subgroup within the LGBTQ community has unique health needs and experiences unique health disparities [2,3].

Transgender and gender diverse (TGD) individuals are particularly underserved and understudied. Transgender individuals identify as a gender other than the one they were assigned at birth and gender diverse individuals prefer an additional or alternative identity to transgender (including, but not limited to, non-binary, two-spirit, genderqueer, and gender non-conforming). TGD individuals may pursue medical interventions, or gender-affirming interventions, to achieve their desired presentation. These gender-affirming interventions alter an individual's body, whether to encourage or discourage vocal cord hyperplasia, stimulate or inhibit bone growth, or atrophy internal sex organs. For someone assigned female at birth (AFAB), such medical interventions may include testosterone therapy, mastectomy, hysterectomy, oophorectomy, vaginectomy, metoidioplasty, phalloplasty, scrotoplasty, urethroplasty, and penile prosthesis placement. For individuals assigned male at birth (AMAB), interventions may include estradiol or progesterone therapy, anti-androgens, mammoplasty, orchiectomy, vaginoplasty, penectomy, labiaplasty, clitoroplasty, laryngoplasty, and cricothyroid approximation.

To date most of the limited research on the biological effects of gender-affirming interventions relates to specific surgical outcomes [4,5]; however, research is needed regarding the potential effects on cancer risk and outcomes. This is important because some gender-affirming interventions, such as hormone replacement, have been shown to modulate cancer risks [6] and gender-affirming surgeries have underexplored effects on cancer development [7]. Reforming biobanking practices to be more inclusive of TGD populations is a necessary first step to facilitate research in this domain. In this short communication, we synthesized the published literature regarding the collection of TGD demographic information in biobanking endeavors with the long-term goal to understand the potential cancer risks associated with gender-affirming interventions.

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https://doi.org/10.1016/j.conctc.2020.100597
Received 17 December 2019; Received in revised form 4 June 2020; Accepted 14 June 2020
Available online 16 June 2020

Table 1
PubMed search terms and results.

	Total	AND tissue	AND specimens	AND pathology	AND histology	AND biospecimens	AND biobank	AND outcomes	AND cancer	Observational Studies	Case Reports	Reviews or Systematic Reviews	Clinical Trials
Total Search Results[a]													
Transgender	5449	159	33	170	130	0	1	715	329	26	195	699	56
Transsexual	1213	159	10	106	149	0	1	45	84	3	256	130	24
Gender-Affirming Intervention	165	11	4	6	2	0	0	59	12	0	3	29	0
Sex Reassignment	1214	196	12	92	165	0	0	151	72	13	172	219	20
Total	**6986**												
Search Results Meeting Inclusion Criteria[b]													
Transgender	153	13	5	7	5	0	1	81	5	4	4	36	0
Transsexual	32	13	1	0	0	0	1	19	3	0	1	12	0
Gender-Affirming Intervention	148	11	4	6	2	0	0	59	3	0	3	29	0
Sex Reassignment	60	6	3	5	5	0	0	36	3	3	2	22	0
Total	**153**												

[a] These 6986 articles reflect total search results, prior to removing studies that did not meet inclusion criteria. Of note, 99% of search results for 'gender-affirming intervention' and 76% for 'transgender' were published in the last 5 years (this search was conducted in August 2019). In contrast, only 21% of search results for 'transsexual' and 44% for 'sex reassignment' were published in the last 5 years. Additionally, most of the above search results were unrelated to TGD populations according to their abstracts; for example, when excluding 'men who have sex with men' (a term predominantly used in studies that overlook transgender women) from the 'transgender' search, only 1849 results returned.

[b] These 153 articles reflect total search results after removing studies that did not meet inclusion criteria. There was considerable overlap between the terms 'transgender' and 'gender-affirming intervention.

2. Methods

In August 2019, PubMed was queried to identify published literature involving biospecimens from TGD patients and/or inclusion of TGD populations in biobanking research. The four core search terms used were 'transgender,' 'transsexual,' 'gender-affirming intervention,' and 'sex reassignment.' These search terms were chosen to identify both older and newer literature, as 'transsexual' and 'sex reassignment' have more recently been replaced by 'transgender' and 'gender-affirming intervention.' Each of these four search terms were searched and linked by 'AND' with each of the seven biospecimen-focused terms in Table 1. A total of 28 keyword searches were performed with 'All Fields' selected for each keyword to widen the search beyond MeSH terms. For each of the four search terms, the numbers of existing case reports, reviews and systematic reviews, clinical trials, and observational studies were reported using PubMed's internal categorization system.

To determine if these search results actually addressed the subject of gender-affirming interventions in TGD populations, titles and abstracts were reviewed for inclusion in this review with the following criteria: human studies, transgender or gender diverse subjects, at least one reference to a gender-affirming intervention, at least one reference to tissue analysis, English language, and published before August 2019. Abstracts meeting any of the following criteria were ex-

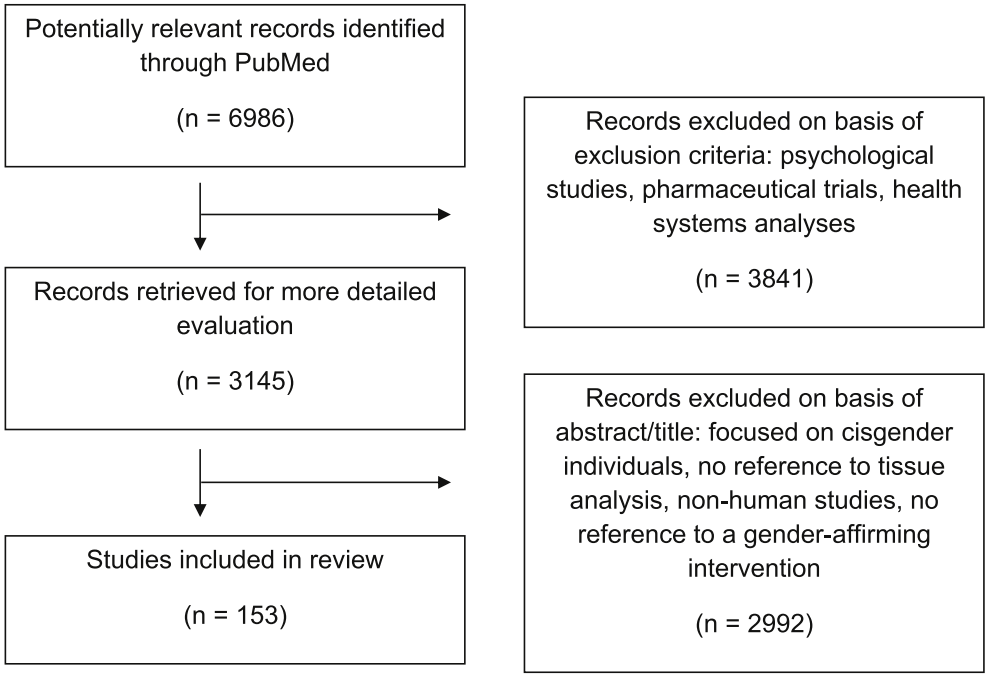

Fig. 1. Prisma flow diagram of studies reviewed.

Table 2
Florida pancreas collaborative gender-affirming intervention questions.[a].

Question	Options for AFAB patients	Options for AMAB patients
1. Please check any therapies or operations you have ever undertaken.	Testosterone hormone replacement therapy, mastectomy, hysterectomy, oophorectomy, vaginectomy, metoidioplasty, phalloplasty, scrotoplasty, urethroplasty, testicular/erectile prosthesis placement, "cosmetic" masculinization procedures or surgeries, other: please specify	Estradiol hormone replacement therapy, progesterone hormone replacement therapy, androgen blockers, augmentation mammoplasty, orchiectomy, vaginoplasty, penectomy, labiaplasty, clitoroplasty, laryngoplasty, "cosmetic" feminization procedures of surgeries, other: please specify
2. How old were you when you first began [insert selected hormone therapy from Q1 here] ?* *For AFAB, could be testosterone. For AMAB, could be estradiol, progesterone, and/or androgen blockers.	_ years old	_ years old
3. In total, how long have you taken [insert hormone therapy from Q1 here] throughout your lifetime, not including any breaks that you may have taken?	<6 months, 6–12 months, 1–2 years, 2–5 years, 5–10 years, >10 years	<6 months, 6–12 months, 1–2 years, 2–5 years, 5–10 years, > 10 years
4. What type of [insert 'testosterone' if AFAB or 'estradiol' if AMAB] hormone replacement therapy have you used for the majority of your lifetime?	Intramuscular injection, transdermal patch/gel/cream, subcutaneous pellet, oral, sublingual/buccal, other: please specify	Intramuscular injection, transdermal patch/gel/cream, oral, sublingual/buccal, other: please specify
5. How old were you when you underwent [insert selected operation(s) from Q1 here] ?	_ years old	_ years old

[a] These questions have been added to the demographics section of the Florida Pancreas Collaborative Baseline Questionnaire [30]. An additional question was also added that ascertains whether the patient's hormone therapy has changed in any way since their pancreatic cancer diagnosis.

cluded: psychological studies, pharmaceutical trials, health systems analyses, and cisgender subjects. A second researcher replicated the search using the chart string of MESH terms with 100% reliability.

A search of online biorepositories was conducted to determine the status of TGD demographics and gender-affirming interventions as data points including the National Clinical Trials Network (NCTN) Navigator [8], the Cooperative Human Tissue Network [9], and the Specimen Resource Locator [10].

3. Results

Of the initial 6986 PubMed results, 153 (2.2%) assessed the effect of gender-affirming intervention(s) on TGD tissues (Table 1 and Fig. 1). Among the 153, there were 124 (81%) focused on surgeries and 29 (19%) focused on hormone therapy. Tissue changes after gender-affirming interventions for AFAB individuals were the focus of 77 (50.3%) papers and AMAB changes were the focus of 62 (40.5%). Nine papers focused on fertility outcomes [8,11–18] and five papers focused on cancer risks [19–23]. A single case study was found on 'biobank AND transgender' [24].

4. Discussion

Overall, we found that TGD demographic information and history of gender-affirming interventions are largely not being documented in biobanks. Of the 153 studies on the effects of gender-affirming interventions on tissues, only one focused on biobanking. In this single study on TGD biobanking, Millican-Slater et al. found that a transgender man's breast tissue was significantly modified by testosterone and argued the biobank now containing this specimen was improved by its addition [24]. Additionally, TGD demographic information was not documented in the NCTN Navigator [8] and only had gender options for 'Male' and 'Female' in their biospecimen search engine. TGD demographic data has not been suggested or requested as a data point for the Cooperative Human Tissue Network or the Specimen Resource Locator.

Potential adverse biological effects and risks of transition-related hormone therapy are currently unknown. Such information is especially salient among relevant cancers such as prostate, anal, and breast for AMAB patients and breast, ovarian, cervical, vaginal, and endometrial cancers for AFAB patients [6]. There is evidence that chronic inflammation from surgeries such as vaginoplasty can increase risk of malignancy in TGD population [7]. This is concerning because of the increasing number of TGD people pursuing gender-affirming interventions with limited data on biological effects [25]. The most common reasons why TGD individuals who seek partial treatment (gender-affirming interventions that are not considered complete sex reassignment) rather than complete sex reassignment are uncertainty of risk and outcomes [26]. Aptly, Mahfouda et al. [27] proposed research on an international scale to clarify long-term functionality and safety of gender-affirming interventions.

Revealing potential adverse biological effects of gender-affirming interventions is complicated by the personalization of variables such as age of treatment, hormone mode of delivery, time on hormone replacement, combination of gender-affirming surgeries, and small population size. Additionally, the outdated practice of grouping sexual orientation minorities with TGD individuals as one 'LGBTQ' population, as seen in investigations of anal cancer in men who have sex with men that fail to stratify transgender women within their analyses, further obfuscates the study of cancer rates in TGD patients.

Significant social barriers to care exist for TGD individuals that may contribute to disparate cancer rates. These include lower rates of health insurance compared to cisgender individuals [28], avoidance of health care due to perceived discrimination [29], dysphoria in gendered medical spaces (including cancer screenings), and difficulty

finding inclusive health care providers [1]. In terms of outcomes, TGD populations may have different smoking rates than LGB populations and other factors such as HPV and obesity have not been evaluated for prognostication of cancer outcomes in TGD populations.

A parallel to the challenges of studying the effects of gender-affirming interventions can be drawn to the early challenges of studying AIDS and the novel solution of creating the AIDS Specimen Bank. Complex factors that drove AIDS research included an unknown method of transmission, disease course unpredictability, patients' low socioeconomic status, and stigmatization. In response to these challenges, the AIDS Specimen Bank was established in 1982, and is now a preeminent resource where researchers across disciplines intersect in their biospecimen-driven investigation of HIV/AIDS. As such, biobanking may present a similar solution to understanding the biological effects of gender-affirming interventions.

5. Conclusions and future directions

Investigation into publicly-searchable biorepositories indicates that TGD demographic information and gender-affirming interventions are not being catalogued with specimens. Further investigation of specific biobanks within these databases is warranted to explore whether TGD demographic and intervention data are being collected but not classified as searchable data points. If the latter is the case, these data should be re-classified as important variables alongside race, ethnicity, and age. Strategies for biorepositories to expand their collection of TGD demographic information include:

1. Modifying clinical intake forms and demographic questionnaires to include sex assigned at birth (alternatively, organs present at birth) and gender identity with TGD-inclusive options.
2. Adding a module to questionnaires to explore if a TGD patient has pursued any gender-affirming interventions. An example of such a module has been adapted from the Florida Pancreas Collaborative Biorepository [16] and is shown in Table 2.
3. Making a targeted effort to recruit TGD patients for biobanking studies.

Researcher knowledge of and attitudes towards the cancer health disparities of TGD populations should be evaluated. If biobanking researchers are not motivated to collect TGD information, then the establishment of a biobank specifically for specimens from TGD cancer patients may be necessary to investigate tissue changes most efficiently.

Declaration of competing interest

None.

Acknowledgments

A summer stipend from the National Cancer Institute-funded SPIRIT-CHD Summer Internship Program (P20 CA202920) was provided for Nat Jones to conduct this research. We also wish to acknowledge Dr. Kaleena Dezsi for her unwavering support of this research.

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