Title: The Impact of Family History and Decision Support on High-Risk Cancer Screening
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Introduction. Risk assessment through family health history (FHH) permits tailoring of prevention strategies and treatment regimens to an individual's familial risk level. Although FHH is commonly accepted as an important risk factor for common, chronic diseases, it is rarely used in clinical practice as part of a structured risk assessment due to time constraints for the office visit, lack of standardization of FHH collection, failure to consolidate access into one location, and lack of confidence in identifying high-risk patients.[1-3]

The Genomic Medicine Model (GMM) was developed by our university affiliate colleagues to address barriers to providers' use of structured risk assessment. The GMM comprises three components: 1) education of primary care providers (PCPs) and patients; 2) an IT-based platform, MeTree, that collects FHH from patients and generates a pedigree and decision support reports for patients and PCPs; and 3) provides support for patients and PCPs to interpret FHH information and adhere to recommendations. A standardized FHH assessment accompanied by decision support facilitates 3 important objectives: 1) identification of patients at higher risk, 2) genetic consultation referral for patients at risk for hereditary cancer syndromes, and 3) recommendation of guideline-based preventive care for patients of all risk levels.

Currently, the Veterans Health Administration (VA) has no system-wide, comprehensive, validated method for assessing FHH or providing decision support. The GMM offers a promising strategy for identifying patients at risk and providing risk-appropriate referrals and screening.

The goal of this study is to evaluate the feasibility and effectiveness of the GMM components (i.e., educational materials, FHH collection via MeTree, and decision support) in VA primary care practices to improve risk-appropriate CRC referrals and screening. This 3.5-year, mixed methods study involves a cluster randomized trial in which PCPs and their patients are randomized to immediate vs. delayed (wait-list control) patient-entered FHH data collection and decision support. The primary aims are:

> **Aim 1:** Determine whether FHH collection via MeTree improves identification of patients at higher familial risk for CRC by comparing rates of high-risk identification in the medical record prior to study enrollment to rates of high-risk identification following MeTree completion.
> **Aim 2:** Evaluate whether providing decision support to patients and PCPs improves risk-appropriate PCP referrals for, and patient uptake of, CRC screening/surveillance.

The secondary aims are:

> **Aim 3:** Assess experience with decision support and effects on workflow from PCPs, and obtain information to inform eventual implementation in the VA healthcare system from administrative leaders, via qualitative interviews.
> **Aim 4:** Conduct cost-consequence and budget-impact analyses of implementing FHH collection and GMM decision support in VA.

If MeTree effectively increases identification of high-risk Veterans, and decision support effectively increases appropriate CRC screening for high-risk Veterans, then we will be poised to inform and evaluate implementation of GMM in VA on a larger scale and for a larger disease set.

Methods for Aims 1 and 2

Sample selection and enrollment. We will enroll primary care providers (PCPs) and patients from the Madison VAMC, Durham VAMC, Raleigh, Hillandale, and Greenville clinics. To achieve our target sample size of 500 patients who complete MeTree, we will enroll all eligible providers. We anticipate enrolling 40 providers, with 12-13 patients per provider; however, the number of patients enrolled per provider may vary if fewer providers enroll. PCP and patient eligibility will be determined from the following study inclusion/exclusion criteria.

PCP inclusion criteria will be determined from clinic administrative staff:

- Primary care physician, physician assistant, or nurse practitioner
- Working in one of the targeted primary care clinics
- At least one half-day of primary care clinic per week

We will email recruitment letters briefly describing the study and informing PCPs that we will be attending a staff meeting to discuss study details. Following methods used in other Durham HSR&D studies, Drs. Voils, Fisher, and Wu will attend staff meetings to inform providers about the study goals and methods. We will emphasize that the study is not meant to increase burden in their already busy clinics, but, rather, to facilitate guideline-appropriate referrals. No education regarding family health history (FHH) or colorectal cancer (CRC) will be provided during these meetings.

Providers will be recruited in a manner similar to previous HSRD-funded projects. We request a waiver of documentation of informed consent from providers. Study staff will introduce the study to providers in one of two ways: 1. during a provider/staff meeting or 2. via a recruitment email. Providers who attend the meeting and would like to consent may sign the consent for at the time of the meeting. Study staff will email all PCPs who did not attend or provide consent at the meeting a message containing a description of the study and all required elements of informed consent to participate in the study. These PCPs may to participate in the study via an affirmative email response. If the study team does not receive a response from a provider at the time of the provider meeting or within 1 week from sending the email, the study team may re-contact the provider by email, or approach the provider in-person to ask whether they are willing to participate. The method of consent and consent date will be documented in the study tracking database. The study team will also keep the email responses as documentation of willingness to participate. We will use a rolling recruitment strategy to capture any new providers.

Consented providers will be randomized to the immediate or delayed condition, in which a small subset of their patients will complete MeTree and receive decision support at enrollment or 12 months later. PCPs randomized to the immediate group will then receive additional with details of the study and educational materials throughout the study's recruitment period (those randomized to the delayed group will receive this information 12 months later). This additional detail includes information on the role of FHH in CRC and a description of the procedures to ensure that the decision support documents are available for the patient appointments. We will ask PCPs in this group not to discuss the decision support documents, process, or experience with other clinicians. We will minimize education provided to delayed wait list (control) providers by sending separate educational materials prior to initiating family history completion and decision support to wait-list control participants 12 months post-enrollment.

Patient eligibility criteria will be determined by electronic data abstraction:

- Assigned to one of the enrolled PCPs
- At least one primary care appointment in the 18 months prior to enrollment
- Upcoming PCP appointment with assigned PCP
- Aged 40-64 years, confirmed via telephone screening

- No previous history of CRC (V10.05, V10.06, ICD-9 153, 154), inflammatory bowel disease (555.0, 555.1, 555.2, 555.9, 556.0) or adenomatous polyps (indicated in pathology report)
- No endoscopy within the previous 3 years, indicated in inpatient/outpatient encounter data and confirmed via telephone screening

Additional patient eligibility criteria will be determined by telephone screening:

- English as preferred language
- No plans to relocate or leave the VA healthcare system in the next 12 months
- No more than 2 errors on a validated 6-item screener for cognitive impairment
- Have at least some knowledge of FHH of first- and second-degree predecessor relatives, even if adopted
- Willing to have their family history data maintained at Duke for future research use
- No concurrent enrollment in a competing research study (related to colon cancer)

Patients with an upcoming appointment (usually at least 6 weeks out) with their assigned PCP will receive a recruitment letter by mail in addition to an informational brochure about MeTree. Patients may opt out of the study by calling a toll-free number; otherwise, study staff will contact potential participants by telephone to describe the study, confirm knowledge of FHH, and obtain verbal consent. Verbal consent is used because participants may elect to complete the family history tool online; in such cases, the only purpose in attending an in-person visit would be to provide written informed consent. (HIPAA Authorization may be obtained by mail or fax, as explained below, or may be waived.)

After providing verbal consent, participants will complete a telephone survey of self-reported screening (Appendix 1). One measure will be a self-report questionnaire that assesses the various recommended CRC screening test modalities, which was previously validated in the Veteran population by Drs. Fisher, Voils, and Coffman.[39] For the other types of cancer screening, we will query receipt of breast magnetic resonance imaging, mammogram, , pelvic ultrasound, or genetic testing for screening purposes; these data will be examined in exploratory analyses. An advantage of collecting self-reported data is that we can capture receipt of any test received outside the VA. At this time, we will also administer a validated tool designed to assess computer proficiency, as this is a computer-based intervention. After completing the survey, participants will be informed of their randomization assignment, which is determined by whether their PCP was randomized to the immediate vs. delayed condition.

Immediate Condition. Participants in the immediate group will be provided with the choice of completing MeTree on their own online (at home, library, or wherever they can access it) or in person prior to their PCP visit. Participants in the delayed group will have this choice 12 months later. After receiving the signed HIPAA authorization form, or after completing the consent process when HIPAA is waived, study staff will log into the Duke software to register the patient user and will provide the patient with username and password, both of which will be identical, non-identifying, and generated by our tracking database. The username and password will be provided to the participant by mail, text message, or MyHealtheVet Secure Messaging, depending on veteran preference.

Delayed (wait-list control) Condition. We will inform control participants that we will contact them 12 months post-consent to complete MeTree. We will ask for contact information for a family member or friend to facilitate future contact. These participants will be informed that there is little risk associated with waiting, as CRC takes 7-10 years to develop. During the 12-month period, neither control patients nor their providers will receive further contact from study staff. Ten to 11 months following consent of the first participants, we will contact wait-list PCPs to provide the same

education that was provided to the immediate group. Also at 10 months following patient consent, we will mail a reminder letter to control patients informing them about the process to complete MeTree. At 11 months following baseline, we will telephone control participants to assess preference for mode of completion using the aforementioned procedures. If we are unable to reach control participants by telephone by 12 months following consent, we will mail another reminder letter. We will continue to try to reach control participants by telephone for up to 6 weeks following the 12-month time point. Note that control participants may not have an appointment scheduled at the 12-month time point. We will follow the same procedures as in the immediate arm with regard to uploading the PCP decision support document requiring PCP signature. PCPs may choose to order tests or schedule an appointment with control participants who are identified as high-risk. Likewise, patients who are informed that they are high-risk by the patient decision support document may call to request an appointment with their PCP following usual care procedures.

Provider Departure. If a patient's provider leaves before they are contacted by the study team, the participant's randomization will match that of their new provider, or the patient will be ineligible if the new provider does not consent to participate. Participants who have already completed MeTree prior to their provider leaving the VA will keep their assigned randomization per intent-to-treat principles.

Procedures (both groups). Consented participants will be provided with access to a worksheet to assist them in collecting FHH from their family members prior to logging onto MeTree. The worksheet is available for download from the MeTree website, but can also be mailed to the participants, depending on timing and preference. The worksheet queries names of children, parents, siblings, nieces/nephews, aunts/uncles, and grandparents; age now or at death of these individuals; diseases these individuals have had and age at diagnosis; and cause of death. A list of types of cancers, hereditary cancer syndromes, and other diseases is provided, along with definitions of various diseases and causes of death. Participants will be asked for their FHH for all of these diseases because MeTree has been designed to collect information on these diseases and decision support for additional diseases is ongoing. In this study, the primary outcome relates to CRC, with referrals and uptake of recommendations related to these other diseases as secondary outcomes.

Information for accessing the MeTree website will not be granted until a signed HIPAA Authorization has been received, unless HIPAA is waived during the consent process. Participant login information will be generated by Lesa Powell, OIT programmer, to meet all VA security requirements. The list with the login information and pin will be kept in a separate file from the database containing participant data (phone numbers) on a Durham HSR&D server (\\vhadurhsmcifs01.v06.med.va.gov \Family History), with access only available to VA team members. This will not contain PHI, and will be told to participants via a phone call, letter or text message. All text messages will be sent from a study specific phone number used only for texting and calling participants. All family history data will be entered on the Duke MeTree site. The family history data will be maintained indefinitely by Duke and combined with family history data collected using the MeTree software from non-veterans at other sites. These data will be used for future research purposes at Duke. All other data, including those abstracted from participants' CPRS records, will be kept in VA files only. Patients will be contacted by study staff with reminders as needed (by text message, MyHealtheVet Secure Messaging, or phone) to return their signed HIPAA Authorization form, and to complete MeTree before their appointment. If necessary, patients may meet study staff to complete MeTree on a study computer. Participants who initially elect to complete MeTree in person, and who later elect to complete MeTree with a study staff member because they did not do it on their own, can complete the HIPAA Authorization in person prior to completing MeTree on a study laptop in the presence of study staff. Patients who are screened as eligible but who never log in to complete MeTree either on their own or in person will not provide data for the study and thus will not be counted toward the required sample

size of 500. Thus, we may screen and consent up to 850 patients in order to enroll 500 who complete MeTree.

Once patients have completed MeTree, they will be able to download the patient decision support document and print it. Study staff will log into a secure Duke website to download the provider decision support document, which will be identified by a random study ID number and saved to the project folder on the VA server. A study staff member will input the decision support document findings as a CPRS note requiring signature (and thus review) from the PCP. Because participants are recruited based on an upcoming PCP appointment, this CPRS note should be recent and will be easy for PCPs to find. PCPs will be responsible for ordering recommended tests, including consults to GMS as they deem clinically appropriate for the patient (given patient preference, comorbidities, etc.). Patients who complete MeTree on their own (outside clinic) will have access to download and/or print the decision support documents, whereas participants who complete MeTree in person can receive the decision support document from study staff. All veteran participants will receive $50 after completion of MeTree. This will be paid in a check or by electronic funds transfer via the agent cashier or a payment voucher.

Twelve months following consent, participants in both arms will be contacted by telephone to complete the same survey of self-reported cancer screening as completed at baseline. This follow-up survey will also ask about several additional screenings, including the fecal occult blood test (FOBT) for colorectal cancer and the CA-125 blood test for ovarian cancer. All participants will complete an exit survey about acceptability of using MeTree (Appendix 2). This survey will be administered via telephone call or by mail, with data entered into an Illume survey. In the *immediate* arm, the exit survey will be administered via telephone call placed after patients have completed MeTree; in the delayed arm, the exit survey will be administered in the same call in which self-reported screening is assessed.

Then CPRS and administrative data will be reviewed to determine the baseline rate of patients identified at increased risk for CRC based on FHH. This rate will be compared to the rate obtained subsequent to completing MeTree so that the effectiveness for increasing the identification of higher risk patients can be determined. CPRS data abstraction will be completed by research staff at either site (Durham or Madison). Study staff at both sites (Durham and Madison) will have National Electronic Health Record (EHR) access, using VistAWeb or Joint Legacy Viewer (JLV), in order to complete these data abstractions. Medical records will be accessed using VistAWeb, JLV, or CPRS and the resulting data will be recorded in DatStat Illume, behind the VA firewall.

Blinding cannot be ensured because the MeTree decision support document for PCPs will be scanned into CPRS, and there is no practical way to prevent the RA from seeing it. At baseline, all patients enrolled in the study will have their EMR audited to determine whether they have been identified as high risk for CRC as observed by either: (1) a diagnosis of high-risk for CRC (diagnosis code: V16.0) or (2) documentation in CPRS. The RA will review progress notes from all providers for documentation of FHH of CRC, including the relationship and age at diagnosis or explicit statement of no FHH of CRC. This will be accomplished with a text search. Initially, we will validate our search terms by reading all progress notes in a subset of 25 patients. If necessary, the terms will be adjusted to accommodate those found in the progress notes, and validation will be repeated on an additional 25 patients.

Analyses for Aims 1-2

Sample Size and Power Considerations. The CRC screening rate of patients aged 50 years and older in VA is high, around 80%.[44] However, this is based on the assumption that all patients are average-risk; as such, the risk-appropriate referral rate is not well-characterized. We estimate that the risk-appropriate CRC screening referral rate is 60% to 70%. Our final sample size calculation is based conservatively on the screening referral rate of 60%. Based on a type I error rate of 5% and Z test for the difference of two proportions adjusted for provider clustering, we will need approximately 480 patients (240 in each arm) to detect a 13% difference (i.e., 73% in the immediate arm) with 80% power. Table 1 provides estimated differences that can be detected with this sample size for different CRC screening referral rates. Lost to follow-up either due to death or the Veteran leaving the VA system will be minimal as outcome data are collected administratively. We inflated the sample size to 500 patients to account for a 4% loss to follow-up. Patients who screen as eligible but who never log in to complete MeTree either on their own or in person will not provide data for the study and thus will not be counted toward the required sample size of 500. Thus, we may screen and consent >500 patients in order to enroll 500 who complete MeTree.

Table 1. Estimated differences in CRC screening referral rates that can be detected between arms for different baseline screen referral rates with 80% power

Sample size (per arm)	Baseline referral rate for control arm	Estimated difference between arms
240	60%	13.2%
240	65%	12.1%
240	65%	12.0%

By design, patients may not be independent because they are clustered within a participating provider. The “relatedness” of patients within a PCP is measured by the intraclass correlation coefficient (ICC) and must be considered in the sample size estimation. We have a fixed number of PCPs (20 in each arm). The sample size for difference in proportions is adjusted by the intraclass correlation coefficient (ICC); we used an ICC of 0.02.[45] Although an ICC is difficult to estimate in advance of a study, we believe this is an appropriate and conservative estimate based on our own and others’ research findings. A recent survey article reviewing outcomes from 31 studies found a median ICC of 0.01 (IQR 0 to 0.03).[46] PASS 2008 was used for all sample size calculations.

For the secondary outcome, uptake of risk-appropriate CRC screening, our sample size is smaller as this outcome is only available for Veterans that were referred for a CRC screening/surveillance test. We used a hypothesized CRC referral rate of 60% in the wait-list control arm and 73% in the immediate arm for the power calculation. Based on a hypothesized CRC screening/surveillance uptake rate of 60% in the control arm, type I error rate of 5%, and an ICC of 0.02, we can detect a difference of 18% in uptake of CRC screening test rates between arms with 80% power. Table 2 provides estimated differences that can be detected with this sample size for different CRC screening/surveillance uptake rates. For Aim 1, the analysis is a pre-/post- type comparison of high-risk CRC identification rates. With a sample of 500 Veterans, we will have adequate power to detect clinically reasonable differences in the rates of high-risk CRC identification.

Table 2. Estimated differences in CRC screening/ surveillance uptake that can be detected between arms for different baseline screening/surveillance uptake with 80% power as well as different CRC screen referral rates

Baseline referral rate for control arm	Sample size (control/ immediate)	Baseline screening/ surveillance uptake for control arm	Estimated difference between arms
60%	100/120	60%	18.0%
65%	100/120	65%	17.2%
70%	120/140	70%	15.0%

The outcome for Aim 1 is rate of high-risk categorization. The analysis for this aim does not compare the outcome between arms as our aim is to determine if using MeTree to collect FHH improves the rate of high-risk identification for CRC compared to what is currently available administratively in VA. In our study design, both arms use MeTree to collect FHH, so the design for the aim is a pre-/post- comparison within Veterans. A binary variable will be created for each participant (1=presence of high-risk for CRC, 0=absence) at baseline (current practice) and following MeTree administration. We will test whether the rate of high-risk identification is higher following the MeTree administration compared to what is available in the medical record under current practice using a McNemar's test adjusted for PCP clustering.[40,41] In addition to examining identification rates, specification of the source of identification of high-risk CRC will be important to formulating a standard identification strategy for clinical follow-up (e.g., referral to or receipt of colonoscopy screening).

The primary effectiveness outcome for Aim 2 is risk-appropriate CRC screening/surveillance referral for all patients, regardless of risk level. Outcomes will be compared between arms to determine the impact of decision support on risk-appropriate referrals and screening/surveillance. The risk-appropriate screening/surveillance referral will be determined based on the MeTree algorithm. A binary variable will be created for each patient (1=adherent to risk-appropriate referral, 0=non-adherent to risk-appropriate referral) at 12-month follow up. The appropriateness of the referral will take into account if they were previously (prior to baseline visit) appropriately referred based on the current determination of their risk profile using the MeTree FHH data collection for both arms.

Data on whether the referral was made will be extracted in a multi-phase process that maximizes efficiency and accuracy. First, we will examine administrative data. FOBT codes are G0328, 82270, 82274, FOBT, FOBT1, FOBT2, FOBT3. We previously found that for 2,836 of 2,989 patients (95%) FOBT use identified by CPT code in the OPC was confirmed in the records of the local VA laboratory performing the test. Similarly, for 2,842 of 2,943 patients (97%) with an FOBT documented in the laboratory records, a CPT code was found in the OPC database.[31] If administrative data reveal a CPT code for colonoscopy or FOBT, then patients will be considered to have undergone that test. If not, then we will examine orders. If no order exists, then we will examine laboratory reports and VISTA imaging. If no evidence of referral or screening is found at this point, then notes will be reviewed to determine whether participants refused, no-showed, received screening outside VA, or there is medical justification (e.g., life-limiting illness) for not receiving screening. The appropriate referral guideline will be based on the risk-categorization of the patient from their FHH. Patients will be coded as risk-appropriate referral or not; recommendation of any option listed as risk-appropriate will be classified as a risk-appropriate referral. Nonadherence to risk-appropriate referral could result from a referral being too aggressive based on risk categorization (e.g., a 40-year old without a FHH of CRC) or that the risk-appropriate referral was not made.

Patient uptake of CRC screening/surveillance recommendation will be evaluated as a secondary outcome. The patient uptake of CRC Screening/Surveillance referral will be examined for the subset of patients that received risk-appropriate referral by having an order in their record following the baseline visit for a CRC screening/surveillance referral. A binary variable will be created for each patient that was referred for CRC screening/surveillance (1=uptake of referred CRC screening, 0=no uptake of referred

CRC screening) at 12-month follow up. Data on whether participants completed the CRC screening test will be obtained in a multi-step process. At the time of data abstraction, we will make a determination about whether to examine fee basis files for screens performed by non-VA providers according to whether the Durham and/or Madison VA is outsourcing CRC screening.[42] Patients will be considered adherent if their medical record shows any risk-appropriate CRC test(s) performed in the time between completion of the computer program in clinic and 12-month follow-up.

Referral for genetic consultation will be examined as a secondary outcome. This outcome is risk-appropriate referral for genetic consultation or not. Because the Durham VAMC is online with GMS, a consult option will be generated to refer patients to GMS for genetic consultation, which may or may not include genetic testing. The Madison VAMC is not online with GMS. Therefore, fee basis files will be reviewed to determine if genetic counseling or testing was performed outside VA. The RA will review PCPs' consults and progress notes subsequent to the visit associated with completion of MeTree FHH regarding recommendations for genetic consultation. GI notes will also be reviewed to determine if a consult to GMS was made. Appropriate referral based on risk level will be classified as adherence. We will also examine the rate of receipt of a genetic consultation by conferring with GMS (which may be lower than the referral rate if the patient declines). As a relatively small proportion of participants are expected to receive genetic referral (6.4% in the Cone Health study), we will be underpowered to detect a significant effect. However, the descriptive rates will be informative from a policy perspective.

Process data will be collected to inform eventual implementation. During the study, process data will be collected, including detailed records on enrollment, field notes from the study coordinator regarding the need to assist participants in completing MeTree, modifications to the program or decision support sheets, and any communication with PCPs (comments, questions). Enrollment and completion rates (the number of patients contacted who agree to have a baseline visit and who complete MeTree) will be calculated from information collected in the tracking database. At the end of the study, all enrolled PCPs will complete an exit survey about their experience with the intervention and impact on workflow.

Analyses will compare the risk-appropriate referral rate between patients randomly assigned to the immediate vs. waitlist control arm. A binary variable will be created for each patient (1=adherent to risk-appropriate referral, 0=non-adherent to risk-appropriate referral) at 12-month follow up. Patients with the same PCP may have more similar outcomes as compared to patients with a different PCP. Therefore, we plan to use Generalized Estimating Equations (GEE) as our primary analysis tool.[43] The regression coefficients from a GEE model have essentially the same interpretation as those from a standard regression analysis but are more appropriate because they properly incorporate the within-PCP correlation. When using GEE methods, it is only necessary to specify the general structure of the mean and correlation between repeated observations. Because the outcome is binary, we will use a GEE with a logit link function and an exchangeable correlation structure. In addition, we will use empirical standard errors for inference because they are robust to misspecifications of the correlation structure. The hypothesis for Aim 1 will be tested using the following model of the mean structure: $\text{logit}(\pi_{ij}) = \beta_0 + \text{ARM}*\beta_1$ where π_{ij} represents probability of risk-appropriate testing adherence for patient i seen by physician j. ARM is the dummy-coded intervention arm. A positive, significant estimate for β_1 provides evidence that patients who receive the intervention immediately have higher risk-appropriate referrals for CRC screening/surveillance than those in the wait-list control arm. PROC GENMOD in SAS (Cary, NC) will be used to fit the GEE model.

Secondary outcomes for Aim 2 are uptake of referred CRC screening test and risk-appropriate referral for genetic counseling. A binary variable will be created for each patient (1=uptake of referred CRC screening, 0=no uptake of referred CRC screening). Note that determination of uptake will depend on each patient's risk-appropriate referral. For patients for whom multiple tests are appropriate, uptake will be

defined by performance of any of them. For the referral for genetic consultation outcome, all patients eligible for genetic consultation based on their risk profile from FHH will have their EMR audited to determine whether a risk-appropriate genetic consult referral was documented. A binary variable will be created for each patient (1=presence of risk-appropriate genetic consult referral, 0=absence) at 12-month follow up. A similar variable will be created to indicate whether participants received the recommended genetic consultation. As these secondary outcomes are binary, we will follow the same modeling strategy using GEE as described for the primary outcome. In exploratory analyses, similar outcomes will be created for the other cancer types (breast and ovarian) as described for CRC. We will calculate descriptive statistics for these outcomes and, if sample size is adequate, we will fit similar GEE as described for CRC.

The primary analyses for this cluster-randomized trial will be conducted on an intent-to-treat basis; participants will be analyzed in the group to which they were randomized, regardless of intervention adherence. Additional supporting analyses focusing on alternative, more restrictive analytic cohorts (e.g., per-protocol analysis) may be considered as exploratory analyses to provide additional information about the impact of amount of exposure to the intervention. Given that the outcomes will be determined based on EMR review over a 12-month period, there should be very little missing data. The most likely scenarios are that a participant dies during the study or leaves the VA system before completion of the 12-month follow-up period. However, we do not expect this to occur at a high rate; as needed, we will explore the impact with sensitivity analyses.

The main conclusions drawn from this trial will be based on the pre-specified primary and secondary hypotheses outlined previously and will be tested with two-sided p-values at the standard 0.05 level. For both primary and secondary outcomes, stratification variables (provider type and patient age categorization) will be included in GEE models. Statistical analyses will be performed using SAS for Windows (Version 9.2: SAS Institute, Cary, NC) and R (http://www.R-project.org).

Aim 3

The evaluation of Aim 3 employs a single, holistic case study design with the participating Durham and Madison VA primary clinics as the unit of analysis.[66] Although GMM will be used in 3 different clinics, our focus is to examine the holistic nature of GMM implementation. Should we find clinic-level variation in identification, referral, or screening/surveillance rates (Aims 1-2), we will use a replicated case study design to describe implementation experiences for each clinic. Case study design is well-suited for describing the implementation of GMM in the VA system, which has not been examined before. In addition to permitting in-depth analysis of individual cases, case study methods offer strategies for systematic contextual analysis from multiple sources of information.[66,67]

To ensure that implementation evaluation in this case study includes all the relevant evidence and includes rival or conflicting interpretations, we will employ a mixed methods approach, collecting information about GMM implementation from multiple sources of data.[66,68] Quantitative data will come from EMR and administrative data collected in Aims 1-2. Qualitative data will be collected via semi-structured interviews with clinic staff and administrators in Aim 3, conducting at the conclusion of Aims 1 and 2. These interviews will provide rich contextual data regarding clinic structure and operations that are otherwise unobservable in secondary data.

Potential participants will include PCPs and clinic leaders (nurse manager, charge nurse, and clinic director) from each site, the Chief of Ambulatory Care, and the Chief of Medicine. A recruitment letter will be emailed; this letter will note that leaders/PCPs may opt out by contacting one of the study team members. If we do not hear from them, then we will follow up by telephone. Purposeful sampling in

qualitative research is directed toward the selection of information-rich cases to draw "illustrative inferences" regarding "possibility."[69] Accordingly, we will recruit a subset of participating PCPs who are available and willing to answer the qualitative questions. We aim to interview 4-5 PCPs per clinic who had at least 10 patients complete MeTree. We also aim to interview clinic leaders who were not involved in the trial. Thus, we will enroll up to 25 VA employees for this aim. Patients are not key informants for this aim because they are not involved in clinic implementation, and their reactions to the FHH collection process will be assessed with quantitative measures immediately following completion of MeTree.

Interview protocols will be pilot-tested among team members to ensure that questions draw responses to critical data from each respondent. A member of the research team will conduct interviews in-person or by phone. Prior to starting the conversations, written or verbal informed consent will be obtained. We will use a semi-structured script to conduct the interviews. All interviews will last 15-30 minutes and be digitally audio-recorded to facilitate data analysis. All interviews will be audio-recorded using a sparky USB device and saved to a folder on the VA network. Audio-recorded interviews will be transcribed verbatim, and the information will be systematically coded for analysis by Drs. Sperber, Wang and Voils using a directed approach to content analysis.[70] We will develop codes based on predetermined categories, such as those that will form the interview questions; any text that cannot be categorized with the pre-determined scheme will also be identified and categorized. This is a more structured approach to qualitative analysis, and is appropriate when there are *a priori* notions of key concepts or variables that can form initial codes. The coding scheme will be developed and finalized through a process of discussion and consensus among the team and then applied to all transcripts. Through the constant comparison process, Drs. Sperber, Wang and Voils will sort related codes into larger thematic categories and refine the categories by comparing them with one another within and between transcripts.[71] Reports for all text segments will be generated for each code to assess fit between our data and constructs from Weiner's framework. From this, we will identify themes in the coded data and assess whether constructs affected implementation. A checklist matrix will visually display construct valences to identify patterns between (and within, if applicable) clinics.[51,72] Finally, we will generate a conceptually clustered matrix to enable between analysis of implementation facilitators and barriers by each construct.

Aim 4

To derive intervention cost, we will take an implementation perspective. Study-related costs, such as study staff time to consent and randomize patients will not be included. Development costs, such as designing MeTree and decision support materials, will be treated as a one-time "sunk cost" that has already been incurred. Intervention costs will be calculated for the computer required for MeTree use in clinic, providing the decision support documents, and the labor cost of providing assistance to patients to use MeTree and generate notes in CPRS for each patient's PCP. We will collect a sample of times required to perform each of these tasks and apply appropriate wage and fringe benefit rates to calculate labor cost. In the follow-up physician survey and qualitative interviews, we will ask PCPs in the immediate arm whether this process affected the length of their clinic visits, and, if so, by how much. If PCPs report an increase or decrease in time spent with patients, then we will apply a wage-per-minute cost to the time difference to derive an incremental visit time cost for the appropriate study arm.

The intervention may differentially impact utilization of health care services. We will derive *screening costs* of FOBT, flexible sigmoidoscopy, or colonoscopy from the VA's Decision Support System outpatient and inpatient extracts datasets. We will collect a sample of times required to provide CRC genetic counseling and wage and fringe benefit rate for genetic counselors from GMS to estimate the cost of providing CRC genetic counseling. For patients that receive genetic testing, we will apply the prevailing market rate for a genetic test at study conclusion to the analysis. Although intervention and screening costs are likely to be higher in the immediate arm, at least some of this cost may be mitigated by cost savings from CRC cases

being averted. As the short time frame of this study will not allow for the appropriate capture of such costs savings, we will rely on the literature to project long-term cost savings from averting CRC cases.

Personnel Training and Quality Control. Drs. Voils will train the PC and RA in standard survey and outcome assessment methods:[93] 1) Careful scheduling and timely monitoring of the schedule to ensure that complete visits occur; 2) Collection of contact information at each visit; 3) Prompt contact and rescheduling of missed visits; 4) Review and documentation of the reasons for missed visits; and 5) Review and edit of participant data promptly to identify problems or missing values that can be completed by follow-up.

To decrease the risk of ascertainment bias and to standardize the abstraction, a detailed record abstraction protocol with data dictionary will be created, and training will be conducted by Dr. Fisher. An electronic database will be developed for this purpose and will include quality measures such as mandatory fields and range checks. Quality will be further ensured by independent abstraction and data entry of 15% weekly by the study staff throughout the study, with comparison of the two abstractions and correction and retraining as needed.

Safety Monitoring Plan. Study staff will report any adverse event or unanticipated problem to the PI, Dr. Fisher (gastroenterologist) immediately. These individuals will review all such events and determine the likelihood they were due to the study. The PI will report any serious, unexpected, and study-related adverse event or unanticipated problem to the local IRB according to the institution's requirements. The IRB will review all adverse events during continuing review, which will occur at least annually.

Data Management, Storage, and Transfer. Regarding privacy, research personnel will use only those parts of the medical record necessary to determine eligibility and follow the research protocol. Measures will be taken to maintain confidentiality during in-person sessions, such as scheduling them in a private room where other patients cannot overhear the conversation. All information security and privacy incidents will be reported to the ISO and PO immediately.

MeTree is stored on a Duke server, where it is continuously updated and maintained. Moving the software to VA would require resources (time and money) well beyond the scope of this research study. Moreover, it is our position that moving the software is not justified until we can demonstrate clinical benefit; the goal of this study is to determine if there is clinical benefit. If there is, then future efforts will be directed toward implementation, which may include moving MeTree to VA.

Patients may provide HIPAA Authorization (by mail/fax if completing online or in person if completing in clinic) indicating that their data will be entered and stored at Duke, or may waive HIPAA authorization during the verbal consent process. The data will be entered on a secure Duke website that meets VA security standards. Duke will maintain the family history data without identifiers and may combine these data with data they obtain from other studies. To prevent the exposure of personal identifying information or protected health information, we will use the following procedures. Each potential participant will be assigned a study participant number for tracking purposes. An electronic key linking identifiers to study numbers will be stored on a Durham HSR&D server (\\vhadurhsmcifs01.v06.med.va.gov \Family History), with access only available to VA team members. VA team members in Madison will be granted permission to access the study folder. Patients will be encouraged not to enter identifying information into the Duke website (e.g., provide age instead of date of birth); they do so at their own risk. The decision support documents generated by MeTree will be downloaded by the study staff from a secure Duke server (to which study staff will have access) to the Durham VA server (for Durham patients) or to server in Madison (for Madison patients). A copy of the documents will be scanned into CPRS, and a copy will be stored in the electronic study files. Throughout the study, Duke staff may provide the study statisticians with MeTree data for analysis. This will be done using the VA-approved Safe Access File Exchange (SAFE),

as a method to safely send files electronically. The data files can be emailed to the statisticians using SAFE, then saved in the study folder on the Durham HSR&D server. As an alternative to using SAFE, Duke staff can also provide data to the VA statisticians by encrypting data (compliant with FIPS 140-2) on a VA-issued CD or USB/thumb drive, or using Azure RMS for electronic data transfer.

For chart abstractions, study staff in Durham and Madison will use VistAWeb, JLV, or CPRS to access medical records. The data collected through these chart abstractions will be recorded using the VA-approved DatStat Illume, and data will be saved behind the VA firewall on a Durham HSR&D server (\\vhadurhsmcifs01.v06.med.va.gov or \\vhadurhsmcifs01.v06.med.va.gov).

All hard copies of documents (e.g., consent forms, case report forms) will be stored in the office or lab space of the PI. Electronic data files will be password-protected and maintained on a password-protected VA server, with access only available to approved study staff and investigators. This includes the study database, which contains the link of study identification numbers to identifying information. All data will be retained for at least 10 years and will be destroyed according to VA guidelines. The removal of access to research study data will be accomplished for study personnel when they are no longer part of the research team.

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