The Clinical Genomic Studies Unit (CGSU) at the Institute for Genome Sciences and Policy (IGSP) will serve as the Clinical Coordinating Center and Data Coordinating Center for this study.

The Coordinating Center (CC) responsibilities include study design, project management, data acquisition and storage, QA, statistical analysis, site coordination and training, as well as thought leadership. The policies and procedures of Duke Office of Clinical Research (DOCR) and the CGSU serve to assure appropriate standards are met, including federal regulations of privacy and security and also to assure that analyses are validated prior to publication.
The main responsibilities of the Coordinating Center will be: 1) Protocol development; 2) Dissemination of DUHS IRB approved protocol and all related documents (e. g. consent form templates, recruitment materials, surveys) to participating sites; 3) Conducting site visits for site assessment and personnel training; 4) Providing a central study coordinator to facilitate subject enrollment (creating subjects accounts for the online study access); 5) Data management and analysis; 6) Overall study monitoring to ensure sites compliance with regulatory requirements.

Each site is responsible for the selection of their research subjects recruitment. There are two populations of subjects – providers and patients. Consenting providers is the responsibility of the enrolling sites. Coordination of patients online consenting is the responsibility of the Coordinating Center. The Coordinating Center will confirm that all enrolled subjects provided informed consent. The CC does not have a role in assessing subject's capacity to give legally informed consent. The protocol does not allow the inclusion of subjects unable to provide informed consent.

Purpose of the Study – The purpose of this study is to address the key question of whether and how family health history (FHH) is adopted as a tool to more efficiently manage patients at risk for breast, colon, ovarian, and hereditary cancer syndromes as well as thrombophilia and coronary heart disease (CHD) and to provide evidence supporting clinical utility -- improved health behaviors in patients and physician screening recommendations. Five health care delivery organizations will participate in this demonstration project: Duke University, the Medical College of Wisconsin, the Air Force, Essentia Health, and the University of North Texas Health Science Center. The study will take place in 'real world' clinical, socio-cultural, and demographically diverse (rural, underserved, academic, family medicine) clinics (n=34) in 5 states (CA, MN, NC, WI, TX) that include genomic medicine 'early adopter' and 'naïve' sites, as well as those that are EMR-enabled and others that are not, and will use a cluster randomized controlled pragmatic hybrid type III implementation-effectiveness observational study design. We anticipate enrolling **7000 English or Spanish speaking adult participants (at a minimum) over a 3-year period**; to reach this goal we need to enroll ~300 participants from each intervention clinic (assuming 10 of the 34 clinics will be dedicated controls). Specifically we will use Healthcare Effectiveness Data and Information Set (HEDIS) measures as intermediate clinical effectiveness measures for CHD and the selected cancers as well as survey/formative data and electronic medical record (EMR)

data as outcomes measures. The research model is purposely designed to mimic clinical delivery as an important step toward widespread implementation and sustainability. In addition we will use a cost-effectiveness analysis to compare usual care to the FHH guided preventive health model. **The completion of this project will result in an optimal strategy for integration of FHH data collection and clinical decision support (CDS) tools into an EMR and demonstrate the utility of the FHH intervention among diverse primary care patients, their settings, their providers, and the health systems that deliver their care.**

Specific Aim 1: To optimize the collection of patient entered FHH in diverse clinical environments for coronary heart disease, thrombosis, and selected cancers

Specific Aim 2: To export FHH data to an open clinical decision support (open CDS) platform and return CDS results to providers and patients (and to EMRs where relevant). To explore the integration of genetic risk and FHH data at selected sites.

Specific Aim 3: To assess the clinical and personal utility of FHH using a pragmatic observational study design to assess reach, adoption, integrity, exposure, and sustainability, and to capture, analyze, and report effectiveness outcomes at each stakeholder level: patient, provider, and clinic/system.

Specific Aim 4: To take a leadership role in the dissemination of guidelines for a FHH intervention across in diverse practice settings.

Background & Significance – In 2002 the CDC launched the Family History Public Health Initiative, founded upon the principle that family history is an underutilized but effective tool for risk stratification. Among the stated goals were to develop tools to enhance family health history (FHH) collection and to evaluate whether FHH-based strategies work in practice. Because primary care providers account for the majority of care encounters in the US they are a natural choice as partners to study the implementation of FHH into care delivery and medical decision-making.

FHH assessments have clearly been shown to identify persons at higher risk for common chronic disease, enabling preemptive and preventive steps, including lifestyle changes, health screenings, testing, and early treatment as appropriate[1]. More recently Qureshi has shown prospectively the potential *to identify presymptomatic individuals at elevated risk for common, chronic diseases and activate them to modify their risks*[2] *- an enormous opportunity to improve public health by implementing risk-based screening and prevention strategies.* Yet, although FHH is a standard component of the medical interview and professional guidelines recommend screening strategies based upon FHH, its widespread adoption is hindered by three major barriers: (1) standard collection methods; (2) health care provider access to FHH information; and (3) clinical guidance for interpretation and use of FHH.

The Rationale for Using FHH Tools. FHH is underutilized by practitioners and therefore represents a significant missed opportunity for risk stratification[3]: a systematic review found a 46-78% improvement in data recording by FHH tools as compared with the use of standard practice[4]. FHH tools show excellent concordance with structured pedigree interviews and the gold standard three-generation pedigree[5]. In a study of 1124 primary care patients not only was medical record documentation insufficient in two-thirds of charts for FHH assessment of six common diseases, but also 23% had no evidence of risk in their medical record yet had a moderate or strong risk for at least one disease as assessed by the Family Healthware™ tool[6].
FHH collection, analysis, and risk stratification can be performed efficiently and effectively using a variety of software platforms that have the potential to overcome the barriers created by a reliance on physicians to gather, record, and analyze FHH. Implementation of automated FHH linked to clinical decision support (CDS) is feasible in the community setting as shown by use of HughesRiskApps in over 25,000 individuals, leading to referral of 3.6% of patients for breast and ovarian cancer genetic counseling and consideration of genetic testing[7]. In our own experience using the MeTree™ FHH tool, the mean completion time by 1320 primary care patients was 23 minutes, and 35% were classified as having strong or moderate risk for at least one of five common diseases. It is absolutely clear that to elicit information for a comprehensive FHH is a significant time commitment making it clear that *patients, not physicians*, need to serve as the main locus for data input.

Electronic Medical Records and FHH. The American Health Information Community (AHIC) Personalized Health Care (PHC) Workgroup, part of the U.S. Department of Health and Human Services (HHS) Personalized Health Care Initiative, has put significant effort into developing standards for incorporating FHH into the electronic medical record (EMR). However, there are important roadblocks to realizing the full potential of FHH: for example, for the ~150 EMR vendors, FHH information is primarily recorded as free text and no EMRs have graphical pedigree drawing functions. In addition, among the few structured data sets, none are compliant with the AHIC core data set standard[8]. Highlighting the fact that EMRs do not provide a solution to FHH capture, in query of data from the EPIC EMR at Medical College of Wisconsin in ~ 721,000 patient encounters 85% lacked a FHH, and only 1% of records had recorded three generation data (Dimmock D, personal communication). Stand alone software packages may provide the needed functionalities such as pedigree-drawing, and algorithms but none of these are interoperable with EMRs and EMR vendors avoid linking one-off programs to their own packages. A key point is that CDS (see below) capabilities remain limited in most EMRs and are virtually non-existent for FHH. In the current proposal we will use a modular approach whereby FHH collection is centralized, key data elements are exported to a program that applies specific algorithms, and the data are then returned to the EMR where CDS strategies can be applied[8].
Clinical Decision Support. CDS is a critical prerequisite to realizing the full potential of the EMR to facilitate evidence-based medicine[9]. HHS, the CDC, and the Secretary's Advisory Committee on Genetics, Health, and Society have designated Health Information Technology and CDS as priorities for achieving the goals of personalized

medicine[10-12]. The goal of CDS is "to provide the right information, to the right person, in the right format, through the right channel, at the right point in workflow to improve health and health care decisions and outcomes" and a roadmap has been developed to achieve this goal[11]. A systematic review found that adoption of CDS significantly improved clinical practice with a 94% success rate when CDS provided computer-generated recommendations at the point of decision-making and was integrated into the clinical workflow[13]. This proposal will develop an open source risk-stratified CDS system that can be accessed by diverse EMRs. We will adopt the standards for FHH to exchange, integrate, manage, and share key data elements that were developed and approved by HL-7 (Health Level 7)[14].

Clinical utility of FHH. Qureshi et al.,[2] recently implemented systematic collection of FHH for cardiovascular risk assessment in 24 family practices in the UK using a pragmatic cluster randomized controlled trial design, and demonstrated a highly significant (40%) increase in identification of individuals at high risk. Surprisingly, given that the study was not powered to detect a difference in health behaviors, there was also a highly significant increase in successful smoking reduction or cessation in the intervention group compared to controls. This was the first rigorously designed prospective study to show that systematic collection and use of FHH in a primary care setting can improve risk stratification and health behaviors for CHD and provides an important proof of concept for the work in this proposal. However, in general, the gold standard of a randomized clinical trial (RCT) has not been achieved for FHH. Challenges faced by RCTs including feasibility, expense, and applicability to 'real world' situations, make comparative effectiveness research (CER) and pragmatic implementation trials an appealing solution. CER broadens the scope of methodologies to include not only RCTs but also decision analysis and observational studies[15].
Clinical utility of an FHH intervention can be established using measurable outcomes that include clinician and patient behaviors, as well as mechanisms that facilitate these behaviors[16]. Provider behaviors include the use of optimal decision-making, counseling the patient, and direct the use of medical services. Mechanisms that promote these behaviors include perceived value of FHH and risk, competencies to collect and discuss FHH, and education. Patient behaviors include increased or reduced screening and use of preventative services, and improved lifestyle behaviors (e.g., diet, exercise, and smoking cessation). Mechanisms such as patients' perceived value of FHH, their ability to obtain the information, family communication, and especially patients' risk perception affect patient behaviors. This approach was highlighted in two studies at the NIH State-of-the-Science Conference - one showed improvement in mammography screening, breast self-examination and clinical breast examination with systematic collection of FHH in a primary care/general population setting[17]. The other, the Family History Impact Trial[18] coupled one-time tailored messages to computerized FHH in 3786 healthy primary care patients and assessed self-reported behavior change at 6 months. Those in the intervention group showed increased fruit and vegetable consumption and improved physical activity[19]. Use of a touch-screen kiosk in a comprehensive cancer clinic was associated with increases in cancer screening and prevention behaviors and communication with family members[20].

Design & Procedures – This study will: 1) utilize a software platform entitled MeTree, which electronically captures participant-entered FHH and links to a web-based risk stratification and CDS system for prevention of CHD, breast cancer, colon cancer, and hereditary cancer syndromes. The risk stratification and CDS system pull together established, standard of care guidelines and validated risk calculators in one place to facilitate provider decision making. The output (pedigrees and reports with evidence-based risk stratified prevention recommendations) will be integrated into the EMR, and capture patient behaviors and attitude changes through a series of web-based computer surveys; and 2) provide just-in time education embedded within the CDS output to activate patients and providers and improve awareness of and adherence to FHH risk-stratification and risk-stratified prevention plans.
Multiple clinics at each participating institution will be recruited to participate, but providers will individually be able to participate at their own discretion. One comparator clinic will be randomly assigned as a "control" to be used to assess any changes in the standard clinical care between the participating clinics and the control.

This study will also include the administration of an Organizational Readiness to Change (ORCA) survey to identified personnel at each participating clinic, and followed by qualitative interviews for key personnel (Key informant interviews) identified at each participating clinic. .

ORCA survey design: an Organizational Readiness to Change Assessment (ORCA) will be administered as a survey by the Duke coordinating center personnel through a web-based electronic data capture program, with personnel in identified roles (provider, nurse, administrator) within participating clinics from each of the five health systems. Survey completion will occur prior to the implementation of the MeTree family health history tool, and will provide information about the organization's climate and culture about integrating and implementing change.

Key informant interview design: Individual semi-structured qualitative interviews will be conducted over the telephone with key informants from each of the five health systems. Interviews will occur prior to and post-implementation. Pre-implementation interviews will provide information about barriers to implementation of MeTree, which will allow us to develop a tailored implementation plan at each site. Post-implementation interviews will provide information about the success and outcomes of the implementation of MeTree. Interviews will be conducted by telephone by Drs. Voils and Sperber of Duke University Medical Center, who are experienced interviewers with qualitative research expertise. The conversations will be audiorecorded and transcribed, and data will be analyzed using content analysis.

Providers will be consented in person by local staff at each participating Institution during the pre-implementation phase (first six months of the study) and will receive FHH and education about the Genomic Medicine Model. After providers are consented, they will undergo formative evaluation to assess the needs of their clinic for optimal

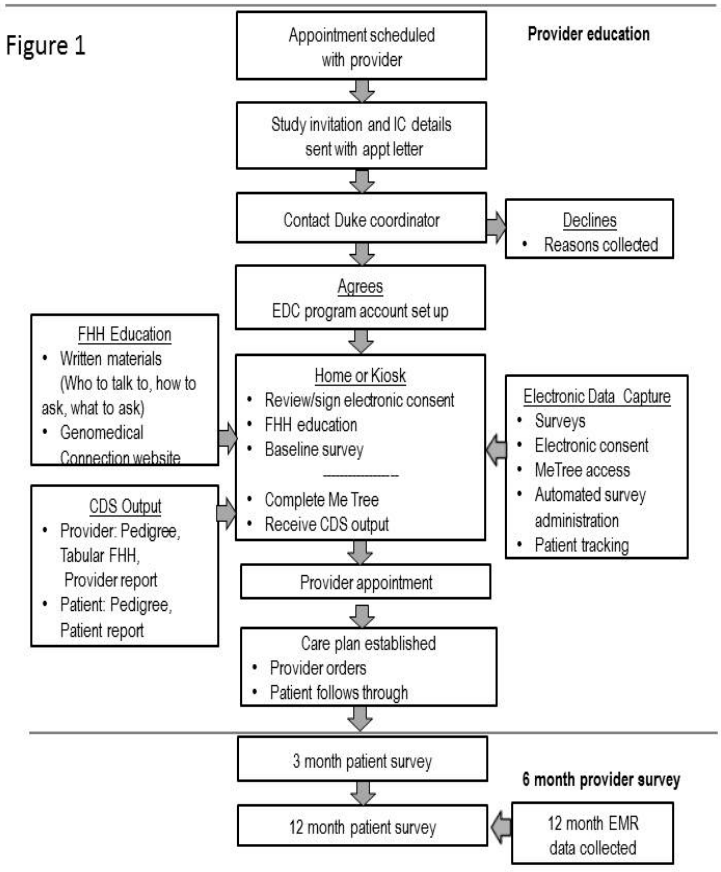
integration of the system and complete a web-based survey at 6 months to assess their response to the intervention and to inform adaptations to improve efficiency and efficacy.

ORCA survey participants will be invited based on their role of provider, nurse, and administrator in participating clinics within the five health systems. The number of survey respondents will depend on clinic composition and degree of heterogeneity in clinic organization. We anticipate inviting 365 providers and roughly an equal number of nurses and administrators – for approximately 450 respondents.

Key informants will be selected based on their role at each clinic. To obtain necessary information, we will sample physicians, nurses, and schedulers. The number of key informants to be interviewed will depend on clinic composition and degree of heterogeneity in clinic organization. For example, if two clinics within a health system are highly similar in organization and planned implementation procedures, then we may interview only one scheduler to represent those two clinics. The number of key informants should be sufficiently large to capture varying organizational structures, viewpoints and experiences with MeTree implementation, yet small enough so as to be feasible. We anticipate interviewing 40-80 key informants.

Participants will be enrolled through a central Duke research coordinator. Electronic consent, survey administration, FHH education and MeTree™ access will be web-based. They will have access to assistance for questions, but will view all educational resources electronically and collect and enter their own FHH from a computer, mobile device, or a dedicated clinic kiosk. After receipt of CDS output (pedigree, tabular FHH, and provider report for providers and pedigree and patient report for patients), the clinical encounter proceeds as usual. Participants may receive reports through a personal health record, patient

Figure 1



portal, email, or clinic printer, depending on the optimized process for each individual clinic setting.

Once enrolled, each participant will be provided an account to the electronic data capture system, through which the participant will first sign the electronic consent form As of 04/08/2016 the study team has implemented and will continue to follow "Procedure for Updating Consent Documents.IT.SOP" located in the Full Protocol of the eIRB. , and then access the computer survey program and the MeTree family health history collection tool. For this process, they will electronically be provided education about how and what to collect for FHH; along with materials including brochures and a worksheet. In addition, they will be educated about the electronic surveys, electronic consent process, benefits and risks of study participation, how to use MeTree (the FHH collection tool), how to receive their CDS output, and who to talk to about questions. Each consented participant will then complete the baseline survey prior to the scheduled primary care provider visit. The baseline survey is re-administered with a request to the participant via email at 3 and 12 months to capture changes in health related activities, activation and risk perceptions. Patients or providers can communicate their desire to discontinue participation at any time to the study coordinator or the PI (figure 1).

Standard health behavior surveys (SF12 and PAM) will be used to collect data covering diet, exercise, knowledge, screening practices, activation, attitudes and perception of risk for cardiovascular disease and the study cancers, and family health history. Each subject will be assigned a Unique Study ID and only trained research staff will have access to the list of IDs and patient names, for the purpose of tracking surveys and collecting medical record data.

Resulting outcomes data, including all referrals, diagnoses, laboratory and genetic test results, medical procedures, office and ER visits, hospitalizations and medications that occur will be abstracted from patient medical record files prior to patient enrollment and throughout the study period by the participating clinics after patient participation has been concluded at each site and provided to the Duke statistical analysis team with only the patient's unique ID number.

Selection of Subjects –
Population: Study subjects will be comprised of providers and patients at the diverse clinics within in each of the 5 organizations (Duke University, Medical College of Wisconsin, Essentia Health, University of North Texas Health Science Center, and the Air Force).

Providers: all providers in the participating clinics will be selected to be included in the study. We anticipate 100% participation, for an expected enrollment of 365 providers.

ORCA survey participants will be providers, nurses, and administrators at participating clinics at each institution which are involved in MeTree implementation.

Key informants will be providers, nurses, and schedulers at each participating clinic which is involved in MeTree implementation.

Patients: All adult English or Spanish speaking patients scheduled for non-acute visits within 2 weeks will be invited to enroll when they schedule an appointment with their physician. Since this proposal focuses upon prevention and not disease management strategies, those with a study disease (breast, or colon cancer, hereditary cancer syndromes, or CHD) will not be excluded from enrollment but will be excluded from analyses relevant to their disease. We anticipate enrolling 7000 participants at a minimum (to achieve significance for effectiveness measures), but as an observational study will continue to enroll as many as are interested in order to maximize our ability to assess differences across settings, populations, and sociodemographic factors. To reach this goal we need to enroll ~300 participants from each intervention clinic (assumes 10 of the 34 clinics will be dedicated controls). Assuming 20% enrollment (from MeTree™ pilot -see preliminary data), we anticipate being able to enroll at least 9,100 participants.

All documents (consent forms, educational brochures, surveys, etc) will be translated as appropriate to Spanish-language version. The MeTree software program user interface will also be translated into Spanish with a choice for the participant to have it displayed in English or Spanish.

Subject Recruitment and Compensation –
Provider recruitment will involve invitations to providers through telephone, letter and email communication from the study PI and/or his designee to invite participation in qualitative research regarding the integration of family health history, risk stratification and clinical decision support for their patients.

ORCA Survey participant recruitment will involve the collection of appropriate personnel at each participating clinic from each institution. Potential survey respondents will receive a recruitment email (see attached recruitment email) describing the study, purpose of the survey, risks and benefits and other elements of informed consent, and a link to the web-based electronic data capture program that hosts the ORCA survey.

Key informant recruitment will involve the collection of appropriate key informants from each site champion. Potential key informants will receive by e-mail a recruitment letter (see attached recruitment letter) describing the study and purpose of the interviews. When key informants respond to the invitation letter and state that they want to participate, the Duke scheduling coordinator will schedule a time for the interview and email the informed consent document (see attached email consent document) with the time/date for the interview.

Recruitment flow for ORCA survey participants and Key informants will be as follows:
Week one: Initial invitations to potential ORCA survey participants are sent

Week two: Reminding invitations to potential ORCA survey participants are sent
Week three: Initial invitations for qualitative interviews to potential Key informants are sent
Week four: Reminding invitations or follow up phone calls for qualitative interviews to potential Key informants are initiated to those who have not responded.

Patient recruitment will be initiated with requests to participate mailed when a well visit appointment is made or a reminder sent from the scheduling service at each intervention study site. Each invitation will include all the elements of informed consent, including a description of the study, its risks and benefits, further information about the surveys and description of the electronic consent process. Those who are interested will contact the central Duke study coordinator who may briefly review the study again. If the patient is interested, the Duke study coordinator will provide the participant with a web-based computer survey program account where they will complete the enrollment and consent process.

If the invited patients do not respond within the expected time window prior to their scheduled appointment the local site coordinators may follow up with a phone call to provide additional information about the study and to encourage their participation. If during this phone call patients express interest in enrolling the site coordinator will advise them to call Duke central office directly or will offer to contact Duke on their behalf. If latter, local site coordinators will collect/verify the following information and will submit in a secure email to support.familyhistory@duke.edu:

a. name (first, middle if any, last)
b. email address (this will be the participants login, and to which all emails will be sent)
c. did they set up this email specifically to participate in this study?
d. institution
e. verification that the participant is 18 years of age or older
f. phone number
g. gender
h. date of birth
i. clinic name
j. provider name
k. appointment date
l. preferred language (English / Spanish)
m. Medical record number or local unique identifier

Upon receipt of this information Duke study coordinator will complete the registration and notify participant via email. The local site coordinator will monitor this process in the site specific census.

There will be no compensation to provider, other clinic personnel, or patient participants.

Consent Process:

Providers will be consented in person by local study staff at each participating Institution after they have been provided with onsite education (by the local study staff) about the study and as to why they would want to participate. Should they agree, they will sign the consent form and receive an electronic survey link via email.

ORCA survey participants will have an implied consent process. The potential survey respondent will receive a recruitment email with all the elements of informed consent and it is expected that participants who access the survey are actively consenting to the study through the action of accessing the survey and completing it.

Key Informants will be contacted and consented separately for pre-implementation and post-implementation interviews. At the beginning of the conversation, the study interviewer will confirm that the participant received the written information about the study and consent process. If the key informant states that s/he has received the information, then the interviewer will reiterate key parts of the consent information that was emailed, including the purpose of the study, the key informant's rights as a study participant, and the confidentiality of the interview (see attached verbal informed consent document). If the key informant states that s/he has not received or reviewed the consent information, then the interviewer will read the informed consent document verbatim and email another copy of the informed consent document. All key informants will be asked if they agree to participate in the study and have the interview audio recorded. For participants who agree to audio recording, the interviews will be recorded using an approved digital recording device. For participants who do not agree to audio recording, the interviewer will take copious notes on a memo template and will not record the interview. Study interviewers enter will keep an electronic verbal consent log (e.g., in an Excel spreadsheet).

Interviewers will use an interview guide, which contains open-ended questions that direct the interview in a natural topical flow and suggested probes for more in-depth information, as is standard with semi-structured interviewing. The interview guides for this study were created based on theoretical constructs from Weiner's Theory of Organizational Readiness for Change and specify questions relevant for each type of key informant (physician, nurse, scheduler). The pre-implementation guide contains questions relevant to understanding policies and barriers that may affect implementation; the goal is to inform a tailored implementation plan for each site. The post-implementation guide contains questions relevant to understanding experiences and outcomes of MeTree implementation.

Patients will be consented via an electronic consent process: each is provided via email a web-based computer survey program account in which a full version of the consent form is initially presented and electronically signed and dated by the participant to complete the consent process. Once signed, the participant is provided access to the baseline survey, the MeTree program for completion of family health history, and education about collection of FHH. Access to these online tools will be available from

computer or mobile device via the web or the clinic via a kiosk. In addition, a local study coordinator will be available for assistance.

Subjects' Capacity to Give Legally Effective Consent – Subjects who cannot give legally effective consent will not be included in the study since they would not be able to adequately perform the risk assessment or survey evaluations.

Study Interventions – see Design and Procedures section

Risk/Benefit Assessment –
Risks: Potential risks to the subjects include anxiety related to family health history results and breach of confidentiality of their study data. 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. Patients and providers will discuss CDS output during their appointment and study and clinical staff are available if needed.

Provider participants do not have any anticipated risks.

The alternative for potential participants is not participating in the study.

Benefits: Two aspects of the study will provide information that will improve patient care in primary care: 1) Enhancing primary care physician decision making by the application of individualized evidence-based algorithms based on patient characteristics and 2) Enhancing patient decision making by using active patient facing tools to promote patient engagement and activation. Overall we anticipate greater patient and provider satisfaction and the potential for streamlined workflows with improved information exchange. Risk stratification with decision support can assist in decision making for both patients and providers by 1) increasing knowledge, 2) lowering uncertainty, 3) reducing the likelihood of indecision, and 4) increasing the match between decisions and values. These effects have both cognitive and emotional components that can influence “decisions” by shifting perceptions of: disease, disease risk, treatment, and treatment benefits. Patients are also given a copy of their pedigree which can be shared with and distributed among family members as well as retained by the patient as documentation of their effort to collect the family history and to share with other clinical providers involved in their care.

Costs to the Subject – There will be no costs to patients or providers for their participation, though it does requirement a small time commitment.

Data Analysis & Statistical Considerations – *Effectiveness data* will be summarized with descriptive statistics and plots. Generalized linear ordinal regression models (GLO)(the function ordglm from the R statistics package) will fit ordinal survey outcomes to the continuous outcome variables. Associations will be considered significant when the regression coefficient is not zero; a false discovery rate of 5% will be used to correct

for multiple comparisons. Multivariate analysis will control for clinic and provider. A p-value of <0.1 in stepwise regression will identify significant factors such as demographics, intent to change, and their interactions. The analyses for the multiple outcomes will follow the same procedure as the survey outcomes but using a logistic regression model that includes the 7 covariate factors (see sample size section). Although the study is implemented at the level of the clinical practice, the likelihood of clustering is low given that all participants undergo the intervention and the intervention is aimed at both the patient and the provider; however, to address the possibility of clustering, we will calculate a design effect; if it is 1 we will use standard tests and generalized linear mixed models with clinic and state as random effects, if not we will adjust the confidence intervals using a conditional logistic regression. Effect size bias is extremely unlikely in this study as all individuals within the clinics are offered the intervention, preventing the imbalance in treatment assignment that can lead to inaccurate point estimates.

ORCA survey data will be analyzed using this validated survey's scoring method. The results will be used to categorize institutions and/or the individual clinics according to their flexibility for adapting to new ideas/technologies, which will then be included as an explanatory variable in the analysis of the effectiveness data captured during the trial as well as to help understand barriers encountered during the implementation process.

Key Informant Interview data analysis will proceed with an initial review of the transcripts conducted independently by study investigators. Each coder will identify major thematic categories included in the *a priori* theoretical model and emergent categories. The coders will work together to develop a revised schema for content coding. Once the schema has been finalized, the coders will code the transcripts for relevant categories and have discussions that may lead to further revision and refinement of the code book. Findings from the pre-implementation interviews will be used to create a tailored implementation plan at each site.

As of 01/20/2017Corrine Voils is no longer on key personnel for this protocol, however she has been added to outside key personnel and will assist with writing study publications. She will see data summaries only, and not individual data.

Data & Safety Monitoring – Dr. Ginsburg, the study PI, Dr. Orlando, the Co-I, and Dr. Ginsburg's designees will be responsible for monitoring adverse events that occur as a result of participation in this study. They will also oversee that all appropriate measures are taken to ensure data security.

Privacy, Data Storage & Confidentiality – Each subject will be assigned a Unique Study ID and only trained research staff will have access to the list of IDs and patient names for the purposes of scheduling follow-up surveys tracking subject participation. All survey and family health history data will be entered through a web-accessibly software program (each subject will have a unique login and password) and saved on a

Duke University Health system server that is HIPAA compliant and where applicable, GINA compliant. All data will be gathered and stored using protocols and privacy & security standards that comply with HIPAA and, where applicable, GINA. All patient family health history 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. All data gathered for the proposed studies will be treated with the same degree of confidentiality as a medical record. Only group information without personal identifiers will be included when sharing process implementation data and outcomes with approved collaborators.

ORCA survey data will be stored on a secure server in the same manner as the data collected from patients. Datasets will be downloaded and de-identified for analyses. These datasets will be kept on a shared departmental server.

Key informant interviews: The audio recordings will be stored on a pass-word protected folder on the Duke server accessible only to study staff. The recordings will be reviewed by the study team and transcribed by a transcription service contractor. The de-identified transcripts will be analyzed with approved qualitative coding software.

In compliance with NIH Genomic Data Sharing (GDP) Policy collected MeTree data will be deposited in the **d**ata**b**ase of **G**enotypes **a**nd **P**henotypes (dbGaP). The data elements to be released are listed in Appendix A.

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APPENDIX A.

MeTree data elements for release to dbGaP

Demographics:

- Gender:
  - Male
  - Female
- Age
- Race:
  - American indian or alaska native
  - Asian
    - Asian indian
    - Chinese
    - Filipino
    - Japanese
    - Korean
    - Vietnamese
    - Other asian
    - Unknown
  - Black or african-american
  - Native hawiian or other pacific islander
    - Chamorro
    - Guamanian
    - Native hawaiian
    - Samoan
    - Unknown
  - White

- Ethnicity:
  - Hispanic or latino
    - Central american
    - Cuban
    - Dominican
    - Mexican
    - Other hispanic
    - Puerto rican
    - South american
  - Ashkenazi jewish

Not hispanic or latino

Vital signs:

Blood pressure
Weight
Height
Waist circumfrence

Labs:

LDL
HDL
Total cholesterol
Hs-CRP
CA-IMT
Calcium CT score
HgbA1c

Diseases and age of onset:

These are collected about the individual and about their family members so assume they would need to be identified using different mechanisms.

Abdominal aortic aneurysm
DVT
Factor V Leiden Mutation
Prothrombin mutation
Antithrombin III deficiency
Protein S deficiency
Protein C deficiency
Cancer
- Cancer that isn't one of specific ones below
- Bone cancer
- Brain cancer
- Colon cancer
- Esophageal cancer
- Renal cell carcinoma
- Leukemia
- Hepatocellular carcinoma
- Lung cancer
- Sarcoma
- Ovarian cancer
- Pancreatic cancer
- Prostate cancer
- Rectal cancer
- Skin cancer (any type)
- Small bowel cancer

- Stomach cancer
- Thyroid cancer
- Uterine cancer

Hereditary cancer syndrome
- Syndrome that isn't one specified below
- Cowden or listed PTEN gene mutation
- Familial adenomatous polyposis or listed APC gene mutation
- Hereditary Breast and Ovarian or listed BRCA mutation
- Li-fraumeni syndrome or listed TP53 gene mutation
- Lynch or listed MLH1, MSH2, MSH6 gene mutation

Carotid stenosis
Dementia
Diabetes type 1
Diabetes type 2
Gestational diabetes
Colon polyp
Crohn's disease
Irritable bowel
Ulcerative colitis
GI disorder (other than the 5 listed above)
Atrial fibrillation
Heart attack/CAD
Heart disease not listed above 2
Hereditary cardiovascular syndromes
- Syndrome that isn't one specified below
- Long qt
- Brugada
- Catecholaminergic polymorphic ventricular tachycardia
- Hypertrophic cardiomyopathy
- Left ventricular non-compaction syndrome
- Arrhythmogenic right ventricular dysplasia
- Any cardiomyopathy
- Ehlers danlos
- Marfan
- Familial hypercholesterolemia

Hyperlipidemia
Hypertension
Poly Cystic kidney disease
Diabetic nephropathy
Nephrosis
Nephritis
Nephrotic syndrome
Kidney disease (other than the 5 listed above)
Alpha 1 antitrypsinase deficiency
Auto immune hepatitis
Hemochromatosis
Primary biliary cirrhosis

Sclerosing cholangitis
Wilson's disease
Asthma
Copd
Chronic bronchitis
Emphysema
Lung disease (oter than 4 listed above)
Systemic lupus
Multiple sclerosis
Osteoporosis
Peripheral arterial disease
Alcohol abuse
Drug abuse
Anxiety
Add/adhd
Autism
Bipolar disorder
Depression
Eating disorder/bulemia/anorexia
Obsessive compulsive disorder
Panic disorder
Personality disorder
Ptsd
Schizophrenia
Social phobia
Rheumatoid arthritis
Ischemic stroke
Hemorrhagic stroke
Thyroid disease (any type)

Medically related

- Menopause
- Age at Menopause
- Taken hormone replacement therapy in the past
- Currently taking hormone replacement therapy
- Pregnant, breastfeeding, or taking the medication tamoxifen or raloxifen
- Had pre-eclampsia, pre-term birth, or birth of infant small for gestational age
- Hysterectomy
- Uterine hyperplasia
- Radiation therapy to the chest between the ages of 10 and 30
- Breast biopsy
- More than 1 breast biopsies
- Breast biopsy with hyperplasia
- Breast biopsy with atypical hyperplasia
- Breast biopsy with lobular carcinoma in situ
- Unknown breast biopsy result

- Age first menstrual cycle
- Age of first live birth

Family related

- Were you born a twin (for you and family members)
- If twin are you identical or fraternal (for you and family members)
- Were you adopted (for you and family members)
- Are your parents consanginous (only you)
- Still alive (only family members)
  - -- if yes age
  - --if no cause of death (accident, cancer, diabetes, heart disease, infection, lung disease, natural causes, SIDS, stroke, unknown, other)
  - --if no, age of death

Diet/Exercise

- Average cups of fruit you eat per day
- Average cups of vegetables you eat per day
- Do you eat more whole grain products than refined flour products
- Average times per day you eat salty or sugary foods
- Do you eat more monosaturated fat than trans- or saturated fats
- Average days per week performing moderate exercise for 30 min
- Average days per week performing vigorous exercise for 20 min
- Average days per week performing strength training

Tobacco

- Tobacco packs per day
- Tobacco number of years
- Tobacco year that you quite