Family History and Cancer Risk Study
NCT NCT05079334
IRB 201202
Protocol
7/9/24

FOREST (Family History and Cancer Risk Study)

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Created: November 27, 2019
Revised: April 6, 2020, June 29, 2021, September 17, 2021,
October 26, 2021, July 14, 2022, January 30, 2023, June 5, 2023, July 9, 2024

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1. Background

From the earliest recognition of cancer-prone families over 100 years ago, clinicians have depended on the family health history (FHH) to identify and treat patients and family members who may have a familial cancer syndrome. Once identified, patients can be offered lifesaving, evidence-based management strategies for many of these conditions. To fully realize the benefits of genetic healthcare, however, at risk individuals must be recognized, offered genetic counseling and testing, and then referred for specialized therapy or enhanced screening. While this is a promising time for these patients and families, there are significant challenges to implement a modern and efficient care delivery model across the many patient, provider and health system stakeholders.

The practice of genetic medicine is changing as genetic discoveries are translated into new tests for an increasing number of health indications. In fact, the prevalence of high-risk individuals who are at risk for hereditary cancer has been rising due to new testing strategies. This has placed enormous pressure on the hospitals and clinics providing care for high-risk patients. Coupled with the healthcare system's need for greater efficiency, the traditional genetic clinic-based practice has become untenable. Barriers and challenges include low numbers of trained genetic workforce, lack of integrated FHH platforms for patients and physicians, and long wait times for available clinic appointments. Further, while cancer syndromes are seen across all groups, gaps in care exist as underserved populations are often not recognized and referred for care.

MeTree is a computer platform that has been developed by researchers at Duke University that electronically collects FHH information for hereditary cancer syndromes and other health conditions directly from the patient. MeTree then calculates hereditary cancer risks for the patient and creates a personalized patient report and evidence-based clinical decision support for the provider. In previous studies, MeTree demonstrated improvements in the identification of those at risk and highlighted ongoing challenges particularly around undergoing genetic counseling and testing, and awareness of risk. Co-investigators from Duke/MeTree collaborate on this grant.

2. Rationale and Specific Aims

SA1. Deploy a care delivery model that will facilitate systematic risk assessment for hereditary cancers in diverse clinical environments.

- Up to 3,500 participants will be enrolled and complete the MeTree FHH risk assessment
- Deploy in 2 academic medical centers; Vanderbilt University Medical Center (VUMC) and Meharry Medical College (MMC)
- Assess participants perceptions using online survey and qualitative semi-structured interviews

SA2. Improve access to genetic healthcare providers for participants at risk for hereditary cancer syndromes.

- 300 high risk participants in the VUMC Hereditary Cancer Clinic will be enrolled
- Extend clinic capacity by lessening the need for in-clinic family history collection and basic counseling
- Expand reach of clinic by using telephone and video genetic counseling; referral to specialists

SA3. Explore the feasibility of our care delivery model to improve family engagement for cancer risk assessment

- Participants extend invitations to family members to MeTree's family resource center to share results of genetic tests
- Assist with education and referral needed for cascade testing for pathogenic variants

3. Inclusion/Exclusion Criteria

Inclusion

- Receiving medical care at Vanderbilt University Medical Center or Meharry Medical College
- Age 18 years or older
- Able to read and communicate in English
- Willing to use the Internet
- Current My Health at Vanderbilt (MHAV) user or willing to sign up and use (Vanderbilt participant requirement only)

Exclusion

- Non-VUMC/MMC patients
- Diagnosed with a terminal illness
- Unable to speak/read English
- Unable/unwilling to use the Internet (specifically MeTree)
- Previous genetic testing and/or counseling through the Hereditary Cancer Clinic

4. Enrollment

Participants will enroll through My Health at Vanderbilt (MHAV)*. MHAV is VUMC's patient portal where the patient may sign up and participate in managing his/her health care. MHAV can also be used for sending mass research recruitment messages to a predefined cohort of patients who meet certain study-specific inclusion/exclusion criteria, have explicitly said OK to Contact for research purposes, and have an active MHAV account. The messaging process is managed centrally by the VICTR/Health IT teams, sending the messages on behalf of the study team.

MHAV: Initial e-mail notification the patient receives about the research study invitation

1. If patients have email notifications turned on, they will receive the standard, system-generated email stating they have a research invitation.
   "You have a new message in My Health at Vanderbilt! Please sign in to read your message.
   Thanks for using My Health at Vanderbilt,
   Vanderbilt University Medical Center"
2. Once a patient logs in, they will be taken to the research studies dashboard and will see the following patient-friendly study title and description under the heading "Studies you may be able to join".

Once a patient clicks on the link from the email/text notification or from the MHAV homepage, he/she will be taken to the Research Studies page. Here the new study will be listed under the heading – Studies you may be able to join – with the following information (**Appendix H**):

If a patient clicks, I'm Interested, the REDCap Participant Updater Module will create a record in the study database that includes patient MRN and the enrollment status of Interested. Once the Updater Module creates a new record, it will trigger REDCap to fetch the email address to facilitate sending the follow-up email from REDCap, which will include more information about the study and a link to the survey.

If a patient clicks, No, Thank You, the REDCap Participant Updater Module will create a record in the study database that includes patient MRN and the enrollment status of Not Interested. This will prevent any further communication to the patient about this study.

Once the eligible participant enters the REDCap study pre-screen, they will be able to complete the eligibility survey, electronic consent, and pre-MeTree survey. At the end of the pre-MeTree survey, participants will be given a link to the MeTree platform to begin the questionnaire. At any time, they can leave MeTree and re-enter by using the link from the REDCap message or by the link in their MHAV portal. Participants will receive a $10 gift card for completing the eligibility, eConsent, and pre-MeTree surveys.

After completing the eligibility, eConsent, and pre-MeTree surveys, participants will receive an email with the link to MeTree (**Appendix K**). Participants have three weeks to complete their MeTree questionnaire. After completing the questionnaire, participants will receive a report from MeTree. After receiving the report from MeTree, and once the study team has concluded the enrollment of the 3,500 participants, 300 “high risk” participants will be referred to the Hereditary Cancer Clinic to discuss their results with a Genetic Counselor. The consent will include information about this step to inform participants that they may be contacted for counseling.

*My Health at Vanderbilt (MHAV) language is used to describe the workflow at Vanderbilt.

5. Study Procedures

As described in Section 4, participants will be recruited and enrolled electronically. * This process will take approximately 30-45 minutes, depending on the answers to screening questions. Once enrolled, they will be asked to complete the MeTree Family Health History (FHH) questionnaire (See Appendix A for actionable conditions, Appendix B for actionable recommendations, Appendix C for MeTree participant report example, and Appendix D for MeTree provider report example).

Upon entry into the MeTree platform, participants will be able to immediately enter FHH information into the program or download the worksheet for collecting the information requested by MeTree from family members and return later to enter the information into the MeTree platform (The printable worksheet is named Appendix E). The time involved to complete MeTree may vary significantly depending upon the number of relative’s participants enter data on and the availability of the FHH information. This will be mitigated by providing a smart link to finish the FHH in pieces, rather than all at once. Participants are advised in the consent form that answering the FHH questions may make them uncomfortable.

For participants who may want additional instructions for the MeTree questionnaire, we will provide a how-to power point (included as Appendix F).

Vanderbilt: Participants who do not access MeTree within 30 days of consent will be sent reminder emails once per week for up to 4 weeks. Once participants complete data entry in MeTree and the post-MeTree survey, participants will be sent a $20 gift card. Participants will be sent a web-based survey via an email link 4 to 6 weeks after completing MeTree (post-MeTree survey). If the survey is not completed within 1 week of the initial invitation, reminder emails will be sent weekly for up to 4 weeks. Participants will receive a $20 gift card for completing the post-MeTree survey.

Meharry: For enrolling and completing the baseline (pre-MeTree) survey, participants will receive $10 cash (if on site) or Amazon or Visa gift card (sent to your home). For the completion of the MeTree questionnaire, participants will receive an additional $50 cash (if on site) or gift card. Participants may receive $10 cash or gift card for any additional surveys after completing the MeTree questionnaire.

Once data entry in MeTree is complete all participants will receive a personalized patient report within the platform outlining their familial and genetic risk status the included medical conditions according to current evidence-based guidelines. Participants' providers will be notified via one of several methods (email without PHI, EPIC messaging, or an alert) that their patient has a MeTree clinical decision support report available in the medical chart (accessible via a SMART link). Outside providers will receive an email or letter. The templates for these messages is located in Appendix I. The process to upload the MeTree report and provide accessibility to providers is approved by the Medical Forms Committee and the Center for Health Information Management (CHIM) Committee.

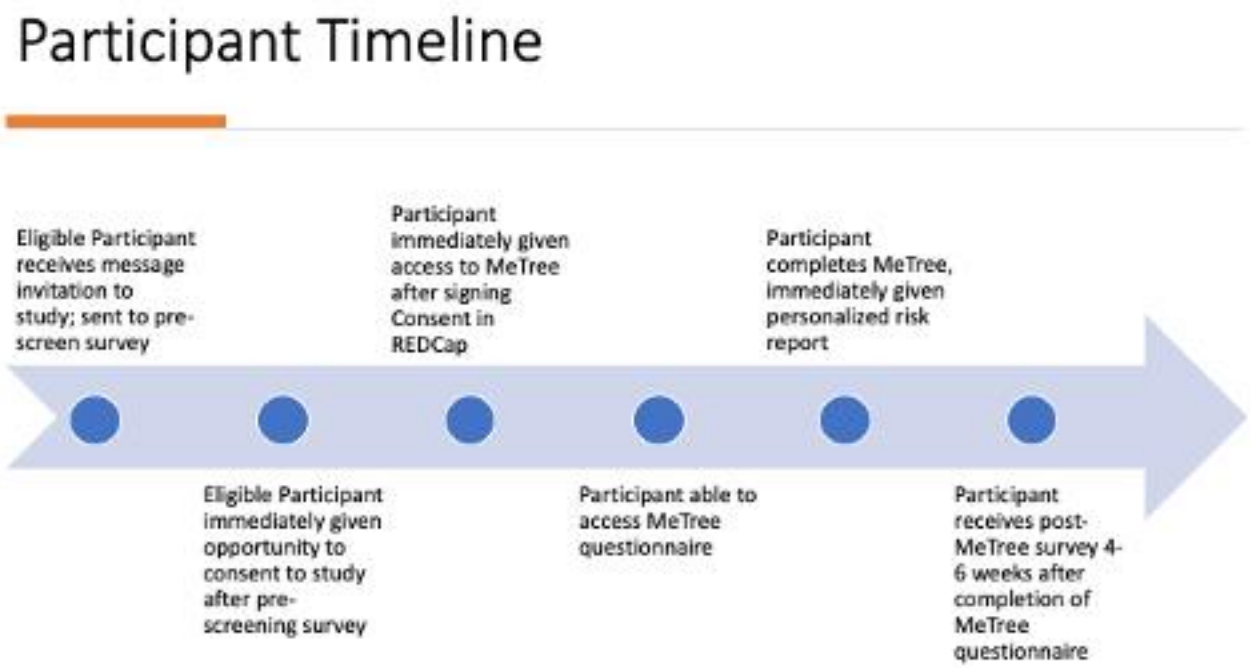
As previously stated, in Aim 2 participants who are identified as at high genetic risk (n=300) will be contacted by the study nurse (as part of their standard of care) to schedule a genetic counseling appointment (Appendix J, High risk patient email). The number and length of genetic counseling appointments will be recorded in order to evaluate the change in clinic capacity for those with a pre-recorded FHH in the MeTree platform as compared to routine patients who have not participated in the study and completed MeTree. The frequency of genetic testing and outcomes of the testing will also be recorded in REDCap from data collection in the Hereditary Cancer Clinic at VUMC.

To analyze the time saved by completing MeTree prior to a clinic visit, the study team will perform a retrospective review of control patients, selected by the study team, to assess the amount of time in clinic with the genetic counselors. This will be done through time stamps in eStar and chart review. Control patients will not be a part of the study, nor will their information be shared with anyone. The study team will only review for time spent in clinic versus the study participants' clinic visits.

Additionally, genetic counselors who see participants from this study will be surveyed to better understand their perspective of the use of MeTree. This portion of the study will be in a separate IRB.

To promote awareness of the need for cascade testing among relatives, participants who undergo genetic counseling and testing in the Hereditary Cancer Clinic and are found to have a strong family history and/or a pathogenic gene mutation, will be encouraged to share the study information with family members (Aim 3). We will not ask for identifying information regarding their family members. The study team will only accrue data on how many times the participant's MeTree web link was shared and accessed (clicked on). Patients are not required to share any information with family members if they feel uncomfortable.

The timeline below reflects an individual's timeline from entry into the study.



**We will attempt to enroll participants electronically when possible. However, we understand that there are some participants who may not be able to enroll electronically and manual enrollment (by paper, tablet, or phone) will be available and will conform to all CDC pandemic guidelines.*

As a result of reviews from the first third of completed MeTree reports, a notes section was added to the MeTree reports to indicate any versioning/changes to the report. The notes will include any changes to the report (such as an updated pedigree) and where they can be found. If any technical or clinical changes are made to reporting, participants may receive an updated report, and will be notified if an updated report is available. Updated reports may or may not affect their high-risk report status or report recommendations.

6. Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

All researchers will report all events that are serious, unexpected, and study-related to the PI by phone, fax or email within 24 hours of becoming aware of the event. We will promptly report to the IRB any participant complaints about the conduct of any element of the study or concerns about potential harms, including copies of any written communication with the participant addressing those concerns. Further, all conversations with participants that indicate a level of concern about a study component - even if not a complaint - will be documented and distribution of any participant education materials in response to such queries will be documented in the participant's research (REDCap) record.

7. Study Withdrawal/Discontinuation

Participants can choose to stop being a part of the study at any time. **Vanderbilt** participants will need to notify the study team either by a phone call to (615) 936-2660 or email to FOREST_Team@vumc.org. **Meharry** participants will need to **contact** the study manager, Dr. Clasherrol Edwards, at (615) 327-5519 or forestteam@mmc.edu.

The participant may be taken out of the study if:

- They do not complete the MeTree Survey within 12 months of enrolling
- If they move out of the state
- Or stop receiving care at VUMC or Meharry Medical College

Withdrawing participation
We will continue to utilize the participant data in analyses unless the participant asks for the data to be withdrawn. Data will still be within the EHR, MeTree, and the research database (REDCap), but data will be excluded from analyses.

Active declining participation
Some participants may begin the study but at some point, feel uncomfortable continuing to participate. Participants who decline to further participate may withdraw from the study if they wish. If the participant declines to continue and alerts the study team, the protocol above will be followed. If the participant declines to proceed any further, study data will continue to be used in pertinent analyses.

Surveys of declination or withdrawal
Participants that decline or withdraw from the study will be asked why they are making this choice.

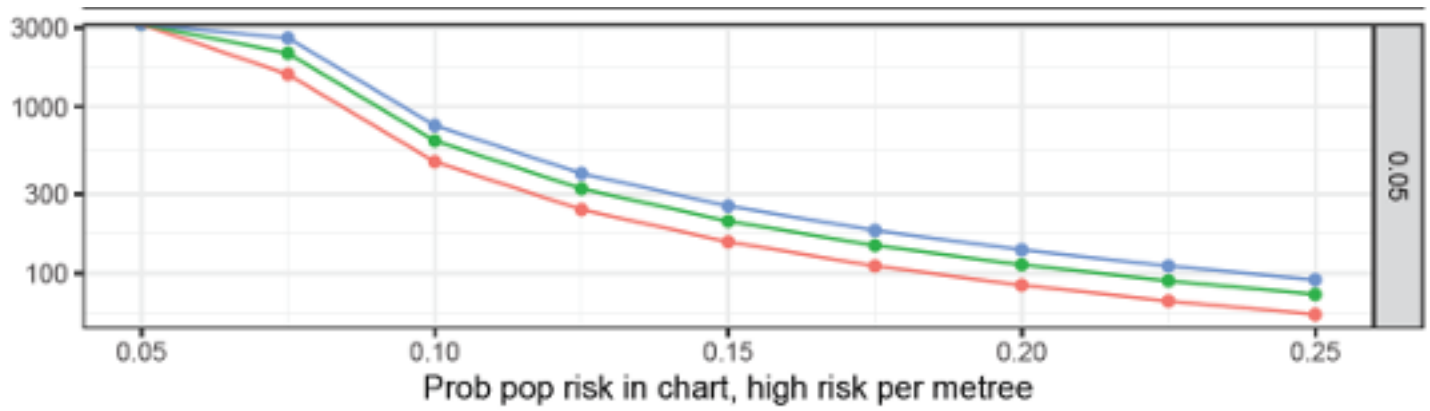
Non-responders (Passive Decline)
Participants who enroll but do not complete the MeTree questionnaire or subsequent surveys will be treated as enrolled but excluded participants (i.e., non-responders). Participants who are delayed in filling out the questionnaire but still complete the questionnaire prior to analyses of the data will be included, despite the delay.

Deceased participants
The study will utilize the data of deceased participants even if they pass before the conclusion of the study.

8. Statistical Considerations

We will use a case-control design for statistically analyses. Cases are defined as the study participants who have completed the MeTree tool (intervention). We will utilize data from the Hereditary Cancer Clinic registry (IRB # 141203) to fine patients identified at risk of a hereditary cancer syndrome in the usual care (control) and intervention conditions. The control condition utilizes historical data from the participants prior to their enrollment date in FOREST to determine the number and proportion of participants who would be identifiable as at risk without the implementation of MeTree. We believe this is the most effective method to analyze the MeTree platform's effect on hereditary cancer testing and outcomes. Power calculations estimate a sample size of up to 3,500 (minimum of 3,000) is needed to produce statistically significant results.

In the graph below, the blue line represents 90% power to detect the primary endpoint with a p-value of 0.05, the green line, 85% power, and the red, 80% power. The x-axis represents how many participants are identified as being at high risk by MeTree.



In prior studies of primary care populations, on average 20% were newly found to be at high risk (had not previously identified). However, in order to accommodate differences in a population that has a proactive hereditary cancer clinic, we used a lower estimate of 10% for the power analyses. Thus at 10% risk identification and 95% power we estimated that we would need at a minimum 1,000 participants for a single site and 2,000 participants total to detect differences in identification at the 2 sites (Meharry and Vanderbilt). In addition, these participants flow into aim 2. Based on power analysis to detect an increase in clinic capacity, we need to have 150 high risk patients who complete MeTree in Aim 1 to see a genetic counselor in the hereditary cancer clinic at Vanderbilt. At a 10% identification rate and a 50% follow up rate (estimate based on literature review and the clinic's attendance rate), a minimum of 3,000 participants will need to complete MeTree in Aim 1. We are therefore enrolling 3,000-3,500 participants for this study.

Data elements considered for this analysis:
Primary Endpoint: Participant designated as high risk for cancer.
Assessment pre: chart review (any indicator prior to MeTree, not time-frame dependent)
Assessment post: MeTree report (measured when the report is generated, independent of amount of follow-up time)
Hypothesis: MeTree will increase the proportion of high-risk individuals identified.
Statistical interpretation of the hypothesis: P(of high risk) is a function of the intervention

9. Privacy/Confidentiality Issues

The study data live in a REDCap database. *This project will utilize the REDCap platform for data collection and management. Project team members listed as Key Study Personnel with existing electronic health record (EHR) system access rights may also be granted use of REDCap Clinical Data Interoperability Services (CDIS) tools. These tools are designed to enable transfer of relevant study-related data from the Vanderbilt Research Derivative and/or directly from the EHR into REDCap.*

Participant answers to the survey are linked only to a study ID number in a password protected electronic database. Only study staff will have access to the information, and any paper records are kept in a locked drawer in the study manager's desk. Pragmatic studies are considered minimal risk. All data will be gathered and stored using protocols and privacy & security standards that comply with HIPAA and, where applicable, GINA. All patient FHH data will be gathered from patient portal applications and transmitted to and from the algorithm and clinical decision support databases using industry standard encryption protocols, including HTTPS and TLS. The healthcare systems employ additional protections for the data, including detailed audit logs, insulation from direct SQL queries, and detailed version control.

While participant data such as demographics are collected from the VUMC Epic instance, data are delivered by SFTP to the MeTree platform, housed at Duke University, for participants to complete the FHH questionnaire. FHH results will be transmitted by API to a secure REDCap project at VUMC or MMC. *

*This process is approved by the VUMC Architecture Review Board.

All data gathered for the proposed studies will be treated with the same degree of confidentiality as a medical record. Confidentiality will be maintained for the identity of participants in this study except as necessary for oversight by the Secretary of the Department of Health and Human Services or his designated representative. Only group information without personal identifiers will be included when sharing process implementation data and outcomes with approved collaborators. FHH data collection is already considered standard of care for medical practice and the risk associated with this information or risk-based prevention strategies is considered to be no more than that associated with routine clinical care.

At the beginning of the study, participants will provide the study team with their VUMC health care provider's name. After the participant completes the MeTree questionnaire, a message will be sent to the provider via REDCap to their eStar message basket alerting them that their patient has completed the questionnaire and that there is a provider-version report available for them to view. The provider can click a link in the message and be sent to MeTree, where they can locate the report.

For contact purposes, we will give participants the option to provide a secondary contact in case the participant cannot be reached. This will only be used if the study team loses contact with the participant (i.e., phone line disconnected, email no longer active).

Regardless of primary or secondary findings, the participant is allowed to provide any findings to their family. The study team will not contact family members of the participants, even in the case of death.

10. Follow-up and Record Retention

The study will last 4 years. Paper records will be kept for up to six years after the study ends. Electronic data will be kept indefinitely. Research data entered into REDCap will be kept for an unknown length of time.

11. **Subproject of Family History and Cancer Risk Study (FOREST):** Building more inclusive sex- and gender-related questions for genetics research

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1. Background

It has been less than a decade since the legalization of same-sex marriage; a fact that seems to be forgotten by many. While society has made great strides in the inclusion and acceptance of the LGBTQIA+ (lesbian, gay, bisexual, transgender, queer, intersex, asexual, and other marginalized sexual orientations and gender identities) community, there is still much to be done. As of June 2, 2023, there are 491 anti-LGBTQ+ bills up for vote in the United States. Our healthcare system and research institutions are failing transgender, non-binary, and intersex individuals, as demonstrated by numerous health disparities among these populations and barriers to healthcare. Research has shown the importance of collecting gender identity data as well as surgical history and organ/tissue inventory to ensure equitable healthcare for transgender and non-binary individuals. However, some research studies do not include gender identity questions. Furthermore, when these questions are included, this data may not be used in ways that benefit transgender, intersex, and non-binary participants. When gender identity data is collected, it is not usually performed in a standardized manner, and most existing sex- and gender-related measures (SGM) were not developed in collaboration with members of the transgender, non-binary, and intersex communities. Research shows that members of this community often feel uncertain of how to answer SGM or find existing SGM to exclude or marginalize them further. These impacts may contribute to this community's distrust towards research and fear of discrimination in healthcare.

Automated processes are increasingly utilized throughout the healthcare field and research. These automated processes often rely on the electronic health/medical record (EHR/EMR) and/or demographic information obtained from patients. Due to the increased use of automated processes, it is critical that gender identity information is not only documented, but documented accurately to avoid harm to individuals, such as misgendering participants. The failure to identify transgender patients can lead to improper care of patients. Many patients alter their originally recorded legal sex to match their gender identity. For example, if someone changed their sex on their identifying documents from female to male they may be identified within the EMR system as male. Even for patients who do not change their legal documentation, organs and tissues change when participants undergo transition-related medical care, so these patients may have tissues that are not associated with their documentation (e.g., transgender women with breast tissue who still have a legal sex of male). Automated processes that drive reminders for important screening methods for ovaries, uterus, breast tissue, cervix, and other organs and tissues could be missed, thus increasing this individual's risk of illness or disease.

The Family History and Cancer Risk Study (FOREST) is evaluating an automated hereditary cancer risk assessment (MeTree) with referral to genetic counseling for those deemed to be "high risk" for a hereditary cancer syndrome. Evaluations of the responses from already enrolled transgender and non-binary participants within the FOREST study show that the SGM utilized were interpreted differently by participants. For example, the FOREST question about sex was sometimes interpreted to be asking about a person's sex assigned at birth, while other times it was interpreted as representing gender identity. Because the MeTree risk calculations rely on sex-related information provided by participants, it is of clinical importance to have valid measures for these variables. These differences in interpretation of the same question demonstrate a critical need for redesign and standardization of SGM for research studies and clinical care, especially as relates to genetics care, which requires knowledge of both sex assigned at birth (for risk algorithms), and detailed information about phenotypic sex, hormonal milieu (mixture of endogenous and exogenous hormones), and past procedures (e.g., organ removal) to inform appropriate genetic risk management. For example, a

person who is receiving gender-affirming surgeries or hormone care may need screenings not often provided for those of their assigned sex at birth (ASAB; e.g., mammograms are not typically provided for people assigned male at birth, but may need to be provided for transgender women and other people assigned male at birth who develop breast tissue from exogenous gender-affirming hormone therapy). Similarly, knowledge of hereditary cancer risk can inform choice of surgical procedure for chest reconstruction for patients seeking breast tissue removal and inform needed screenings for patients who have already had this procedure. As a result, routine family history risk assessment is a critical component of transgender care – but unfortunately, this component is often overlooked.

2. Rationale & Specific Aims

To reduce potential harms, thoughtful and inclusive standardized SGM and guidelines for ethical data collection and usage need to be developed in collaboration with members of the transgender, gender- and sex- diverse (TGSD) communities. We have chosen the terminology TGSD to broadly encompass a subset of individuals from the NIH Sexual and Gender Minorities definition, those 1) who are transgender, non-binary, or intersex, 2) whose gender identity does not align with their sex assigned at birth, 3) who have a difference of sex development, or 4) whose gender identity or expression, or reproductive development is characterized by non-binary constructs of gender and/or sex. To this end, we plan to conduct semi-structured interviews with TGSD individuals who participated in the FOREST study to understand their interpretations of the SGM used. Additionally, we aim to evaluate the potential clinical and psychosocial harms associated with use of various SGM data models used in genetics, including that used in FOREST. We will obtain participant's advice for improving upon the MeTree SGM and guidance on usage of this data in automated systems. This information will be used to provide recommendations for the thoughtful and inclusive standardization of those questions for future genetics studies and in genetics clinical care. We hypothesize that in semi-structured interviews participants will elucidate gaps in the MeTree and FOREST SGM, reveal potential social and clinical harms associated with current models, and provide recommendations for designing thoughtful and inclusive SGM. These recommendations for SGM will provide greater validity for incorporation into automated care processes. In semi-structured interviews we will:

Aim 1. Explore TGSD participants' interpretation of SGM used in the FOREST study to assess measure validity.

We will evaluate TGSD participants' interpretation of SGM used in the FOREST study, as well as alternative question/response formats from the literature. These descriptive evaluations will provide insight into the validity of sex- and gender-related question/response structure used in FOREST as well as alternative formats.

Aim 2. Evaluate the psychosocial and clinical impact of SGM on TGSD participants and assess harms.

We will evaluate potential individual- and group-level psychosocial and clinical harms of the FOREST study design. The results of this aim will inform a framework for ethical collection and usage of sex- and gender-related data.

Aim 3. Ascertain participant recommendations for ethical collection and use of SGM in clinical genetics and translational genetics research, especially those reliant on automated processes.

We will provide participants with study reasons for collecting sex- and gender-related variables in genetics care and collect participant recommendations to improve the performance of SGM

in this population, with particular attention to questions and/or answer choices that participants found confusing or harmful. Further, we will ascertain participant-guided recommendations for automated processes that rely on sex- and gender-related variables.

The data from Aims 1, 2, and 3 will inform a final ethical framework for sex- and gender-related data collection and usage in genetics studies, including incorporation into automated processes. Together these aims will allow us to propose updated measures for sex- and gender-related variables for MeTree that are directly guided by members of the marginalized community these questions intend to benefit. We expect that these standardized questions and responses, developed in collaboration with TGSD individuals with genetics applications in mind, will reduce clinical and psychosocial harms to future participants and patients in both genetics research and clinical genetics settings by improving the accuracy of data collected and participant/patient experiences. Additionally, we anticipate that involving the community in the co-creation of standardized SGM and recommendations for their usage will improve these populations' trust of research and the medical system.

3. Inclusion/Exclusion Criteria

3.1. Inclusion:

- Participants will have been previously consented to and enrolled in The Family History and Cancer Risk Study (FOREST).
    - As a result, participants will meet FOREST eligibility criteria: they will be 18 years of age or older, English-speaking, and, if a Vanderbilt patient, have a My Health at Vanderbilt (MHAV) account.
- Identified via the EHR (using diagnosis, procedure, or billing codes or gender identity/sex assigned at birth data) to be TGSD, or identified via responses on the FOREST survey or the MeTree family history application with a response consistent with being TGSD, or responses on MeTree that they prefer not to disclose a gender identity or do not know their sex assigned at birth ("Unknown"). Note that FOREST consented participants have already consented to the use of FOREST-collected data and their EHR data by the main study.
    - The following response selections on FOREST and MeTree will be considered eligibility criteria for recruitment to interview: "Other" for the FOREST survey question of "Sex"; "Other" or "Unknown" for the MeTree question of "Birth sex"; "Non-binary," "Transgender male-to-female," "Transgender female-to-male," "Other," "Unknown" or "Prefer not to respond" for the MeTree question of gender identity. Further, we will also include FOREST participants who have any discordant responses amongst these three questions (e.g., those who respond "female" to birth sex and "male" to gender identity), or have an inconsistency between their legal sex in the EHR and their sex assigned at birth in the EHR or their reported FOREST data. We will also include FOREST participants who have EHR diagnosis codes consistent with TGSD identities or receiving gender-affirming care.
    - Because not all FOREST participants have completed MeTree, we will also use a predefined set of EHR-coded data to identify other TGSD participants among enrolled

FOREST participants. These codes have been previously validated in another study (Bick et al., in preparation).

- Must consent to participate in a recorded and transcribed qualitative interview for formal study analysis

3.2. Exclusion:

- Not a FOREST participant
- Does not meet substudy definition of TGSD described above
- Does not consent to recorded interview

4. Enrollment

Recruitment will begin after the substudy has been approved by the IRB and will occur on a rolling basis as individuals who meet eligibility criteria are added to the main FOREST study. Invitations will be sent via email to FOREST participants who meet the substudy eligibility criteria defined above. Follow-up phone call(s) will occur to email non-respondents to enroll participants. Attempts will be made to reach participants up to four times by phone/email. Participants who respond favorably to email or phone within that time will have follow-up communication regarding scheduling for a follow-up semi-structured interview. To ensure that we have a large enough pool of eligible FOREST participants who meet eligibility criteria for this substudy, we will also enhance FOREST recruitment efforts in clinic and community areas that reach VUMC TGSD patients. For this we will distribute FOREST recruitment materials in the adult transgender clinic at VUMC and to LGBTQ+ community interest groups (both online and in person) in the greater Nashville area. In both recruitment avenues, we will tailor recruitment materials (see documentation included in the amendment) to inform TGSD adults of the relevance of hereditary cancer risk assessment to their health care and to acknowledge that we are interested in enrolling TGSD participants for additional interviews about how to make the study more inclusive. These additional materials, as well as all materials associated with this substudy, were designed with the oversight of Mx. Bland and Dr. Mittendorf, two transgender members of the FOREST research team.

Participants who agree to be interviewed in the substudy will either be allowed to use the web conference link to secure software or will be phoned out from secure software, based on participant preference at the time of their scheduled interview. We will use a secure Microsoft Teams web conference or Microsoft Teams web conference phone call; Microsoft Teams is VUMC-approved secure software for this purpose. Prior to the interview, we will send the participant the eConsent link. They can choose to read and sign before the interview or go through the consent with the interviewer on the phone. Before the interview begins, the interviewer will confirm that the consent is signed and if the participant has any questions.

5. Study Procedures

As described above, participants will be recruited through a mixture of electronic and telephone recruitment procedures. Eligible FOREST participants will be contacted up to four times via email and/or phone with the purpose of offering participation in the substudy. In order to track the number of contacts and content of contact, we will record this information in the main FOREST study REDCap used for participant contact tracking. Additional contacts may occur to facilitate interview scheduling or field questions of potential interviewees. A potential participant may request that we cease contacting them about an interview at any time. Participants who state they are not interested will not be further contacted and their desire for no further contact recorded in the study tracking system. Further, participants who are unable to be reached after four contact attempts will be considered non-responders to substudy outreach, and recruitment attempts for the interview substudy will cease. The email sent and recruitment phone voicemail intentionally contain no mention of the relevance of the interview to TGSD participants explicitly, in order to avoid accidentally outing TGSD participants to unsupportive family or associates. Instead, participants who answer the phone and speak to the recruiter or who respond favorably to an email request for interview will be provided details about the subject of the interview at that time. Participants who agree to participate will be scheduled by phone or email for an interview with a study staff member trained in qualitative interview methodology.

Participants who agree to be interviewed in the substudy will be phoned at the time of their scheduled interview from a secure Microsoft Teams conference line, which is VUMC-approved secure software. They will be read a structured consent document and asked for verbal consent. We will request to begin recording prior to consent being read. The consent will then be recorded via Microsoft Teams. During the consent process, participants will be informed that they can choose to skip any question or end the interview at any time due to psychological discomfort. We will reconfirm participant consent to continue recording the interview at the end of the consent process. Consented interviewees will be offered the chance to ask questions regarding the study procedure prior to proceeding.

Semi-structured qualitative interviews will proceed with participants who give verbal consent. Due to the variable nature of response and participant engagement interviews are estimated to last between 30 minutes and 60 minutes. The interview guide includes planned questions that will be asked to every participant. Due to the nature of semi-structured interviews, we may ask appropriate follow-up questions or ask participants to elaborate upon statements made. Study questions include appropriate warnings about the sensitivity of questions, where participants may be asked directly about negative experiences with healthcare or to elaborate on negative study experiences. As appropriate, participants will be reminded that they can take breaks, skip questions they are uncomfortable answering, or stop the interview at any time. Interviews will be conducted primarily by Ms. Martin as part of a Master's of Genetic Counseling research requirement, with Dr. Mittendorf and Mx. Bland to supplement interviews as needed.

Participants who are interviewed will receive a $40 Visa gift card as compensation for their time. Visa gift cards will be sent to interviewed participants via email. Individuals who decide to end the interview early will still be compensated with the same gift card.

Consent to interview and the interview itself will be recorded on secure Microsoft Teams software, which is the preferred secure software of VUMC and transcribed using auto transcription that comes pre-installed with Microsoft Teams. Recordings and raw transcripts will be maintained on a secure study server within Microsoft OneDrive, with access only available to approved study personnel. These transcripts will then be supplemented with manual revisions based on raw recordings (to catch

autotranscription errors) and manual redaction of any identifying information – including about individuals other than the participant. Because of the sensitive sociopolitical climate for TGSD persons, transgender team members (Mx. Bland and Dr. Mittendorf) will review redacted transcripts for potentially sensitive data that falls outside the scope of data that is traditionally considered identifiable, and may choose to apply stricter data censoring at this time. Deidentified transcripts will be uploaded to Dedoose, a cloud-based coding software used to analyze qualitative research.

6. Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

All researchers will report all events that are serious, unexpected, and study-related to the PI by phone, fax or email within 24 hours of becoming aware of the event. We will promptly report to the IRB any participant complaints about the conduct of any element of the study or concerns about potential harms, including copies of any written communication with the participant addressing those concerns. Further, all conversations with participants that indicate a level of concern about a study component - even if not a complaint - will be documented and distribution of any participant education materials in response to such queries will be documented in the participant's research (REDCap) record for the primary study (FOREST). There is the possibility of identifying someone who received inappropriate clinical recommendations from MeTree based on their response to the sex question in MeTree, which is used in assessing clinical risk. If someone like this is identified, this would be reported under the FOREST study protocol, and a new MeTree risk report would be generated.

7. Study Withdrawal/Discontinuation

Withdrawing participation from interview substudy

We will continue to utilize the participant interview data in analyses unless the participant asks for the data to be withdrawn. If a participant requests that data be withdrawn, raw transcripts and recordings will be deleted, as well as any data derived from these that are present in Dedoose or analyses. Participants who request that interview data be withdrawn will be notated as actively withdrawn and that they requested interview data removal in the tracking database, so that we can maintain information about participants. Subjects who wish to withdraw from the main study will be withdrawn from FOREST under the main study protocol.

Active Declining Participants

As noted above, participants can ask to stop the interview at the time, for any reason. If participants wish to stop the interview permanently and not reschedule for a follow-up, they will be considered withdrawn. Withdrawn participants will follow the withdrawing participation procedure above.

Non-responders (Passive Decline)

Potential interviewees who agree to interview, but fail to schedule and are unable to be reached or fail to attend their interview and are unable to be rescheduled will be considered passive decliners. Similarly, if a participant phone call is lost during interview and they are unable to be reached again to reschedule the rest of the interview, they will be considered passively withdrawn and will follow the procedure above regarding the interview data that was collected until the dropped call.

Surveys of declination or withdrawal
Participants that ask to stop the interview, request or withdraw from the study will be asked why they are making this choice. This information will be tracked in the tracking database for the main FOREST study.

Deceased participants
The study will utilize the data of deceased participants even if they pass before the conclusion of the study.

8. Analytic Considerations
Ms. Martin, Dr. Mittendorf, and Mx. Bland will develop a qualitative codebook using inductive and deductive techniques. This codebook will be refined with input from the rest of the FOREST study team and Ms. Martin's thesis committee. Dedoose will be used for coding, with Dr. Mittendorf will act as a dual coder for Ms. Martin. Mx. Bland or another member of Ms. Martin's committee will serve as tiebreaker. Themes will then be identified and findings synthesized.

9. Privacy
As noted above every effort will be made to remove identifying information from study transcripts and participant summaries. There is no intervention in this substudy of FOREST. However, there is the possibility that a participant may report emotional distress when recounting experiences with the FOREST study or previous personal experiences. In the case of this occurring, we will provide participants appropriate numbers to VUMC mental health resources. This referral resource will include the VUMC psychology/psychiatry phone number, helplines, and other helpful resources. Should this occur, it would also be reported to the IRB. All interview data will be deidentified before coding in Dedoose, and only de-identified data will be shared. All identifiable data will be stored on secure servers and only accessible to a minimum subset of study personnel. Given the sensitive nature of participant gender identities in the current societal climate, additional efforts may be undertaken beyond typical requirements under HIPAA to further obscure participant identities or sensitive information. Two key personnel on the primary FOREST study, Dr. Mittendorf and Mx. Bland, who both have transgender identities and are connected to the Nashville transgender community, will guide whether additional data obfuscation beyond HIPAA is necessary to protect participants.