Appendix 1 (as supplied by the authors): Protocols for the three systematic reviews

Appendix to: Meggetto O, Peirson L, Yakubu M, et al. Breast cancer risk and breast screening for trans people: an integration of 3 systematic reviews. *CMAJ Open* 2019. DOI:10.9778/cmajo.20180028.

Review One: Breast Cancer Risk, Prognosis and Mortality in the Trans Population using Cross-sex Hormones: Protocol for a Systematic Review

INTRODUCTION

Rationale and Context

Trans is an umbrella term for individuals with diverse gender identities and expressions that differ from stereotypical gender norms [1]. It includes but is not limited to people who identify as transgender, trans woman (male-to-female), trans man (female-to-male), transsexual, cross-dresser, gender non-conforming, gender variant or gender queer (non-binary) [1]. A population-based study conducted in Massachusetts reported that 0.5% of the adult population identifies as trans [2]. Based on this value, it is estimated that in 2008, there were 53,500 trans individuals over the age of 15 living in Ontario [3].

Many trans individuals seek gender affirming medical interventions such as surgery and/or cross-sex hormone therapy to align their physical appearance with their sense of self, and as such, face unique healthcare needs [4]. The goal of cross-sex hormone therapy in trans individuals is to reduce gender dysphoria by facilitating a physical presentation of gender that is consistent with one's felt gender [5]. Endocrinologic feminization among those who were born male but identify as female, or are on the male-to-female spectrum, is achieved through the use of agents that directly or indirectly suppress the effects of androgens (e.g., gonadotrophic releasing hormone antagonists) and agents that induce female secondary sex characteristics (e.g., estrogen) [5]. Among individuals who were born female but identify as male or are on the female-to-male spectrum, endocrinologic masculinization is primarily achieved through the use of testosterone to induce male secondary sex characteristics [5].

The risk of breast cancer among trans individuals is unclear. Among cisgender women, reproductive factors that influence one's lifetime endogenous exposure to female sex hormones such as early age at menarche, nulliparity and late age at menopause, as well as exogenous use of these hormones (i.e., hormone replacement therapy) have been identified as risk factors for the development of breast cancer [6]. In addition to the presence of varying amounts of breast tissue, the risk of breast cancer in trans individuals is hypothesized to be influenced by the use of exogenous cross-sex hormones that alter one's exposure to female sex hormones [7,8]. Furthermore, the effect of cross-sex hormone therapy on prognostic features at breast cancer diagnosis and mortality from breast cancer is unclear [9,10].

A review of the literature is needed to better understand breast cancer risk, prognosis and mortality in trans individuals who use cross-sex hormones. This knowledge can help inform guidelines and policies related to breast cancer prevention, detection and care for this population.

Appendix to: Meggetto O, Peirson L, Yakubu M, et al. Breast cancer risk and breast screening for trans people: an integration of 3 systematic reviews. *CMAJ Open* 2019. DOI:10.9778/cmajo.20180028.

Objective

The purpose of this systematic review is to identify and synthesize evidence on the impact of cross-sex hormone therapy on breast cancer risk, prognosis and mortality in the trans population. This systematic review, in conjunction with its companion evidence review (on the benefits and harms of breast screening for the trans population) and guideline review (on existing breast screening recommendations for the trans population), will be used to inform policy development for the appropriate inclusion of trans persons in the Ontario Breast Screening Program (OBSP).

Key Questions

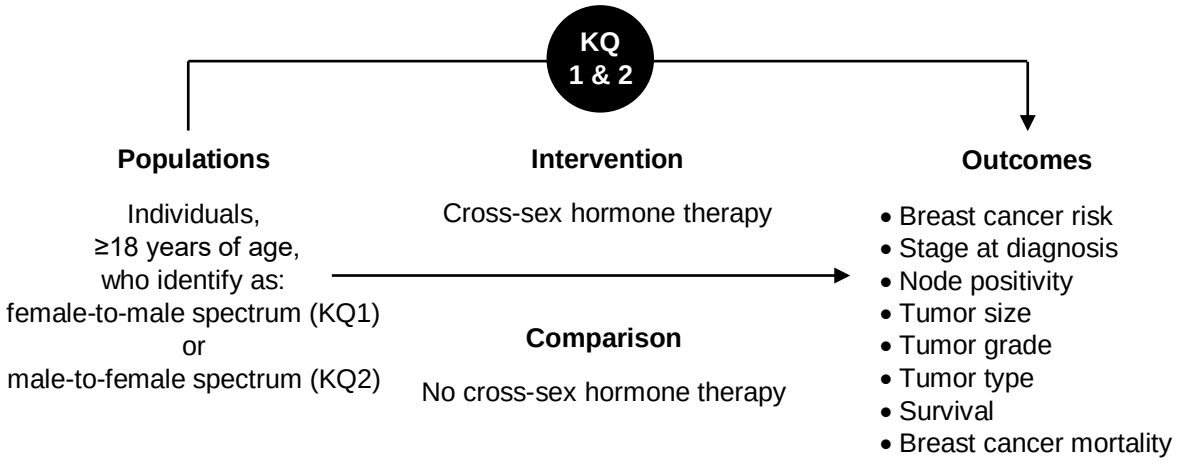
The key questions (KQs) for this review are:

KQ1: Among trans men, what is the impact of cross-sex hormone therapy[1] on breast cancer risk, prognosis and mortality?

KQ2: Among trans women, what is the impact of cross-sex hormone therapy[1] on breast cancer risk, prognosis and mortality?

Analytic Framework

The analytic framework presented below provides a visual illustration of the key questions for this review, showing the links between the populations, interventions, comparisons, and clinically relevant outcomes.



[1] For the purposes of this review, cross-sex hormone therapy is defined as the use of exogenous sex hormones that are opposite to those of an individual's natal sex for the purpose of aligning one's physical appearance to one's self-identified gender. Female cross-sex hormone therapy can include the use of estrogen, anti-androgen agents and progesterone. Male cross-sex hormone therapy generally consists of the use of testosterone [5].

METHODS

Data Sources and Search Strategies

To address the KQs of this systematic review, PubMed, MEDLINE, Embase, CINAHL, the Cochrane Database of Systematic Reviews, and websites of relevant professional associations, government bodies and community organizations will be searched for primary research articles and systematic reviews. The search strategy for PubMed, developed in consultation with a medical librarian, is provided in Table 1. This strategy will be adapted to search the other electronic databases. The medical librarian and members of the working group were consulted to generate a list of relevant websites and keywords for the targeted search (Table 2). Searches will be limited to articles published in English within the last 20 years (i.e., since January 1, 1997). Reference lists of included studies and on-topic systematic reviews will also be checked to identify potentially relevant citations missed by the database searches. Clinical experts within and outside of the requesting group may be contacted to recommend relevant citations.

Table 1: Draft PubMed Search Strategy (Review One)

Search	Query
1	transgender persons[mh] OR health services for transgender persons[mh] OR transsexualism[mh] OR transvestism[mh]
2	transgend*[tw] OR transsex*[tw] OR transman[tw] OR transmen[tw] OR transwom*[tw] OR transfem*[tw] OR transmasc*[tw] OR transmale*[tw] OR transidentified[tw] OR transperson[tw] OR transpeople[tw] OR transpeoples[tw] OR transpersons[tw]
3	((trans*[tw]) AND (sex*[tw] OR gender*[tw] OR woman[tw] OR women[tw] OR female*[tw] OR feminine[tw] OR male[tw] OR males[tw] OR man[tw] OR men[tw] OR masc*[tw] OR identified[tw] OR people[tw] OR peoples[tw] OR person[tw] OR persons[tw]))
4	((gender*[tw] OR sex*[tw]) AND (trans*[tw] OR variant[tw] OR identity[tw] OR non-binary[tw] OR nonbinary[tw] OR queer[tw] OR fluid[tw] OR nonconform*[tw] OR non-conform*[tw] OR reassign*[tw] OR re assign*[tw] OR dysphori*[tw]))
5	female-to-male[tw] OR male-to-female[tw] OR FTM[tw] OR MTF[tw] OR sexual minorit*[tw] OR cross gender*[tw] OR crossgender*[tw] OR transvesti*[tw] OR cross dress*[tw] OR crossdress*[tw] OR cross sex*[tw] OR crosssex*[tw] OR agender[tw] OR bigender[tw] OR bi-gender[tw] OR genderqueer[tw] OR cisgender[tw] OR cis-gender[tw] OR two-spirit*[tw] OR twospirit*[tw] OR 2 spirit*[tw] OR 2spirit*[tw]
6	1 OR 2 OR 3 OR 4 OR 5
7	"Hormone Replacement Therapy"[Mesh] OR "Gonadotropin-Releasing Hormone"[Mesh] OR (hormon*[tw] OR cross-sex hormon*[tw] OR crosssex hormon*[tw] OR sex hormon*[tw]) OR (endocrinologic*[tw] AND (Feminization[tw] OR Feminisation[tw] OR masculinization[tw] OR Masculinisation[tw])) OR ((hormone[tw] OR hormones[tw] OR hormonal[tw]) AND (antagonist[tw] OR supplement*[tw] OR agonist*[tw] OR exogenous[tw] OR management[tw] OR gonadotropin[tw] OR "gonadal releasing"[tw] OR sequel*[tw] OR replacement[tw] OR HRT[tw])) OR (therap*[tw] AND (estrogen[tw] OR testosterone[tw] OR progesterone[tw]))
8	breast neoplasm[mh] OR "Carcinoma, Intraductal, Noninfiltrating"[Mesh] OR ((breast*[tw] OR mammar*[tw]) AND (neoplasm*[tw] OR cancer*[tw] OR carcinoma*[tw] OR tumor[tw] OR tumour[tw] OR tumors[tw] OR tumours[tw] OR malignan*[tw])) OR ((hyperplasia[tw] OR Carcinoma*[tw]) AND (Intraductal[tw] OR DCIS[tw] OR Ductal[tw] OR In Situ[tw] OR Noninfiltrating[tw]))
9	6 AND 7 AND 8 Filters: Publication date from 1997/01/01 to 2017/12/31; English

Table 2: Sources and Keywords for Targeted Search (Review One)

Relevant Websites for Grey Literature Search	Keywords
Professional Association Websites: • Canadian Medical Association • Canadian Professional Association for Transgender Health • College of Physicians and Surgeons of Ontario • Canadian Association of Radiology • Ontario Medical Association • Ontario College of Family Physicians • Ontario Association of Radiologists • American College of Radiology • Canadian Association of Radiologists • The European Society of Breast Cancer Specialists • Society of Breast Imaging • World Professional Association for Transgender Health **Government Bodies and Agencies:** • Public Health Agency of Canada • Canadian provincial and territorial cancer agencies • Health Canada • National Health Service (United Kingdom): Breast Screening Program • Australian Cancer Screening Programs and Guidelines: BreastScreen Australia **Other:** • International Agency for Research on Cancer • World Health Organization • Canadian Cancer Society • American Cancer Society • Fenway Health • Rainbow Health Ontario • Sherbourne Health Centre • Trans PULSE project • Transgender Health Information Program • Trans Care BC • TransGender Care • The GLBT Health Access Project • Center of Excellence for Transgender Health	**Step 1:** • Transgend*/trans gend* • Transsex*/trans sex* • Transwom*/trans wom* • Transman/transmen/trans man/trans men • Nonbinary/non-binary • Nonbinary gender/non-binary gender • Gender variant • Gender identity • Gender reassign* • Genderqueer/gender queer • Gender nonconform*/gender non conform* • Twospirit*/two spirit*/2 spirit* • Crossdress*/cross dress* • Cross sex*/crosssex* • Cross gender*/crossgender* • Sexual minorit* • Male-to-Female/MTF • Female-to-Male/FTM • Gender fluid • Agender • Bigender/bi-gender • Cisgender/cis-gender • Dysphori* **Step 2:** • Cross-sex hormon*/cross sex hormon*/crosssex hormon* • Hormone replacement therapy • HRT • Sex hormon* • Gonadotropin releasing hormone • Progesterone • Estrogen • Testosterone **Step 3:** • Breast cancer* • Breast neoplasm* • Ductal Carcinoma In Situ • DCIS • Noninfiltrating intraductal carcinoma* • Intraductal carcinoma*

Eligibility Criteria

Studies will be selected for this review based on the inclusion and exclusion criteria outlined in Table 3.

Table 3: Eligibility Criteria (Review One)

	In Scope → Include	Out of Scope → Exclude
Populations	**KQ1**: Individuals (≥18 years) born female who identify as non-binary, transmasculine or on the female-to-male spectrum with: • All original breast tissue remaining • Some breast tissue removed (i.e., breast reduction) • Chest contouring surgery (e.g., lipo sculpting, pectoral implants) **KQ2**: Individuals (≥18 years) born male who identify as non-binary, transfeminine or on the male-to-female spectrum with: • Breast augmentation/implant • No breast augmentation/implant	• Individuals <18 years of age • Individuals who have had a complete bilateral mastectomy
Interventions	**KQ1**: Male cross-sex hormone therapy (e.g., testosterone) **KQ2**: Female cross-sex hormone therapy (e.g., anti-androgen agents, estrogen or progesterone)	
Comparisons	**KQ1:** • Trans individuals not taking masculinizing cross-sex hormone therapy • Cisgender females **KQ2:** • Trans individuals not taking feminizing cross-sex hormone therapy • Cisgender males	• Studies without comparison groups
Outcomes	• Breast cancer risk (incidence) • Stage at diagnosis • Node positivity • Tumor size • Tumor grade • Tumor type • Survival • Breast cancer mortality	
Setting	No restrictions	
Study Designs	• Randomized controlled trials • Non-randomized experimental studies • Observational studies with comparison groups (i.e., cohort, case-control or cross-sectional)	• Systematic reviews • Qualitative studies • Modelling studies • Case series or reports
Location	No restrictions	

	In Scope → Include	Out of Scope → Exclude
Document Characteristics	• Published in the past 20 years • Peer-reviewed • Full reports • Published in English • Grey literature • Conference proceedings and abstracts	• Commentaries and editorials • Non-systematic literature reviews

Data Management

Search results will be merged and de-duplicated in EndNote [11]. The remaining citations will be uploaded to DistillerSR [12], a web-based systematic review software program, to manage all phases of citation screening, data extraction, quality assessment, verification tasks and conflict resolution. Forms will be developed *a priori* for the screening levels based on the eligibility criteria and piloted to ensure that the questions are valid and that all reviewers are consistently applying the rules. Forms will also be developed *a priori* for data extraction and quality assessment; forms will be piloted and revised if necessary. All team members involved in screening, data extraction, quality assessment and verification will be familiar with the review protocol, trained to use DistillerSR and instructed in how to complete the forms.

Selection Process

All titles and abstracts identified by the search will be reviewed by two independent reviewers who will not be blinded to journal titles or author details; any citation marked for inclusion by either team member will move forward to full-text relevance testing. Full-text relevance testing will be conducted by two independent reviewers with consensus required for inclusion or exclusion. If consensus cannot be achieved, a third member of the review team will be consulted. Reasons for full-text exclusion will be recorded and reported in a list of studies excluded at full-text. Articles that reach full-text relevance testing but cannot be retrieved in a complete version through an open access source, our membership in the Health Science Information Consortium of Toronto, or through our previously and legally obtained holdings may be excluded. Depending on costs and resource availability, for-purchase articles may be acquired for this review. We will not contact authors to obtain articles.

Data Extraction Process and Items

One reviewer will extract data from each of the included studies using forms that will be tailored for this review and housed on DistillerSR. A second reviewer will verify the accuracy and completeness of all extracted data; disagreements will be resolved through discussion and/or through third party consultation when consensus cannot be reached.

The list below identifies the data to be extracted from each included study, if provided. Information on these items must be contained within the paper(s); study authors will not be contacted for missing data.

- **Study characteristics**: design, objective, eligibility criteria, participant recruitment and selection methods, dates, sample size, geographic location, funding source

- **Participant characteristics**: age at study enrollment (mean, median, range or categorical), self-identified gender/sex (e.g., trans woman, trans man, non-binary), type of surgical procedure(s) undergone (e.g., breast augmentation, implants, breast reduction, total bilateral mastectomy, chest contouring surgery, total hysterectomy, oophorectomy or none), age when each surgical procedure was completed
- **Intervention details**: type of hormone(s) used (e.g., testosterone, estrogen, progesterone) and dosage, route of hormone delivery (e.g., oral, intravenous, transdermal), age at hormone therapy initiation, age at cessation of hormone therapy, duration of hormone use
- **Outcome details:** definitions, how outcomes were assessed, units of measurement, when outcome data were collected and follow-up duration
- **Key results for each outcome:** number (%) with outcome in each group, crude and/or adjusted effect estimates, 95% confidence intervals and/or *p* values

Quality Assessment of Individual Studies

The quality of individual studies will be assessed by a single reviewer. A second reviewer will verify all risk of bias assessment ratings; disagreements will be resolved through discussion and through third party consultation when consensus cannot be reached. The following quality assessment tools will be used: Cochrane's Risk of Bias tool [13] for randomized and non-randomized controlled trials and the Newcastle Ottawa Scale [14] for cohort and case-control studies. We are unaware of a formal tool that is widely used to assess the methodological quality of cross-sectional studies. In light of this, quality assessment of cross-sectional studies using a formal tool will not be conducted. Instead, the methodological quality of cross-sectional studies will be examined qualitatively through consideration of key methodological components such as the selection of participants, exposure and outcome assessment and evaluation of confounding.

Analysis, Synthesis and Reporting

The lead reviewer will conduct the synthesis and a second member of the review team, who is familiar with the included studies, will verify its accuracy and completeness. The results of the literature search will be described using a PRISMA flow diagram and a narrative summary. Similarities and differences in study details, quality, samples and intervention features will be examined across the included studies. Details about the body of included evidence will be presented narratively and in tables. To address each KQ, data relating to each outcome of interest from the included body of evidence will be presented narratively and in tables. Key messages for each outcome will be presented in the light of the quality of evidence.

Given the novelty of this topic, we do not anticipate the ability to perform a meta-analysis. However, where possible and when appropriate, a meta-analysis will be considered. For dichotomous outcomes, the number of events in each group will be used to generate summary measures of effect in the form of risk ratios (RR) with a 95% confidence interval using the DerSimonian and Laird random effect model with inverse variance method [15]. One reviewer will perform and interpret all possible meta-

analyses and any other required statistical tests. All meta-analyses will be performed in Review Manager version 5.3 [16].

GRADE Assessments

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [17,18] to assess the quality of the evidence available for four outcomes: breast cancer risk, stage at diagnosis, survival and mortality. These outcomes have been identified by the requesting group as critical and important for decision-making. GRADE assessments produce overall ratings (high, moderate, low or very low) that reflect the level of confidence in the estimates of effect. The evidence for each outcome will be grouped by study design. As per the GRADE system, evidence from randomized controlled trials will begin with a high quality rating and non-randomized trials and observational studies with comparison groups will begin with a low quality rating. Each body of evidence will be evaluated against the relevant GRADE criteria, rating down if there are serious or very serious concerns related to risk of bias, inconsistency, indirectness, imprecision or publication bias. GRADEpro software [19] will be used to perform these assessments and to generate the Evidence Profile and Summary of Findings tables.

Review Two: Benefits and Harms of Breast Screening for the Trans Population: Protocol for a Systematic Review

INTRODUCTION

Rationale and Context

Trans is an umbrella term for individuals with diverse gender identities and expressions that differ from stereotypical gender norms [1]. It includes but is not limited to people who identify as transgender, trans woman (male-to-female), trans man (female-to-male), transsexual, cross-dresser, gender non-conforming, gender variant or gender queer (non-binary) [1]. A population-based study conducted in Massachusetts reported that 0.5% of the adult population identifies as trans [2]. Based on this value, it is estimated that in 2008, there were 53,500 trans individuals over the age of 15 living in Ontario [3].

It is recognized that the trans population is medically underserved [20]. A retrospective study demonstrated that trans individuals were less likely to pursue breast screening with mammography as compared to women who do not identify as trans (i.e., cisgender women) [21]. A survey of 431 trans individuals living in Ontario found that, among those who reported a perceived need for a mammogram, 30% of female-to-male individuals and 25% of male-to-female individuals were unable to access one [22]. While these studies demonstrate that trans individuals face barriers in accessing and participating in breast screening, the evidence pertaining to the effectiveness, performance and harms of breast screening in the trans population has been lacking [8].

Currently, the Ontario Breast Screening Program (OBSP) screens average risk women between the ages of 50 and 74 years old biennially with mammography, and high risk women between the ages of 30 and 69 years old with annual mammography and magnetic resonance imaging [23]. Cancer Care Ontario is currently developing a policy pertaining to the appropriate inclusion of trans persons in its organized breast screening program. Screening recommendations for trans individuals should be based on the best available evidence, thus a thorough review of the potential benefits and harms of breast screening with various modalities is needed.

Objective

The purpose of this systematic review is to identify and synthesize evidence on the potential benefits and harms of breast screening in the trans population. This systematic review, in conjunction with its companion evidence and guideline reviews for both breast and cervical screening, will be used to inform policy development for the appropriate inclusion of trans persons in the OBSP and the Ontario Cervical Screening Program.

Key Questions

The key questions (KQs) for this review are:

KQ1. Is breast screening with mammography, magnetic resonance imaging (MRI), ultrasound, clinical breast exam (CBE) or breast self-exam (BSE) effective in

reducing breast cancer-specific mortality or all-cause mortality in the trans population?

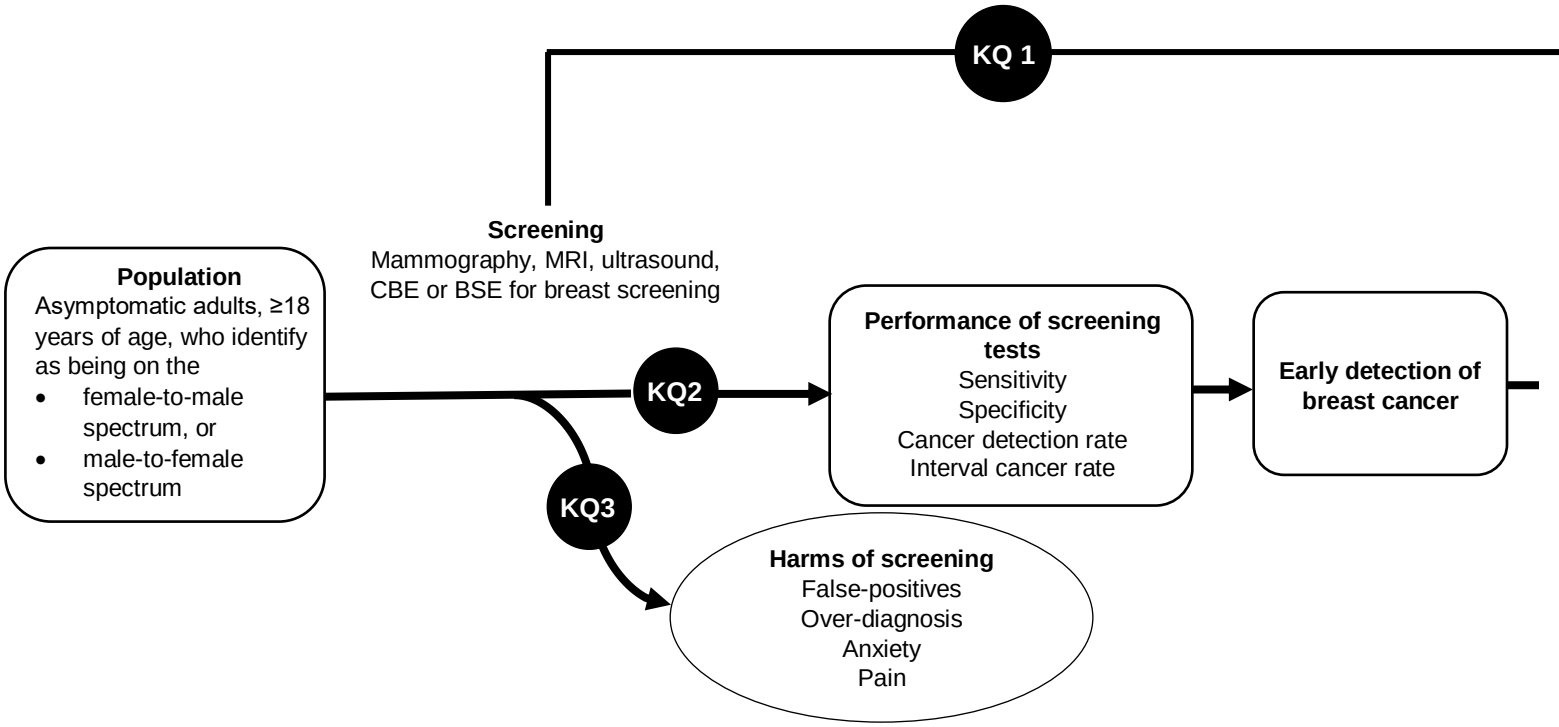
SQ1a. Does the effectiveness of breast screening in the trans population vary by screening modality?

KQ2. What is the performance of mammography, MRI, ultrasound, CBE or BSE for breast screening in the trans population?

KQ3. What are the potential harms of breast screening with mammography, MRI, ultrasound, CBE or BSE in the trans population?

Analytic Framework

The analytic framework presented below provides a visual illustration of the key questions, showing the links between the population, intervention and clinically relevant outcomes.



Appendix to: Meggetto O, Peirson L, Yakubu M, et al. Breast cancer risk and breast screening for trans people: an integration of 3 systematic reviews. *CMAJ Open* 2019. DOI:10.9778/cmajo.20180028.

METHODS

Data Sources and Search Strategies

To address the KQs of this review, PubMed, MEDLINE, Embase, CINAHL, the Cochrane Database of Systematic Reviews, and websites of relevant professional associations, government bodies and community organizations will be searched for primary research articles and systematic reviews. A draft search strategy for PubMed, developed in consultation with a medical librarian, is provided in Table 4. This strategy will be adapted to search the other electronic databases. The medical librarian and members of the working group were consulted to generate a list of relevant websites and keywords for the targeted search (Table 5). Searches will be limited to articles published in English within the last 20 years (i.e., since January 1, 1997). Reference lists of included studies, on-topic systematic reviews and literature reviews will also be checked to identify citations missed by the database searches. Clinical experts within and outside of the requesting group may be contacted to recommend relevant citations.

Table 4: Draft PubMed Search Strategy (Review Two)

Search	Query
1	transgender persons[mh] OR health services for transgender persons[mh] OR transsexualism[mh] OR transvestism[mh]
2	transgend*[tiab] OR transsex*[tiab] OR transman[tiab] OR transmen[tiab] OR transwom*[tiab] OR transfem*[tiab] OR transmasc*[tiab]
3	(trans[tiab]) AND (sex*[tiab] OR gender*[tiab] OR woman[tiab] OR women[tiab] OR female*[tiab] OR male[tiab] OR males[tiab] OR man[tiab] OR men[tiab] OR identified[tiab])
4	(gender*[tiab]) AND (trans[tiab] OR variant[tiab] OR identity[tiab] OR non-binary[tiab] OR nonbinary[tiab] OR queer[tiab] OR fluid[tiab] OR nonconforming[tiab] OR non-conforming[tiab] OR reassign*[tiab] OR re assign*[tiab])
5	Female-to-Male[tiab] OR male-to-female[tiab] OR FTM[tiab] OR MTF[tiab] OR sexual minority[tiab] OR sexual minorities[tiab] OR cross gender*[tiab] OR crossgender*[tiab] OR transvesti*[tiab] OR cross dress*[tiab] OR crossdress*[tiab] OR agender[tiab] OR bigender[tiab] OR bi-gender[tiab] OR genderqueer[tiab] OR cisgender[tiab] OR cis-gender[tiab] OR two-spirit[tiab] OR twospirit[tiab]
6	1 or 2 or 3 or 4 or 5
7	mass screening[mh] OR early detection of cancer[mh] OR mammography[mh] OR magnetic resonance imaging[mh:noexp] OR ultrasonography, mammary[mh]
8	clinical breast exam[tiab] OR breast self-exam[tiab] OR CBE[tiab] OR BSE[tiab] OR mammogr*[tiab] OR xeromammogra*[tiab] OR tomosynthesis[tiab] OR Scintimammogra*[tiab] OR MRI[tiab] OR magnetic resonance imaging[tiab] OR ultrasound*[tiab] OR ultrasonograph*[tiab] OR imaging[tiab]
9	7 or 8

Search	Query
10	breast neoplasm[mh] OR ((breast*[tiab] OR mammar*[tiab]) AND (neoplasm*[tiab] OR cancer[tiab] OR carcinoma[tiab] OR tumor[tiab] OR tumour[tiab] OR tumors[tiab] OR tumours[tiab] OR malignan*[tiab]))
11	6 and 9 and 10 Filters: Publication date from 1997/01/01 to 2017/12/31; English

Table 5: Sources and Keywords for Grey Literature Search (Review Two)

Relevant Websites for Grey Literature Searches	Keywords
Professional Association Websites: • Canadian Medical Association • Canadian Professional Association for Transgender Health • College of Physicians and Surgeons of Ontario • Canadian Association of Radiology • Ontario Medical Association • Ontario College of Family Physicians • Ontario Association of Radiologists • American College of Radiology • Canadian Association of Radiologists • The European Society of Breast Cancer Specialists • Society of Breast Imaging • World Professional Association for Transgender Health **Government Bodies and Agencies:** • Public Health Agency of Canada • Canadian provincial and territorial cancer agencies • Health Canada • National Health Service (United Kingdom): Breast Screening Program • Australian Cancer Screening Programs and Guidelines: BreastScreen Australia **Other:** • International Agency for Research on Cancer • World Health Organization • Canadian Cancer Society • American Cancer Society • Fenway Health • Rainbow Health Ontario • Sherbourne Health Centre • Trans PULSE project • Transgender Health Information Program • Trans Care BC • TransGender Care • The GLBT Health Access Project • Center of Excellence for Transgender Health	**Step 1:** • Transgend* • Transsex* • Transwom* • Transman/ transmen • Non-binary • Gender variant • Gender queer/ genderqueer • Gender nonconforming • Non-binary gender • Two spirit*/ two-spirit*/ 2 spirit*/ 2-spirit* • Cross dresser/ crossdresser • Male-to-Female/ MTF • Female-to-Male/ FTM • Gender fluid • Agender • Bigender/ bi-gender • Cisgender/ Cis-gender **Step 2:** • Breast cancer screening • Mammography or Mammogram • Magnetic resonance imaging / “MRI” • Ultrasonography or Ultrasound • Clinical Breast Exam or “CBE” • Breast Self Exam or “BSE”

Eligibility Criteria

Studies will be selected for this review based on the inclusion and exclusion criteria outlined in Table 6 below.

Table 6: Eligibility Criteria (Review Two)

	In Scope → Include	Out of Scope → Exclude
Populations	**All KQs:** Asymptomatic individuals (≥18 years) born female who identify as non-binary, transmasculine or on the female-to-male spectrum with: • All original breast tissue remaining with a history of male hormone use • Some original breast tissue remaining (i.e., breast reduction) with or without a history of male hormone use • Chest contouring surgery (e.g. lipo sculpting, pectoral implants) with or without a history of male hormone use Asymptomatic individuals (≥18 years) born male who identify as non-binary, transfeminine or on the male-to-female spectrum with: • Breast augmentation/implants with a history of female hormone use • No breast augmentation/implants with a history of female hormone use	**All KQs:** • Individuals born female with all breast tissue remaining and do not have a history of male hormone use • Individuals born female who have had a complete bilateral mastectomy • Individuals born male who do not have a history of female hormone use (with or without breast augmentation/implants)
Interventions	**All KQs:** Breast screening using at least one of the following: • mammography • MRI • ultrasound • CBE • BSE	**All KQs:** • Thermography • Tissue sampling • Diagnostic testing
Comparisons or Reference Standard	**KQ1:** Trans individuals not screened for breast cancer **SQ1a:** Comparisons of two or more screening modalities among trans individuals **KQ2:** No comparison group required; however, positive screens must be compared to the reference standard (i.e., pathology results from biopsy) and negative screens must be followed for one year **KQ3**: Trans individuals not screened for breast cancer, or no comparison group	• Studies without a comparison group (KQ1)
Diagnosis of Interest	**KQ2:** Breast cancer	
Outcomes	**KQ1 & SQ1a**: Breast cancer-specific mortality, all-cause mortality, number needed to screen to prevent one breast cancer-related death **KQ2**: cancer detection rate, interval cancer rate, sensitivity, specificity **KQ3**: over-diagnosis, false-positives, patient-reported anxiety, patient-reported pain/discomfort	
Settings	No restrictions	

	In Scope → Include	Out of Scope → Exclude
Study Designs	• Randomized controlled trials • Non-randomized experimental studies • Observational studies with or without (KQ2 and KQ3 only) comparison groups • Diagnostic evaluation studies	• Systematic reviews • Modelling studies • Qualitative studies • Case series or reports
Location	No restrictions	
Document Characteristics	• Published in the past 20 years • Peer-reviewed • Full reports • Published in English • Grey literature • Conference proceedings and abstracts	• Commentaries and editorials • Guidelines • Position statements • Non-systematic literature reviews

Data Management

Search results will be merged and de-duplicated in EndNote [11]. The remaining citations will be uploaded to DistillerSR [12], a web-based systematic review software program, to manage all phases of citation screening and data extraction. Forms will be developed for the screening levels based on the eligibility criteria and piloted to ensure that the questions are valid and that all reviewers are consistently applying the rules. Forms will also be developed *a priori* for data extraction and will be piloted and revised if necessary. All team members involved in screening, data extraction and verification will be familiar with the review protocol, trained to use DistillerSR and instructed in how to complete the forms.

Selection Process

All titles and abstracts identified by the search will be reviewed by two independent reviewers who will not be blinded to journal titles or author details; any citation marked for inclusion by either team member will move forward to full-text relevance screening. Reasons for exclusion at the title and abstract phases will be recorded. Full-text relevance screening will be conducted by two independent reviewers with consensus required for inclusion or exclusion. If consensus cannot be achieved, a third member of the review team will be consulted. Reasons for full-text exclusion will be recorded and reported in a list of studies excluded at the full-text phase. Articles that reach full-text relevance screening but cannot be retrieved in a complete version through an open access source, our membership in the Health Science Information Consortium of Toronto, or through our previously and legally obtained holdings may be excluded. Depending on costs and resource availability, for-purchase articles may be acquired for a review. We will not contact authors to obtain articles.

Data Extraction Process and Items

One reviewer will extract data from each of the included studies using forms that will be tailored for this review and housed on DistillerSR. A second reviewer will verify all extracted data; disagreements will be resolved through discussion and/or through third party consultation when consensus cannot be reached.

Data items to be extracted include:

- **Study characteristics:** study design, objective, eligibility criteria, participant recruitment and selection methods, study dates, sample size, geographic location, setting (community- vs. hospital-based screening), study funding source
- **Participant characteristics:** age at study enrollment (mean, median, range or categorical), self-identified gender/sex (e.g., trans woman, trans man, non-binary). type of surgical procedure(s) undergone (i.e., breast augmentation, breast implants, breast reduction, total bilateral mastectomy, chest contouring surgery, none), and age when each surgical procedure was completed, past or current use of cross-sex hormone therapy (yes/no), type of hormone(s) used (e.g., testosterone, estrogen, progesterone) and dosage, route of hormone delivery (e.g., oral, intravenous, transdermal), age at initiation of hormone therapy, age at cessation of hormone therapy, duration of hormone use
- **Intervention characteristics:** type of screening test(s) evaluated (i.e., mammography, MRI, ultrasound, CBE, BSE), screening interval
- **Outcome characteristics:** definitions, how outcomes were assessed, unit of measurement, when outcome data was collected and follow-up duration
- **Key results for effectiveness and harms outcomes:** number (%) with the outcome of interest in each group, crude and/or adjusted effect estimates, 95% confidence intervals and/or p-values. If the study does not provide an estimate of the number needed to screen, the event rate in the screening (intervention) and no screening (control) groups will be used to calculate it using the formula:

$$Number\ needed\ to\ screen = \frac{1}{Event\ rate_{control} - Event\ rate_{intervention}}$$

- **Key results for performance metric outcomes:** study reported cancer detection rate, interval cancer rate, sensitivity and specificity will be used. If the study does not report the outcomes of interest, the number of true positives, false positives, true negatives and false negatives will be used to calculate the outcomes of interest using the following formulas:

$$Cancer\ detection\ rate = \frac{number\ of\ breast\ cancers}{total\ number\ of\ screens}$$

$$Interval\ cancer\ rate = \frac{\begin{array}{c}Number\ of\ screen-eligible\ individuals\ who\\ developed\ invasive\ breast\ cancer\ in\ the\ XX\ year(s)\\ following\ a\ normal\ breast\ screening\ result\end{array}}{Number\ of\ screens}\ \text{x}\ 1{,}000$$

where XX is the period of time between scheduled screenings.

$$Sensitivity = \frac{true\ positives}{true\ positives + false\ negatives}$$

$$Specificity = \frac{true\ negatives}{true\ negatives + false\ positives}$$

Information on these items must be contained within the paper(s); study authors will not be contacted for missing data.

Quality Assessment of Individual Studies

The quality of individual studies will be assessed by a single reviewer. A second reviewer will verify all risk of bias assessment ratings; disagreements will be resolved through discussion and through third party consultation when consensus cannot be reached. The following quality assessment tools will be used: Cochrane's Risk of Bias tool [13] for randomized and non-randomized controlled trials, the Newcastle-Ottawa Scale [14] for cohort and case-control studies and the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) II tool [24] for diagnostic evaluation studies. We are unaware of a formal tool that is widely used to assess the methodological quality of cross-sectional studies. In light of this, quality assessment of cross-sectional studies using a formal tool will not be conducted. Instead, the methodological quality of cross-sectional studies will be examined qualitatively through consideration of key methodological components such as the selection of participants, exposure and outcome assessment and evaluation of confounding.

Analysis, Synthesis and Reporting

The lead reviewer will conduct the synthesis and a second member of the review team, who is familiar with the included studies, will verify its accuracy and completeness. The results of the literature search will be described using a PRISMA flow diagram and a narrative summary. Similarities and differences in study details, quality, samples and intervention features will be examined across the included studies. Details about the body of included evidence will be presented narratively and in tables.

For each KQ, results will be organized by screening modality. Key messages for each outcome will be presented in the light of the quality of evidence. Given the novelty of this topic, we do not anticipate the ability to perform a meta-analysis. However, where possible and when appropriate, a meta-analysis will be considered. For dichotomous outcomes, the number of events in each group will be used to generate summary measures of effect in the form of risk ratios (RR) with a 95% confidence interval using the DerSimonian and Laird random effect model with inverse variance method [15]. For continuous outcomes that are measured with the same scale or instrument across studies, the number of participants, mean and standard deviation for the two groups will be used to generate the pooled mean difference (with a 95% confidence interval) between intervention and control groups. One reviewer will perform and interpret all possible meta-analyses and any other required statistical tests. All meta-analyses will be performed in Review Manager version 5.3 [16].

GRADE Assessments

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [17,18] to assess the quality of the evidence available for a limited selection of outcomes. These outcomes will be chosen by the requesting group upon completion of article screening. GRADE assessments produce overall ratings (high, moderate, low or very low) that reflect the level of confidence in the estimates of effect. The evidence for each outcome will be grouped by study design. As

per the GRADE system, evidence from randomized controlled trials will begin with a high quality rating and non-randomized trials and observational studies with comparison groups will begin with a low quality rating. Each body of evidence will be evaluated against the relevant GRADE criteria, rating down if there are serious or very serious concerns related to risk of bias, inconsistency, indirectness, imprecision or publication bias. GRADEpro software [19] will be used to perform these assessments and to generate the Evidence Profile and Summary of Findings tables.

Review Three: Breast Screening for Trans Populations: Protocol for a Systematic Review of Guidelines and Position Statements

INTRODUCTION

Rationale and Context

Trans is an umbrella term for individuals with diverse gender identities and expressions that differ from stereotypical gender norms [1]. It includes but is not limited to people who identify as transgender, trans woman (male-to-female), trans man (female-to-male), transsexual, cross-dresser, gender non-conforming, gender variant or gender queer (non-binary) [1]. A recent population-based survey conducted in the United States reported that approximately 0.5% of the adult population identifies as trans [2]. Based on this value, it is estimated that in 2008, there were 53,500 trans individuals over the age of 15 living in Ontario [3].

It is recognized that the trans population is medically underserved [20]. A retrospective study reported that trans individuals were less likely to pursue breast screening with mammography as compared to women who do not identify as trans (i.e., cisgender women) [21]. Additionally, both the trans and medical communities have identified gaps in the knowledge and training of healthcare providers on trans healthcare needs, as well as appropriate clinical guidance for providing and managing their care [20,25-27]. A recent survey of obstetrics and gynecology care providers across the United States reported that 59% were unaware of the recommendations for breast screening in male-to-female patients, and only 29% were comfortable caring for trans individuals [28].

Currently, the Ontario Breast Screening Program (OBSP) screens average risk women between the ages of 50 and 74 biennially with mammography, and high risk women between the ages of 30 and 69 with annual mammography and magnetic resonance imaging [23]. The risk of breast cancer and effectiveness of breast screening in trans populations has not been well studied [8]. Screening recommendations for trans individuals should be based on the best available evidence, thus a thorough review of existing breast screening guidelines for the trans population is needed.

Objective

The purpose of this guideline review is to identify and synthesize published recommendations for breast screening in trans populations. This guideline review, in conjunction with its companion evidence reviews, will be used to inform policy development for the appropriate inclusion of trans persons in the OBSP.

Key Question

The key question (KQ) for this review is:

KQ1. What are the recommended eligibility requirements, screening modalities and screening intervals for breast screening in trans populations?

METHODS

Data Sources and Search Strategies

To address the KQ of this review, PubMed, MEDLINE, guideline databases, the websites of relevant guideline development groups, professional associations, government bodies and community organizations will be searched for guidelines and position statements on breast screening in trans populations. A medical librarian, members of the requesting group and the Canadian Agency for Drugs and Technologies in Health Grey Matters tool for searching health-related grey literature [29] were consulted to help generate the list of websites, databases and keywords for the targeted search (Table 7). Draft search strategies for PubMed and were developed in consultation with a medical librarian and are outlined in the Tables 8 and 9, respectively. Searches will be limited to documents published in English within the last 20 years (i.e., since January 1, 1997). Reference lists of included documents will be checked to identify citations missed by the database searches. Clinical experts within and outside of the requesting group may be contacted to recommend relevant citations.

Table 7: Sources and Keywords for Targeted Search (Review Three)

Guideline Databases and Websites	Keywords
Guideline Databases: • Agency for Health Research and Quality (AHRQ) National Guideline Clearinghouse • Canadian Medical Association Infobase • Canadian Partnership Against Cancer Standards and Guidelines Evidence Database • Guideline International Network • National Health and Medical Research Council • TRIP Database • Standards and Guidelines Evidence (SAGE) Repository **Guideline Development Groups:** • Canadian Task Force on Preventive Health Care • United States Preventive Services Task Force • National Comprehensive Cancer Network • National Institute for Health and Care Excellence • Program in Evidence-Based Care • Scottish Intercollegiate Guideline Network **Professional Association Websites:** • Canadian Medical Association • Canadian Professional Association for Transgender Health • World Professional Association for Transgender Health • College of Physicians and Surgeons of Ontario • Canadian Association of Radiology • Ontario Medical Association • Ontario College of Family Physicians • Ontario Association of Radiologists • American College of Radiology • Canadian Association of Radiologists • The European Society of Breast Cancer Specialists • Society of Breast Imaging **Government Bodies and Agencies**	**Step 1:** • Transgend* • Transsex* • Transwom* • Transman/ transmen • Non-binary • Gender variant • Gender queer/ genderqueer • Gender nonconforming • Non-binary gender • Two spirit*/ two-spirit*/ 2 spirit*/ 2-spirit* • Cross dresser/ crossdresser • Male-to-Female/ MTF • Female-to-Male/ FTM • Gender fluid • Agender • Bigender/ bi-gender • Cisgender/ Cis-gender **Step 2:** • Breast cancer screening • Mammography or Mammogram • Magnetic resonance imaging / “MRI” • Ultrasonography or Ultrasound • Clinical Breast Exam or “CBE” • Breast Self Exam or “BSE”

Guideline Databases and Websites	Keywords
• Public Health Agency of Canada • Canadian provincial and territorial cancer agencies • Health Canada • National Health Service (United Kingdom): Breast Screening Program • Australian Cancer Screening Programs and Guidelines: BreastScreen Australia **Other** • International Agency for Research on Cancer • World Health Organization • Canadian Cancer Society • American Cancer Society • Fenway Health • Rainbow Health Ontario • Sherbourne Health Centre • Trans PULSE project • Transgender Health Information Program • Trans Care BC • TransGender Care • The GLBT Health Access Project • Center of Excellence for Transgender Health	

Table 7: Draft PubMed Search Strategy (Review Three)

Search	Query
1	"transgender persons"[mh] OR "health services for transgender persons"[mh] OR transsexualism[mh] OR "Transvestism"[mh]
2	transgender*[tiab] OR transsex*[tiab] OR transman[tiab] OR transwoman[tiab] OR transmen[tiab] OR transwomen[tiab] transfem*[tiab]
3	((Trans[tiab]) AND (sexual[tiab] OR sexuals[tiab] OR gender[tiab] OR gendered[tiab] OR woman[tiab] OR women[tiab] OR man[tiab] OR men[tiab] OR identified[tiab]))
4	((gender*[tiab]) AND (trans[tiab] OR variant[tiab] OR identity[tiab] OR variant[tiab] OR "two spirit"[tiab] OR "twospirit"[tiab] OR "non-binary"[tiab] OR “nonbinary”[tiab] OR “non-binary”[tiab] OR queer[tiab] OR "genderqueer"[tiab] OR fluid[tiab] OR “nonconforming"[tiab] OR “non conforming"[tiab] OR reassign*[tiab] OR re assign*[tiab]))
5	"Female-to-Male"[tiab] OR "male-to-female"[tiab] OR "FTM"[tiab] OR "MTF"[tiab] OR "sexual minority"[tiab] OR "sexual minorities”[tiab] OR "cross gender"[tiab] OR "cross gendered"[tiab] OR transvesti*[tiab] OR "cross dress"[tiab] OR "cross dresser"[tiab] OR "cross dressing"[tiab] OR “agender”[tiab] OR “a gender” [tiab] OR “bigender”[tiab] OR “bi-gender”[tiab] or “bi gender”[tiab] or
6	1 OR 2 OR 3 OR 4 OR 5
7	"mass screening"[mh] OR "early detection of cancer"[mh] OR mammography[mh] OR "magnetic resonance imaging"[mh:noexp] OR "ultrasonography, mammary"[mh]
8	"clinical breast exam"[tiab] OR "breast self-exam"[tiab] OR "CBE”[tiab] OR “BSE"[tiab] OR xeromammogra*[tiab] OR "MRI"[tiab] OR magnetic resonance imaging[tiab] OR mammogr*[tiab] OR ultrasound*[tiab] OR ultrasonograph*[tiab] OR Scintimammogra*[tiab] OR imaging[tiab] OR tomosynthesis[tiab]
9	7 OR 8
10	breast neoplasm[mh] OR ((breast*[tiab] OR mammar*[tiab]) AND (neoplasm*[tiab] OR cancer[tiab] OR carcinoma[tiab] OR tumor[tiab] OR tumour[tiab] OR tumors[tiab] OR tumours[tiab] OR malignan*[tiab]))
11	#6 AND #9 AND #10 Filters: Publication date from 1997/01/01 to 2017/12/31; English

Table 9: Draft MEDLINE Search Strategy (Review Three)

Search	Query
1	exp "transgender persons"/ or exp "health services for transgender persons"/ or exp transsexualism/ or exp transvestism/
2	(transgender* or transsex* or transman or transwoman or transmen or transwomen or transfem*).ti,ab,kw.
3	(Trans adj2 (sexual or sexuals or gender* or gendered or woman or women or man or men or identified)).ti,ab,kw.
4	(gender* adj1 (trans or variant or identity or "two spirit" or "twospirit" or "non-binary" or “nonbinary” or “non binary” or queer or "genderqueer" or fluid or "nonconforming" or "non conforming" or reassign* or re assign*)).ti,ab,kw.
5	("Female-to-Male" or "male-to-female" or "FTM" or "MTF" or "sexual minority" or "sexual minorities" or "cross gender" or "cross gendered" or "cross dressing" or "cross dress" or "cross dresser" or “agender” or “ a gender” “bigender” or “bi-gender” or “bi gender” or “cisgender” or “cis gender” or transvesti*).ti,ab,kw.
6	or/1-5
7	exp breast neoplasm/
8	((breast* or mammar*) adj2 (neoplasm* or cancer or carcinoma or tumor or tumour or tumors or tumours or malignan*)).ti,ab,kw.
9	or/7-8
10	exp "mass screening"/ or exp "early detection of cancer"/ or "magnetic resonance imaging"/ or exp "ultrasonography, mammary"/ or exp "mammography"/
11	(ultrasonograph* or ultrasound* or "clinical breast exam" or "breast self-exam" or "CBE" or "BSE" or mammogra* or "magnetic resonance imaging" or "MRI" or xeromammogra* or Scintimammogra* or tomosynthesis or imaging).ti,ab,kw.
12	or/10-11
13	6 and 9 and 12
14	limit 13 to (english language and yr="1997 -Current")

Eligibility Criteria

Documents will be selected for this review based on the inclusion and exclusion criteria outlined in the Table 10.

Table 10: Eligibility Criteria (Review Three)

	In Scope → Include	Out of Scope → Exclude
Populations	Individuals (≥18 years) born female but do not identify as female (i.e., identify as non-binary, transmasculine or as someone on the female-to-male spectrum) with: • All original breast tissue remaining and history of male hormone use • All original breast tissue remaining and no history of male hormone use • Some original breast tissue remaining (i.e., breast reduction) and history of male hormone use • Some original breast tissue remaining and no history of male hormone use • With or without chest contouring surgery (e.g. lipo sculpting, pectoral implants) Individuals (≥18 years) born male but do not identify as male (i.e., identify as non-binary, transfeminine, or as someone on the male-to-female spectrum) with: • History of female hormone use and breast augmentation/ implant • History of female hormone use without breast augmentation/ implant • No history of female hormone use, with or without breast augmentation/ implant	• Individuals < 18 years of age • Individuals born male with no history of feminizing hormone usage • Individuals who have had complete bilateral mastectomy
Interventions	Breast screening using at least one of the following: • mammography • magnetic resonance imaging (MRI) • ultrasound • clinical breast exam (CBE) • breast self-exam (BSE)	• Thermography • Tissue sampling • Diagnostic testing
Domains	Recommendations for breast screening in trans populations with focus on: • eligibility requirements • screening modalities • screening intervals	
Type of documents	• Guidelines • Position statements	• Commentaries and editorials • Systematic reviews without an accompanying guideline • Primary research on breast screening in trans populations
Settings	No restrictions	
Location	No restriction	

	In Scope → Include	Out of Scope → Exclude
Document Characteristics	• Published in the past 20 years • Peer-reviewed • Grey literature • Conference proceedings and abstracts • English	

Data Management

Results of the PubMed and targeted website searches will be merged and de-duplicated in EndNote [11]. The remaining citations will be uploaded to DistillerSR [12], a web-based systematic review software program, to manage all phases of citation screening and data extraction. Forms will be developed for the title and abstract screening and full-text screening levels based on the eligibility criteria and piloted to ensure that the questions are valid and that both reviewers are consistently applying the rules. Data extraction forms will be developed in Excel, piloted and revised if necessary. All team members involved in screening, data extraction and verification will be familiar with the review protocol, trained to use DistillerSR and instructed in how to complete the forms.

Selection Process

Titles and abstracts of the citations located through the electronic database searches will be reviewed by a single reviewer; any citation marked for inclusion will move forward to full-text review. A second reviewer will validate the selection for relevance at the title and abstract screening stage with a partial verification (30%) of the total set of documents. A single reviewer will examine the content of the identified websites and guideline databases using keywords to identify potentially relevant documents for full-text review. Where a search box is available on the website, the reviewer will follow the stepwise search approach specified in Table 7. When a search box is not available, website menus will be navigated to locate relevant documents.

Full-text review will be conducted by two independent reviewers with consensus required for inclusion or exclusion. If consensus cannot be achieved, a third member of the review team will be consulted. Reasons for full-text exclusion will be recorded and reported in a list of documents excluded at full-text.

Documents that reach full-text review stage but cannot be retrieved in a complete version through an open access source, through our membership in the Health Science Information Consortium of Toronto, or through our previously and legally obtained holdings may be excluded. Depending on costs and resource availability for-purchase documents may be acquired for this review. We will not contact authors to obtain documents.

Protocol Amendment (February 17, 2017): As the number of search results was less than anticipated, a second reviewer verified 100% of the citations screened at title and abstract.

Data Extraction Process and Items

One reviewer will extract data from each of the included documents using Excel forms. A second reviewer will verify all extracted data; disagreements will be resolved through

discussion and/or through third party consultation when consensus cannot be reached. Data items to be extracted include:

- Descriptive information about the document (i.e., guideline developer, title, year of publication, jurisdiction/location)
- Recommendation(s) pertaining to breast screening in each identified subgroup of the trans population. Specifically, the recommended screening modality, eligibility criteria, interval for screening, and logistic considerations such as appropriate language and staff sensitivity
- For each included recommendation, the source (i.e., peer-reviewed published, grey literature) and level of evidence (i.e., systematic review, randomized controlled trial, observational study, expert opinion) will be recorded
- Consensus level for each recommendation, if available

Quality Assessment of Individual Documents

Quality assessment of each included guideline will be conducted independently by two reviewers using the Appraisal of Guideline for Research and Evaluation 2 (AGREE II) instrument, a validated tool to assess the quality and reporting of practice guidelines [30]. Quality assessment of position statements will not be conducted as they are unlikely to undergo the same development process as guidelines. In addition, we are unaware of any critical appraisal tools to assess the quality of position statements.

Analysis, Synthesis and Reporting

The results of the search will be described using a flow diagram and a narrative summary. For each trans population subgroup of interest, a cross-document assessment using a high-level matrix will be conducted to identify similarities, differences and gaps in the recommendations for breast screening and their respective evidentiary base.

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