Assessing Breast Cancer Risk Prior to Gender-Affirming Chest Masculinization Surgery in Transgender Men

Short Title
BC Risk Assessment Before Top Surgery

Study Principal Investigator
Chandler Cortina, MD, MS

Version 1.0
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STUDY AND CONTACT INFORMATION

Protocol Long Title: Assessing Breast Cancer Risk Prior to Gender-Affirming Chest Masculinization Surgery in Transgender Men

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Principal Investigator:
Chandler Cortina, MD, MS
Assistant Professor of Surgery
Division of Surgical Oncology
Medical College of Wisconsin
9200 W. Wisconsin Ave.
Milwaukee, WI 53226
Phone: 414-805-1400
Email: ccortina@mcw.edu

Co-investigator:
Erin Doren, MD, MPH
Associate Professor of Plastic Surgery
Medical College of Wisconsin
1155 N. Mayfair Rd.
Milwaukee, WI 53226
Phone: 414-955-1000
Email: edoren@mcw.edu

Co-investigator:
Kristen Klement, MD
Assistant Professor of Plastic Surgery
Medical College of Wisconsin
1155 N. Mayfair Rd.
Milwaukee, WI 53226
Phone: 414-955-1000
Email: kklement@mcw.edu

Co-investigator:
Kate Krucoff, MD
Assistant Professor of Plastic Surgery
Medical College of Wisconsin
9200 W. Wisconsin Ave.
Milwaukee, WI 53226
Phone: 414-955-3860
Email: kkrucoff@mcw.edu

Co-investigator:
Sarah Sasor, MD
Assistant Professor of Plastic Surgery
Medical College of Wisconsin
1155 N. Mayfair Rd.
Milwaukee, WI 53226
Phone: 414-955-1000
Email: ssasor@mcw.edu

Co-investigator
Anna Purdy, APNP
Nurse Practitioner, Department of Surgery
Division of Surgical Oncology
Medical College of Wisconsin
9200 W. Wisconsin Ave.
Milwaukee, WI 53226
Phone: 414-955-1428
Email: apurdy@mcw.edu

Statistician:
Ruta Brazauskas, PhD
Associate Professor of Biostatistics
Institute for Health and Equity
Medical College of Wisconsin
8701 Watertown Plank Rd.
Milwaukee, WI 53226
Phone: 414-955-8687
Email: ruta@mcw.edu

Medical Geneticist (Collaborator):
Samantha Stachowiak, MS, CGS
Certified Genetic Counselor
Medical College of Wisconsin
9200 W Wisconsin Ave
Milwaukee, WI 53226
Phone: 414-955-4222
Email: sstachowiak@mcw.edu

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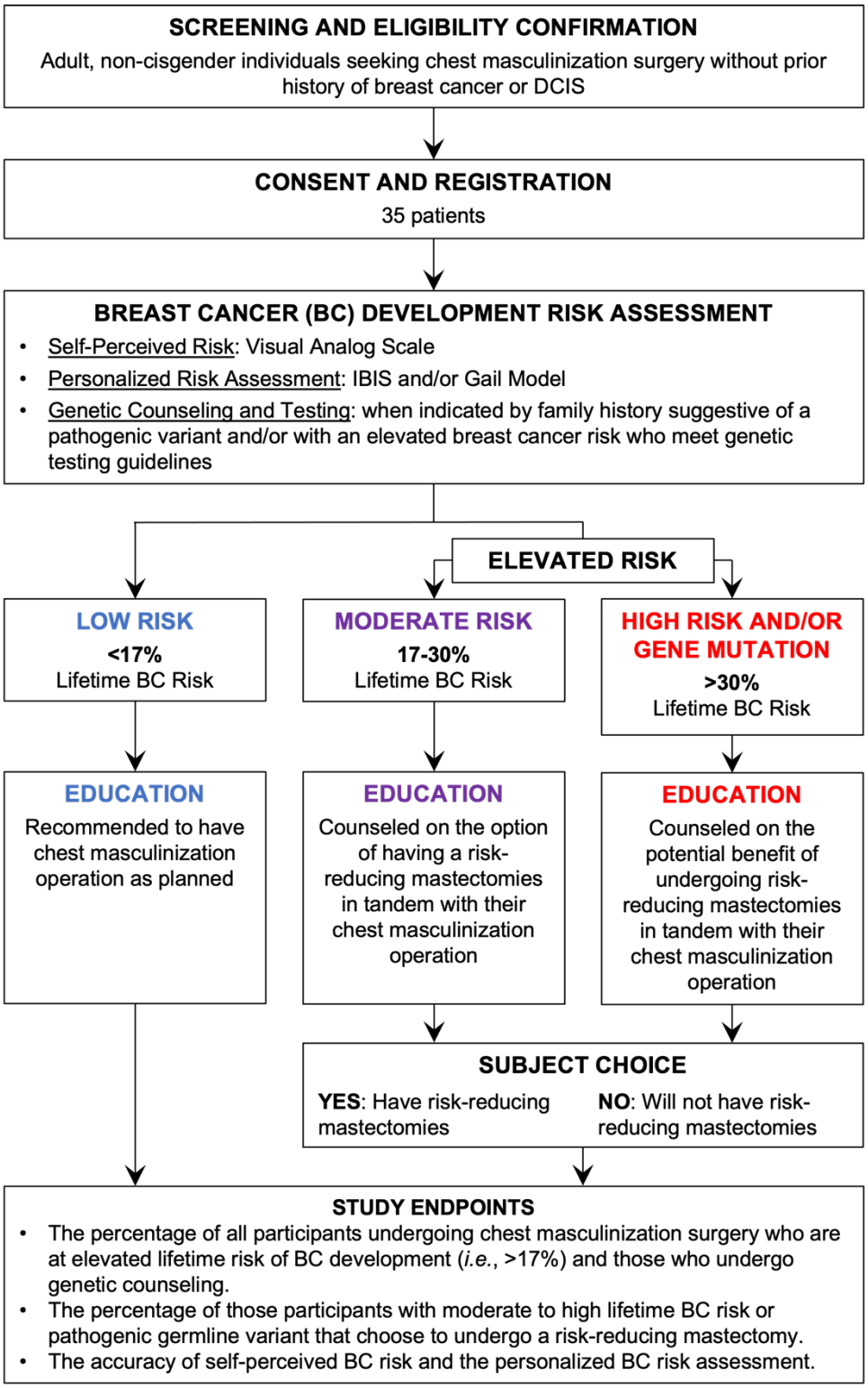
PROTOCOL SUMMARY

Title	Assessing Breast Cancer Risk Prior to Gender-Affirming Chest Masculinization Surgery in Transgender Men
Principal Investigator	Chandler Cortina, MD, MS
Study Sites	Froedtert Health and the Medical College of Wisconsin
Study Population	Non-cisgender adults seeking chest masculinization surgery (top surgery).
Primary Objectives	1. To determine the prevalence of TGNB persons undergoing chest masculinization surgery who have an elevated lifetime risk of breast cancer development and prevalence of those who undergo genetic counseling. 2. To determine whether those TGNB persons at elevated risk of breast cancer development choose to undergo risk-reducing mastectomies as part of their chest masculinization surgery. 3. To assess and compare the self-perceived breast cancer risk with calculated risk.
Primary Endpoints	1. The percentage of all participants undergoing chest masculinization surgery who are at elevated lifetime risk of BC development (*i.e.*, >17%) and those who undergo genetic counseling. Lifetime BC risk will be estimated utilizing the Gail and IBIS models. 2. The percentage of those participants with moderate to high lifetime BC risk or pathogenic germline variant that say they would choose to undergo a risk-reducing mastectomy. 3. The accuracy of self-perceived BC risk, as measured by the Visual Analog Scale (VAS), and the personalized BC risk assessment taken after the VAS.
Main Eligibility Criteria	• ≥18 years old. • Assigned female or intersex at birth and identify as non-cisgender. • Considering undergoing gender-affirming chest masculinization surgery. • Ability to communicate in English. • Ability to understand a written informed consent document, and the willingness to sign it.
Study Design	Prospective, single-arm interventional pilot study designed to test whether a breast cancer risk assessment, genetic testing (when applicable), and surgical oncologist consultation can inform those TGNB patients at elevated risk for breast cancer development to undergo risk-reducing mastectomies in tandem with their gender-affirming chest masculinization surgery.

Intervention	Breast cancer risk assessment and education.
Number of Subjects	35 patients (100 patients screened)
Subject Participation Duration	Breast cancer risk assessment will take approximately 30 minutes. Additionally, we wish to follow participants via record review for up to 1 year.
Estimated Time to Complete Enrollment	One year

STUDY SCHEMA



STUDY CALENDAR

Assessments and Procedures	Screening/ Enrollment Day -60 to -1	Visit 1 Day +1	Cancer Genetics Clinic Visit[b]	Visit 2[c]	Follow-up[d]
Eligibility Confirmation	X				
Informed Consent	X	X[a]			
Patient Registration	X	X[a]			
Visual Analog Scale		X			
Personalized BC Risk Assessment (Gail and/or IBIS model)		X			
Genetic Counseling[b]			X[b]		
Genetic Testing[b]			X[b]		
Surgical Oncologist Risk-Reducing Mastectomy Counseling Session[c]				X[c]	
Data Collection		X	X	X	X
Adverse Events Collection		X	X	X	

Footnotes

[a] During Visit 1, the study team will be available to answer any additional questions the potential participant may have about the study and confirm whether they were consented. If not done so already and as an option, a potential participant will have the opportunity to sign the informed consent form in person.

[b] Only those study participants with a family history suggestive of a pathogenic variant and/or with an elevated breast cancer risk who meet genetic testing guidelines (Appendix 2)[1, 2] will be referred to the Cancer Genetics Clinic to undergo a formal genetic counseling session and possible germline genetic testing. Genetic testing will be performed via the Ambry Genetics® Panel per institutional standards. See Section 6.3 for additional details.

[c] Only those study participants with an estimated lifetime breast cancer risk >17% (defined by the Gail model [https://ibis.ikonopedia.com] and/or IBIS model [https://www.mdcalc.com/calc/3647/gail-model-breast-cancer-risk]) or with a pathogenic germline mutation known to increase breast cancer risk will be offered to meet with the PI to discuss the utility of considering risk-reducing mastectomies as part of their chest masculinization surgery. If a subject is referred to the Cancer Genetics Clinic, Visit 2 is to occur after their Cancer Genetics Clinic visit.

[d] Participants with an estimated lifetime breast cancer risk >17% may be followed-up once within 60 days after the end of the funding period to determine if they either (i) underwent their chest masculinization surgery with or without the risk-reducing mastectomies, (ii) scheduled but did not undergo their chest masculinization surgery with or without the risk-reducing mastectomies, or (iii) say they would choose to schedule/undergo risk-reducing mastectomies as part of their chest masculinization surgery. Regarding (i) and (ii), follow-up data will only be collected from participants that had their procedure(s) performed by a MCW Plastic Surgery team member (study Co-Is) and, in certain instances, the study PI.

LIST OF ABBREVIATIONS

AE	adverse event
BC	breast cancer
CDH1	cadherin 1
CFR	Code of Federal Regulations
CHEK2	checkpoint kinase 2
Co-I	Co-investigator
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTO	Clinical Trials Office
CTSI	Clinical and Translational Science Institute
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
FH	Froedtert Health System
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IBIS	Tyrer-Cuzick Breast Cancer Risk Evaluation Tool
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
MCW	Medical College of Wisconsin
MCWCC	Medical College of Wisconsin Cancer Center
MRI	magnetic resonance imaging
NCI	National Cancer Institute
PALB2	partner and localizer of BRCA2
PHI	protected health information
PI	Principal Investigator
PTEN	phosphatase and tensin homolog
SAE	serious adverse events
SOP	standard operating procedure
SRC	Scientific Review Committee
TGNB	transgender and nonbinary persons
US	United States

1.0 BACKGROUND

1.1 Breast Cancer in Transgender and Nonbinary Persons

The population of transgender and nonbinary persons (TGNB) in Wisconsin and the United States (US) is steadily increasing and as this population grows, the number of individuals seeking gender-affirming therapies, including gender-affirming operations and gender-affirming hormone therapy, is also increasing.[3-5] In calendar year 2021 alone, the Froedtert & Medical College of Wisconsin Inclusion Health Clinic cared for >700 TGNB persons, and this patient population has been steadily increasing since the clinic opened in 2018. An example of gender-affirming surgery is chest masculinization surgery, colloquially called top surgery, in which the majority of breast tissue is removed in a person with a female sex assigned at birth to allow the chest to appear masculine.[6] While chest masculinization surgery removes most glandular breast tissue, some breast tissue is often left behind to allow for appropriate cosmetic contouring of the chest (**Figure 1**) and is not considered synonymous to an oncologic risk-reducing mastectomy.[6, 7] An oncologic risk-reducing mastectomy seeks to remove all breast tissue in an effort to minimize the future risk of breast cancer (BC) development in persons with an elevated lifetime risk of breast cancer.[8-10] Additionally, there is an increasing number of reported cases of TG men developing BC after chest masculinization surgery, secondary to the lack of data to support routine personalized BC risk assessment prior to chest masculinization surgery or for BC screening after chest masculinization surgery.[7, 11-14] Although gender-affirming therapies are associated with improved mental health outcomes and well-being for TGNB persons,[15] the potential long-term effects of these therapies on overall health, including future breast cancer risk, are not well understood.[16-18]

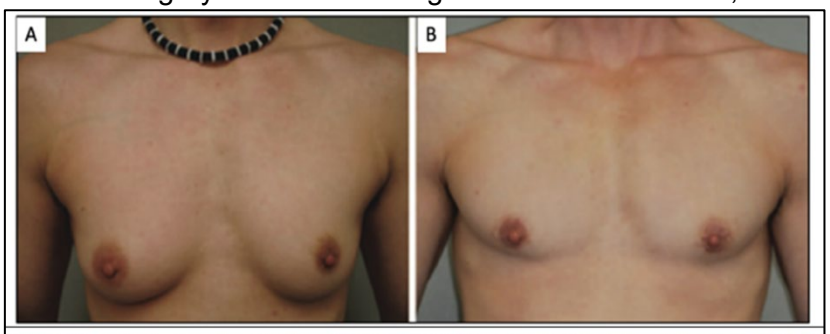


Figure 1. Before (A) and after (B) photos of a TGM after chest masculinization surgery

BC is the most common non-skin cancer in cisgender women. The current average lifetime risk for cisgender women is approximately 13% for a person who lives to be age 85 years in the United States.[19, 20] A person's lifetime risk of BC development may be dramatically impacted by a family history of BC, increased breast density, a personal history of atypical hyperplasia, lobular carcinoma in situ, high-dose radiation to the chest before age 30, or inherited genetic mutations in BC susceptibility genes.[21-29] Two well-validated models have been developed to estimate an individual's personalized percent lifetime BC risk: the Gail Model[30-36] and the Tyrer-Cuzick BC Risk Evaluation Tool (also called IBIS) that incorporate personal history (*e.g.*, first age at menarche, history of breast biopsies) and family breast and ovarian cancer history to calculate future breast cancer risk compared to the average cisgender woman.[37-43] Both models provide a percent estimate of a person's lifetime risk compared to the average women (ex: 35% lifetime risk for a person compared to 12.5% for average risk peer). Cisgender women with a moderate lifetime BC risk (17%-30%)[44] can be offered BC screening at an younger age (prior to age 40 years), enhanced BC screening with magnetic resonance imaging (MRI), or risk-reducing medications such as tamoxifen or raloxifene.[45-49] Those with a high lifetime BC risk, defined as >30%,[44] can be offered the previous options and may also consider risk-reducing mastectomies, a procedure reserved for this group given its potential risks and complications.[1, 9, 50-52] High and moderate penetrant pathogenic variants (BRCA1/2, PTEN, CDH1, PALB2, CHEK2, ATM, etc.) are known to elevate BC risk.[2, 53-57] Pathogenic variants (mutations) may be found through exploratory

processes, such as commercially available kits like 23andMe®, or through formal evaluation by a healthcare provider based on personal or family history. Risk-reducing mastectomies are generally offered to persons with a known pathogenic variant or a lifetime BC risk >30%.[8, 58, 59] While the ability to reduce BC incidence in these populations with risk-reducing mastectomies is well documented, there is insufficient data to determine if the operation provides a clear mortality benefit, with the exception of persons with a BRCA1 mutation.[8, 9, 50, 58, 59]

Self-perceived BC risk has the potential to influence risk-modifying behaviors such as alcohol and smoking use, uptake of cancer screening recommendations, and has been demonstrated to influence the decision for risk-reducing mastectomies in cisgender women with an elevated lifetime BC risk.[60-62] There is no contemporary data on perceived BC risk prior to chest masculinization surgery in TGNB persons, which may potentially influence an individual's decision to undergo chest masculinization surgery ± risk-reducing mastectomies. Given that an increasing number of TGNB persons are undergoing gender-affirming chest masculinization surgery and that no data exists on the operation's ability to reduce the incidence of BC, a clear opportunity exists to perform routine personalized BC risk assessment (± genetic testing) prior to chest masculinization surgery to identify those persons with a high lifetime BC risk who may benefit from undergoing oncologic risk-reducing mastectomies as part of their gender-affirming chest masculinization surgery.[63] Currently, these individuals do not undergo personalized BC risk assessment prior to chest masculinization surgery. Additionally, there is a need to examine both the accuracy of self-perceived BC risk in TGNB persons and how it may influence gender-affirming surgical decision making. Understanding BC risk in TGNB persons is a critical step in mitigating cancer disparities in this underserved population in Wisconsin and across the United States and to ensure patients are informed of this risk prior to undergoing chest masculinization surgery.

The Froedtert & MCW Inclusion Health Clinic opened in July 2018 and is located on the Milwaukee Regional Medical Center grounds within the Sargeant Health Center. The clinic is focused on providing health care for LGBTQ+ individuals. Services include primary and preventive care, obstetrics and gynecology, HIV prevention, gender-affirming care, and psychiatric care. The clinics are the only ones of its kind in Wisconsin and in the 2020-2021 fiscal year, cared for >1,600 individual patients, of which >600 identify as transgender. The unique relation with the Inclusion Health Clinic, the Southeastern Wisconsin LGBTQ+ community, and a skilled Plastic Surgery team allow for a unique opportunity to conduct this investigation.

1.2 Rationale

The goals of this pilot study are to 1) determine the percent of TGNB persons undergoing chest masculinization surgery who have an elevated lifetime risk of BC development (>17%) or a pathogenic genetic mutation that increased the risk of BC development (BRCA1/2, ATM, etc.), 2) measure the percent who are at risk and say they would choose to undergo risk-reducing mastectomies as part of chest masculinization surgery, and 3) assess and compare self-perceived BC risk with calculated risk. The results of this study will substantially inform TGNB patients and surgeons on the utility of personalized BC risk assessment prior to chest masculinization surgery and the accuracy of self-perceived BC risk in TGNB persons. This project has the potential to set a new standard of care that all TGNB persons should undergo a personalized BC risk assessment prior to gender-affirming surgery.

2.0 OBJECTIVES AND ENDPOINTS

This prospective, single-arm interventional pilot study is designed to test whether a breast cancer risk assessment, genetic testing (when applicable), and surgical oncologist consultation can inform those TGNB patients at elevated risk for breast cancer (BC) development to undergo risk-reducing mastectomies in tandem with their gender-affirming chest masculinization surgery. This study is expected to collect and analyze novel data that describes the prevalence of elevated BC risk in the TGNB population and the concordance between self-perceived BC risk and calculated risk, a pressing need for which little is known.

2.1 Primary Objectives

1. To determine the prevalence of TGNB persons undergoing chest masculinization surgery who have an elevated lifetime risk of breast cancer development and prevalence of those who undergo genetic counseling.

2. To determine whether those TGNB persons at elevated risk of breast cancer development choose to undergo risk-reducing mastectomies as part of their chest masculinization surgery.

3. To assess and compare the self-perceived breast cancer risk with calculated risk.

2.2 Primary Endpoints

1. The percentage of all participants undergoing chest masculinization surgery who are at elevated lifetime risk of BC development (*i.e.*, >17%) and those who undergo genetic counseling. Lifetime BC risk will be estimated utilizing the Gail and IBIS models.

2. The percentage of those participants with moderate to high lifetime BC risk or pathogenic germline variant that say they would choose to undergo a risk-reducing mastectomy.

3. The accuracy of self-perceived BC risk, as measured by the Visual Analog Scale (VAS), and the personalized BC risk assessment taken after the VAS.

3.0 SUBJECT POPULATION AND ELIGIBILITY

MCW must follow all MCW IRB requirements and policies regarding subject participation, found here: https://www.mcw.edu/HRPP/Policies-Procedures.htm

3.1 Subject Population

Non-cisgender adults seeking chest masculinization surgery (top surgery).

3.2 Eligibility Criteria

The study team will evaluate eligibility according to the following criteria. Subjects must meet all inclusion and none of the exclusion criteria to be registered on to the study. Any questions or concerns regarding eligibility should be directed to the PI, Dr. Chandler Cortina (ccortina@mcw.edu).

No waivers of protocol eligibility will be granted.

3.2.1 Inclusion Criteria

A potential study subject who meets all of the following inclusion criteria is eligible to participate in the study.

1. ≥18 years old.
2. Assigned female or intersex at birth and identify as non-cisgender.
3. Any individual considering undergoing gender-affirming chest masculinization surgery
4. Ability to communicate in English.
5. Ability to understand a written informed consent document, and the willingness to sign it.

3.2.2 Exclusion Criteria

A potential study subject who meets any of the following exclusion criteria is ineligible to participate in the study.

1. <18 years old.
2. Assigned male sex at birth.
3. Previously underwent chest masculinization surgery or any form of oncological mastectomy for the purposes of risk-reduction or cancer treatment.
4. Any previous or current history of breast cancer, including ductal carcina in situ (DCIS).
5. Inability to communicate in English.

4.0 ACCRUAL GOAL AND STUDY DURATION

The Froedtert and MCW Plastic Surgery Clinics see 75-100 individuals seeking top surgery per year. In 2022, MCW Plastic Surgeons performed 55 chest masculinization operations. Based on our study protocol and budget allotment, we expect to screen 100 patients and recruit 35 participants for this study.

The study is estimated to reach completion approximately 12 months from the time the study opens to accrual.

5.0 PATIENT RECRUITMENT AND REGISTRATION

TGNB individuals seen in the Plastic Surgery Clinic for surgical consultation for gender-affirming chest masculinization surgery will be given the opportunity to participate in the study. The PI or Anna Purdy, APNP will review the Plastic Surgeons' schedules to notify plastic surgeons of potential eligible participants. Patients will be provided a flyer that provides an overview of the study premise, measures, and study team contact information.

Once an individual confirms interest in the study, they will be screened by the PI for eligibility through Epic and then contacted via phone and/or email to discuss the study, answer any question, and the potential participant will be provided with an electronic and encrypted copy of the study's consent form, if interested in participating. Participants may provide their electronic signature and emailed back to the PI prior to Visit 1, at the time of Visit 1, or if meeting in person can provide a written signature.

Eligible participants who want to participate will be scheduled for a 30-minute appointment (Visit 1) in the Breast Care Clinic, located within the Froedtert and Medical College of Wisconsin Clinical Cancer Center, with either Anna Purdy, APNP or the PI. Eligible participants will also be given the given the option to have only a telephone or virtual visit (at the individuals' discretion). Patients who wish to meet in person for this screening assessment will be billed for services if seen formally in-person in the Breast Care Clinic. Participants will be incentivized to participate by receiving a $100 gift card.

6.0 STUDY DESIGN, PROCEDURES, AND MEASUREMENTS

6.1 Overview of the Study Design Workflow

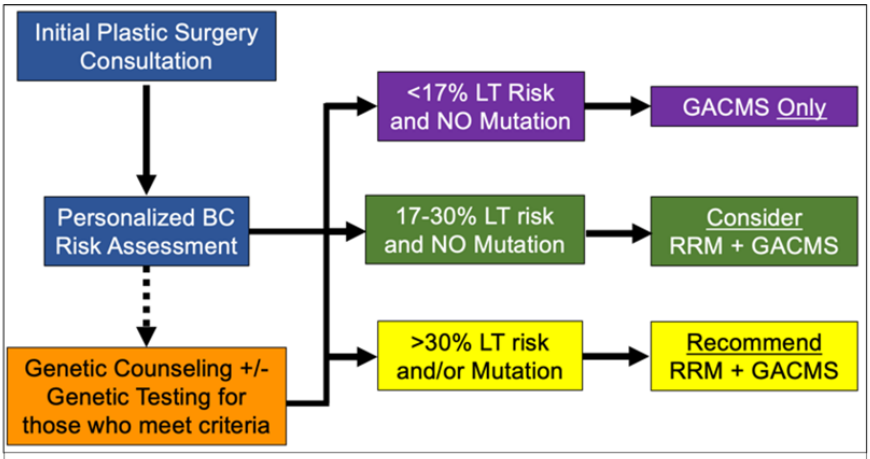


Figure 2. Study Workflow. Key: LT=lifetime, GACMS=gender-affirming chest masculinization surgery, RRM=risk-reducing mastectomy

***Activities that occur after the personalized BC risk assessment are participant choice, standard practice, and will be collected as part of study data.**

6.2 Visit 1: Breast Cancer Risk Assessment, Risk Categorization, and Initial Counseling

Participants will be scheduled within 60 days of initial screening and consent to undergo a personalized BC risk assessment utilizing the Gail and IBIS tools, which are both validated and widely used assessments.[37-43] During Visit 1, participants will identify their self-perceived lifetime BC risk on the Visual Analog Scale (Appendix 1) as part of the initial study intake, which will also acquire identifiable patient data (name, date of birth, and medical record number) and demographic information (race, ethnicity, age, sex assigned at birth, gender, etc; see Section 6.5 for a comprehensive list of data factors to be collected). The PI and Anna Purdy, APNP will enter the risk estimates from the Gail (https://ibis.ikonopedia.com) and IBIS

(https://www.mdcalc.com/calc/3647/gail-model-breast-cancer-risk) models into the same intake form, and calculate the mean BC calculated risk as the average of the two models:

$$Mean\ Lifetime\ BC\ Risk = \frac{Risk\ from\ Gail\ Model + Risk\ from\ IBIS\ Model}{2}$$

For participants <35 years old, in which Gail is not validated, only the IBIS lifetime BC risk will be used, and a mean lifetime risk will *not* be calculated.

Participants with an **average** lifetime BC risk, defined as ≤17%,[44] will be recommended to continue their gender-affirming operation as planned and will not be scheduled for a second visit.

Those with a **moderate** lifetime BC risk, defined as 17-30%, will be counseled on their elevated risk and the option to consider risk-reducing mastectomies as part of their gender-affirming chest masculinization operation. This option will be provided for moderate-risk persons, given the unclear long-term BC risk reduction from chest masculinization surgery alone. Moderate risk individuals will also be counseled on standard risk-reducing strategies, including lifestyle modifications, risk-reducing endocrine therapy options, and increased breast cancer screening strategies.

Participants with a **high lifetime** BC risk, defined as >30%, will be counseled on the potential benefit of undergoing risk-reducing mastectomies as part of their gender-affirming chest masculinization operation, an also be counseled on standard risk-reducing strategies, including lifestyle modifications, risk-reducing endocrine therapy options, and increased breast cancer screening strategies.

Those participants with an elevated lifetime risk based on family history, or with an unknown family history (per NCCN guidelines) will be offered to meet with a Genetic counselor to consider genetic study (see Section 6.3).

Those with a moderate or high risk and/or family history suggestive of pathogenic variant who decline further genetic testing or a 2nd visit with Dr. Cortina will be given the opportunity to express why they declined.

6.3 Breast Cancer Genetic Testing

Study participants with a family history suggestive of a pathogenic variant and/or with an elevated BC risk who meet NCCN genetic testing guidelines (Appendix 2)[1, 2] will be referred to the Cancer Genetics Clinic to undergo a formal genetic counseling session and possible germline genetic testing. Genetic testing will be performed via the Ambry Genetics® Panel, which is our current institution standard.

Persons who undergo genetic testing and are found to have a pathogenic variant for BC will be offered to see the PI, Chandler Cortina, MD, to discuss the utility of risk-reducing mastectomies as part of their chest masculinization operation (see Visit 2). Persons who are found to have a pathogenic variant that infers any other risk besides BC will be referred to the appropriate care teams for further evaluation, as is the current standard practice in our Genetics clinic.

6.4 Visit 2: Surgical Risk-Reducing Mastectomy Counseling

Participants considering risk-reducing mastectomies will meet directly with Dr. Cortina who can perform the operation in tandem with the patient's respective plastic surgeon. Patients who decline risk-reducing mastectomy as part of their surgery will be given the opportunity to express why they declined. This procedure is consistent with the current clinical workflow for cisgender patients. If patients undergo risk-reducing mastectomy as part of their chest masculinization surgery, pathological tissue examination is standard and findings will be collected during the study period.

6.5 Data Factors

Data factors to be collected from study participants for analysis described in Section 9.2.2 include the following:

- Name
- DOB
- MRN
- Age
- Weight (lbs)
- Height (inches)
- BMI
- Race
- Ethnicity
- Highest Level of Education
- Insured?
    - If so, type
- Sex Assigned at Birth
- Gender Identity
- Gender Expression
- Sexual Identity
- History of Gender Affirming Hormone Therapy
    - Duration
    - Dosage
    - Laboratory Values (estrogen, progesterone, and testosterone history)
- Prior Gender-Affirming Surgeries
- Age at First Menstrual Period
- Age at First Live Birth
    - Number of Children
- Family History Status Known or Unknown?
    - Unknown – Maternal, Paternal, or Both Sides?
- Number of 1st Degree Relatives with BC
- Number of 2nd Degree Relatives with BC
- Number of 1st Degree Relatives with Ovarian Cancer
- Number of 2nd Degree Relatives with Ovarian Cancer
- Any Other 1st or 2nd Degree Relatives with Any Cancer Diagnosis and What Type
- Previous Breast Biopsy

    - If Yes, Atypical Cells
    - If Yes, Pathology
- Any History of Hormone Replacement Therapy (Not Including Gender-affirming Testosterone Therapy)
- Any Ashkenazi Jewish Inheritance?
- Date of Risk Estimation
- Participant's Personal Estimation of Lifetime Risk
- Gail Model Risk Estimate
- IBIS Model Risk Estimate
- Average Risk ([Gail + IBIS Risks]/2)
- Recommended to Undergo Risk-reducing Mastectomies as Part of Top Surgery (Risk 17-30%) (Y/N)
- Given the Option to Consider Risk-reducing Mastectomies as Part of Top Surgery (Risk 17-30%) (Y/N)
- Say they would choose to Undergo Top Surgery (Y/N)
- Underwent Top Surgery (Y/N)
- Underwent Risk-reducing Mastectomies as Part of Top Surgery (Y/N)
- Recommended to Undergo Genetic Counseling (Y/N)
- Underwent Genetic Counseling (Y/N)
- Recommend to Undergo Genetic Testing (Y/N)
- Underwent Genetic Testing (Y/N)
    - If yes, results:

7.0 SUBJECT WITHDRAWAL, END OF STUDY, AND STUDY DISCONTINUATION

7.1 Subject Withdrawal

7.1.1 Patient-Initiated Withdrawal

A participant may decide to withdraw from the study at any time.

7.1.2 Investigator-Initiated Withdrawal

The investigator may withdraw a participant whenever continued participation is no longer in their best interests. Reasons for withdrawing a participant include, but are not limited to, a subject's request to end participation, a subject's noncompliance, or simply significant uncertainty on the part of the investigator that continued participation is prudent.

7.1.3 Replacement Policy and Data Usage

Subjects who sign the informed consent form and are enrolled, but subsequently withdraw, will be replaced. Data collected from subjects that withdraw or discontinue from the study will not be used.

7.2 End of Study Definition

A subject is considered to have completed the study if they have completed all phases of the study including the last scheduled procedure shown in the Study Calendar or has been discontinued.

7.3 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause (as determined by the MCW study principal investigator, DSMC, sponsor, and/or IRB). Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the MCW principal investigator (PI) will promptly inform the MCW Institutional Review Board (IRB) and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes.

8.0 ADVERSE EVENTS: DEFINITIONS, COLLECTION, AND REPORTING

This study is considered to be of minimal risk to participants due to its design and the nature of the intervention being tested (*i.e.*, risk assessment, genetic testing, and patient education). As described in Section 11.5.1, participants may experience anxiety or distress upon hearing the results of their personalized BC risk assessment and/or their genetic tests.

Subjects will not undergo an investigational medical intervention for the purposes of this study. While the participants' decision to have risk-reducing mastectomies performed in tandem with their gender-affirming chest masculinization procedure will be assessed, the risk-reducing mastectomy procedure itself or its outcomes does not fall under this study protocol. For these reasons, adverse and serious adverse events are not expected, but will be defined, collected, and reported as described in this section if encountered.

8.1 Definitions

8.1.1 Adverse Event (AE)

Any untoward medical occurrence in a subject or clinical investigation subject administered an interventional product and which does not necessarily have to have a causal relationship with this treatment.

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, located on the CTEP web site:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

AEs may be spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures.

8.1.2 Serious Adverse Event (SAE)

Serious Adverse Event (SAE) means any untoward medical occurrence that results in any of the following outcomes:

- **Death.** Results in death.
- **Life-threatening**. Is life-threatening (refers to an AE in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- **Hospitalization**. Requires inpatient hospitalization ≥24 hours or prolongation of an existing hospitalization.
- **Disability/incapacity**. Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- **Pregnancy**
- **Medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the participant, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

8.1.3 Attribution of an Adverse Event

An assessment of the relationship between the adverse event and the medical intervention, using the following categories:

- **Definitely Related**: *The AE is clearly related to the intervention*. There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

- **Probably Related:** *The AE is likely related to the intervention.* There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

- **Possibly Related:** *The AE may be related to the intervention.* There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events).

- **Unlikely:** *The AE is doubtfully related to the intervention.* A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).

- **Unrelated:** *The AE is clearly NOT related to the intervention.* The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology.

8.1.4 Expectedness of an Adverse Event

Study Investigator or treating physician will be responsible for determining whether an AE is expected or unexpected as indicated in the protocol, informed consent form and/or drug information brochure. An AE will be considered unexpected if the nature, severity, or frequency of the event is NOT consistent with the risk information previously described for the study intervention.

8.2 Collection and Reporting Requirements for Adverse Events and Serious Adverse Events

Adverse and serious adverse events are not expected, but if such events occur, they will be reported per IRB guidelines. Any events reported to the IRB will be reported to the DSMC following the same manner (routine or expedited).

For routine reporting, the events will be reported to the IRB as part of the annual continuing progress report, and the DSMC will review events entered into OnCore™ at the time of scheduled monitoring.

For expedited DSMC reporting, the study coordinator/research nurse must notify the DSMC via email. For AEs, include the subject ID, date of event, grade, relatedness, expectedness, and a short narrative. For SAEs, DSMC will review the SAE report entered into the secure Microsoft Excel spreadsheet used for the study.

8.3 Unanticipated Problem Involving Risk to Subject or Other (UPIRSO)

Unanticipated problems will be submitted to IRB of record and the DSMC, according to local policies and procedures. An unanticipated problem is one that is unexpected, possibly, probably, or definitely related to the research described in the paragraph above, and suggests the research places research participants or others at a greater risk of physical or psychological harm than was previously known or recognized.

Since this is an investigator-initiated study, the principal investigator is responsible for reporting unanticipated problems to any regulatory agency and to the IRB. The study investigators and coordinators follow participants per the schedule of events outlined in the Study Calendar to ensure protocol compliance, participant safety, and quality care. Any unanticipated problems detected will be promptly documented by the study coordinator and submitted to the IRB and DSMC within 5 calendar days of study staff's knowledge. These reviews would pick up any unanticipated negative trends among participants.

8.4 Subject Complaints

If a complaint is received by anyone on the study staff, it will be discussed with the study staff and will be addressed on a case-by-case basis. The PI will be notified of any complaints. Complaints will be reported to the IRB if indicated.

If the subject has questions about his or her rights as a study subject, wants to report any problems or complaints, obtain information about the study or offer input, the subject can call the Medical College of Wisconsin/Froedtert Hospital research subject advocate at 414-955-8844. This information is provided to the subject in their consent.

9.0 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination and Accrual Estimates

This is a pilot patient outcome study with a sample size of N=35, which would result in a 10% margin of error and a 90% exact confidence interval for a true population proportion of TG men with increased risk of breast cancer (assuming that 4 out of 35 participants will be found to have an elevated BC risk). In the future, enrolling 125 TG individuals would allow investigators to obtain a 90% confidence interval with a margin of error of 5%.

The sample size is also in line with reaching our accrual goal within a one-year period, as it represents one third of the patient population currently seen by our plastic surgeons.

9.2 Analysis Plan

9.2.1 Analysis Population

Data from all participants will be used for endpoint analyses. Data from subjects who withdraw or discontinue will be not used.

9.2.2 Endpoint Analysis

Descriptive statistics will be used to summarize participant characteristics and study outcomes for the above study aims. Median and range will be used for summarizing continuous variables; counts and percentages will be used for categorical variables.

To assess and compare the self-perceived breast cancer risk with calculated risk for third primary endpoint, self-perceived risk will be compared to mean BC calculated risk using the Wilcoxon related sample test. Chi-squared tests will be used to assess patient factors associated with under and overestimating self-perceived risk.

9.3 Missing Data

No major missing data relevant to the primary endpoints are anticipated. Unforeseen missing data, if any, will be addressed in consultation with the study statistician.

10.0 DATA AND SAFETY MONITORING PLAN (DSMP)

10.1 Data and Safety Management Overview

The Medical College of Wisconsin (MCW) Data Safety Monitoring Committee (DSMC) and the MCW Institutional Review Board (IRB) will approve protocol-specific DSM plans. A local, investigator-initiated trial will be required to be continuously monitored by the principal investigator of the study with biannual safety and progress reports submitted to the DSMC.

The DSMP for this study will involve the following entities:

10.2 Study Team

The study team minimally consists of 1) the principal investigator, Dr. Chandler Cortina, 2) a nurse practitioner, Anna Purdy, APNP, who is a co-investigator on the study, and 3) the study biostatistician. While subjects are on treatment, the principal investigator will meet periodically with the rest of the study team to review the study status. This review will include but not be limited to reportable SAEs and UPIRSOs and an update of the ongoing study summary that describes study progress in terms of the study schema. The appropriateness of further subject enrollment and the specific intervention for a next subject enrollment is addressed. All meetings including attendance should be documented.

10.3 Quality Assurance

The MCWCC Clinical Trials Office (CTO) provides ongoing quality assurance audits.

This study has been categorized as low risk by the MCW Cancer Center (MCWCC) Scientific Review Committee (SRC) and will be reviewed internally by the MCWCC CTO Quality Assurance Staff according to the MCWCC Data and Safety Monitoring Plan and the current version of the MCWCC CTO SOP, 6.5.2 Internal Quality Assurance Reviews.

10.4 DSMC

The Medical College of Wisconsin Cancer Center places the highest priority on ensuring the safety of subjects participating in clinical trials. Every cancer interventional trial conducted at MCW includes a plan for safety and data monitoring.

More information can be found related to the MCWCC Data and Safety Monitoring Plan at the MCWCC website (Data and Safety Monitoring Plan).

This study will be reviewed by the Medical College of Wisconsin Cancer Center Data and Safety Monitoring Committee (MCWCC DSMC). A summary of the MCWCC DSMC activities are as follows:

- Review the clinical trial for data integrity and safety.
- Review all DSM reports.
- Submit a summary of any recommendations related to study conduct.
- Terminate the study if deemed unsafe for the subject.

A copy of the MCWCC Data and Safety Monitoring Plan and membership roster will be maintained in the study research file and updated as membership changes. The committee will review reports from the study principal investigator twice annually (or more frequently if needed) and provide recommendations on trial continuation, suspension or termination as necessary.

Any available DSMC letters will be submitted to the IRB of record as required.

11.0 REGULATORY COMPLIANCE, ETHICS, AND STUDY MANAGEMENT

11.1 Ethical Standard

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4), consistent with GCP and all applicable regulatory requirements.

11.2 Regulatory Compliance

This study will be conducted in compliance with:

- The protocol.
- Federal regulations, as applicable, including 21 CFR §50 (Protection of Human Subjects/Informed Consent); 21 CFR §56 (Institutional Review Boards) and §312 (Investigational New Drug Application; and 45 CFR §46 Subparts A (Common Rule), B (Pregnant Women, Human Fetuses and Neonates), C (Prisoners), and D (Children), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

11.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout the individual's study participation. Discussion of the risks and possible benefits of this study will be provided to subjects and their families. Consent forms describing in detail the study objectives, procedures, and risks are given to the subject and documentation of informed consent is required prior to enrollment. Consent forms will include the MCW IRB template language and must be approved by the MCW IRB.

The patient will be asked to read and review the document. Upon reviewing the document, the investigators will explain the research study to the patient and answer any questions that may arise. In accordance with 46 CFR §46.111, the patient will sign and date the informed consent document prior to any procedures being done specifically for the study. A witness should only sign when required, per FH/MCW IRB policy. The subjects will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial.

If the patient signs the consent form, the original signed document will become part of the patient's medical records and the patient will receive a copy of the signed document.

11.4 Subject Confidentiality and Access to Source Documents/Data

Subject confidentiality is strictly held in trust by the principal investigator, participating investigators, and any staff. This confidentiality includes the clinical information relating to participating subjects, as well as any genetic or biological testing.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or data will be released to any unauthorized third party without prior written approval of the principal investigator. The conditions for maintaining

confidentiality of the subjects' records are required for the life of the data. These rules apply equally to any and all MCWCC projects.

The principal investigator will allow access to all source data and documents for the purposes of monitoring, audits, IRB review and regulatory inspections.

The study monitor or other authorized representatives of the principal investigator may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

11.5 Risk-Benefit Assessment

11.5.1 Potential and Protections Against Risks

There is the potential for participant anxiety or distress regarding the results of their personalized BC risk assessment and/or their genetic test results. Our study team will do our best to answer questions and assuage concerns regarding anxiety of distress of testing results, we are also supported by the psychiatry and social work teams in the Clinical Cancer Center.

Another risk of taking part in a research study is that more people will handle the personal health information collected for this study. The study team will make every effort to protect the information and keep it confidential (see Section 10.1), but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass the subject or affect his/her ability to get insurance.

11.5.2 Potential Benefits

Participants will be informed of their personal breast cancer risk which may influence if they undergo top surgery and how they undergo top surgery. This may also influence if they should consider genetic testing which may also impact their family members.

Findings from this proposal will inform the TGNB community and healthcare providers on how instituting a personalized BC risk assessment impacts surgical-decision regarding chest masculinization surgery.

For these reasons, the potential benefits of the study are reasonable in relation to the anticipated risks to the study participants.

11.6 Protection of Human Subjects

11.6.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the informed consent process. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

11.6.2 Protection of Privacy

To ensure confidentiality, each participant is assigned an anonymous study ID, which is then used on all study forms that collect participant data. Study IDs are linked to participant names and other private identifiable information in only one location, on an encrypted, firewall protected, electronic document housed on MCW's server. All study forms are to be kept on an MCW password-protected computer, server, or HIPAA compliant data sharing platform, with access restricted to authorized study personnel.

11.7 Changes in the Protocol

Once the protocol has been approved by the MCW IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the investigator and approved by the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to subjects, an amendment may be implemented prior to IRB approval. In this circumstance, however, the investigator must then notify the IRB in writing within five working days after implementation.

The IRB may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB. The investigator will submit all protocol modifications to the sponsor and the regulatory authority(ies) in accordance with the governing regulations.

Changes to the protocol may require approval from the sponsor.

Any deviations from the protocol must be fully documented in the source documents and reported to the IRB per institutional guidelines.

11.8 Investigator Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies).

Onsite Audits: Auditing is essential to ensure that research conducted at the Medical College of Wisconsin (MCW) Cancer Center is of the highest quality and meets MCW and regulatory agency standards.

Regulatory authorities, the IRB, and/or sponsor may request access to all source documents, data capture records and other study documentation for onsite audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

The PI will follow the procedures as outlined above, which will serve as part of the quality control procedure. The PI will also meet with the mentorship team and CRC regularly to ensure data accuracy, appropriate data analysis, and protocol adherence. To ensure the validity and integrity of study data, the PI will discuss data management with the research team and CRC on a regular basis.

12.0 DATA MANAGEMENT

12.1 Data Management Plan

Study electronic data will be stored on a password-protected Microsoft Excel file using password-protected computers on encrypted networks that are backed up nightly. In addition to protected health information (PHI) data (name, date of birth and medical record number), other data to be collected include participant demographic information (race, ethnicity, age, sex assigned at birth, gender, etc.), initial VAS personal estimate, results from the personalized BC risk assessment, possible genetic testing results, and the type of gender-affirming chest masculinization surgery the participant undergoes. Initial intake data will be entered into Qualtrics, a secure online survey platform, at the time of personalized BC risk assessment, and then converted to a Microsoft Excel file where subsequent patient data (genetic test results, decision for surgery) will be directly entered by the PI and Co-I. All data will be de-identified prior to statistical analysis. All consent forms will be kept in locked file cabinets in locked offices.

12.2 Disseminating and Publishing Data

All raw data, data figures, data interpretation, models, and conclusions drawn from this study will be managed by the principal investigator and co-investigators listed in this protocol. The findings from this study may be presented at relevant conferences/meetings, published in a respectable peer-reviewed journal, or used as preliminary data in a grant application to justify extramural funding.

For any manuscript that is to be published in a journal, the role of authors/contributors, the disclosure of financial/non-financial relationships and activities, and the report of perceived conflicts of interest will largely adhere to the recommended guidelines set forth by the International Committee of Medical Journal Editors (ICMJE; Defining the Role of Authors and Contributors, Disclosure of Financial and Non-Financial Relationship and Activities and Conflicts of Interest). The PI, in consultation with the study co-investigators, will determine who will be listed as first, senior, and corresponding author(s). Study team members who have made substantial and significant intellectual contributions to the study and its findings will be listed as contributing authors or, in certain circumstances, acknowledged. Funding sources and any conflict of interests, perceived or actual, will be disclosed and stated within the appropriate section of the manuscript at submission.

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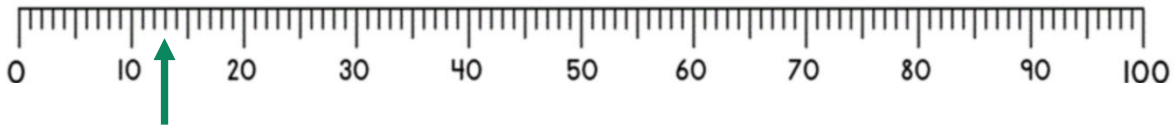
APPENDIX 1. LIFETIME BREAST CANCER RISK ASSESSMENT FORM

Lifetime Breast Cancer Risk Estimation

Name:_____

Date: _____/2022

Participant reported lifetime risk estimation: _____%



Green arrow depicts is the average lifetime risk for cisgender women up to age 85.

Gail model reported lifetime risk estimation (for those 35 and older): _____%

IBIS model lifetime risk estimation: _____%

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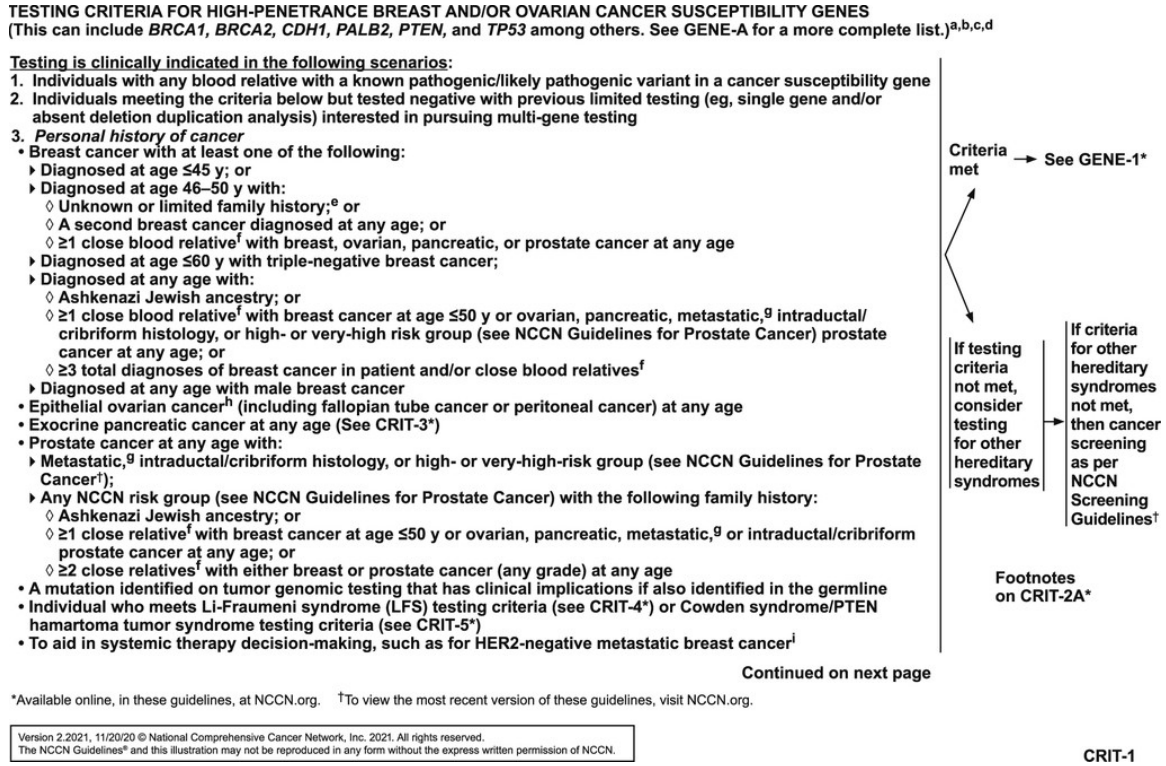
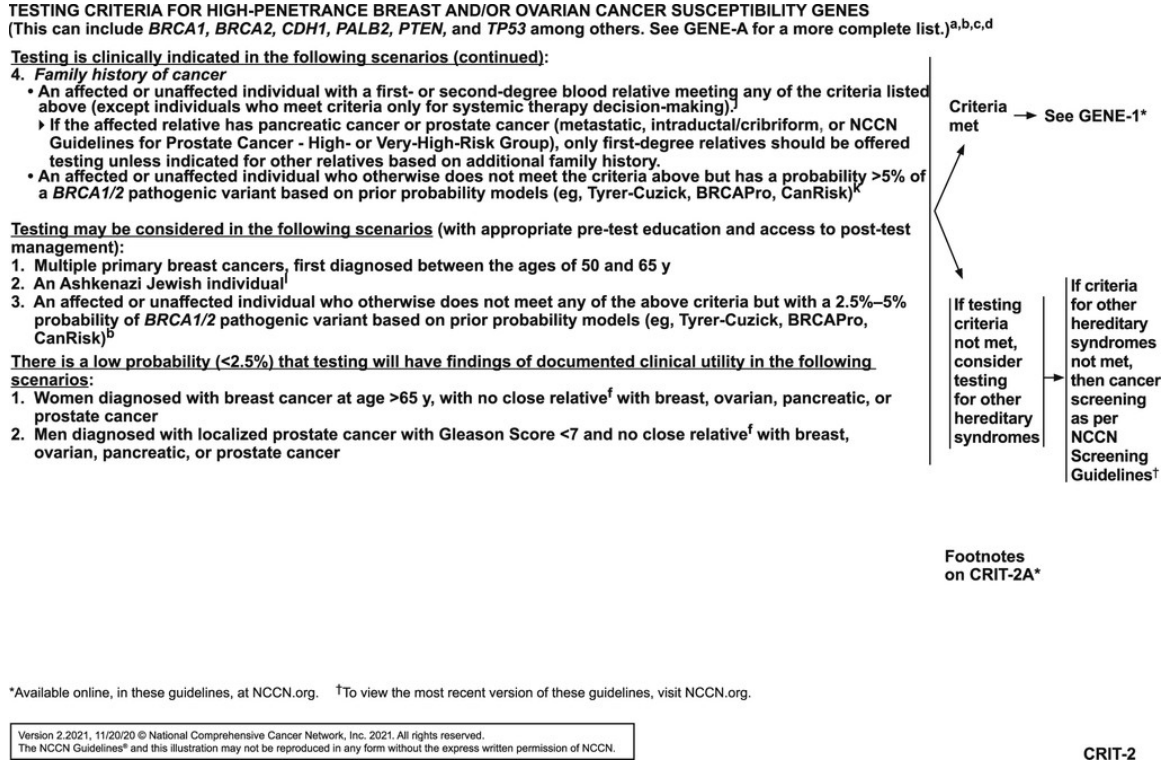
Gail Model: https://www.mdcalc.com/calc/3647/gail-model-breast-cancer-risk

IBIS Model: https://ibis.ikonopedia.com

APPENDIX 2. NCCN TESTING CRITERIA FOR HIGH-PENETRANCE BREAST AND/OR OVARIAN CANCER SUSCEPTIBILITY GENES





Taken from Daly et al., 2021.[2]