



# Cancer Health Assessments Reaching Many (CHARM)

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PROTOCOL | NOVEMBER 11, 2019 (V.29)

# CHARM Protocol

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## 1. Protocol Title

Cancer Health Assessments Reach Many (CHARM) [Proposal Title: Exome Sequencing in Diverse Populations in Colorado & Oregon (CSER2)]

## 2. Objectives

Clinical genomic sequencing is now being used routinely, primarily at academic medical centers, for a range of clinical contexts including evaluation of developmental delay in children, following newborn screening for genetic diseases, analysis of tumors, and assessment of hereditary cancer risk. In addition, genetic services are routinely provided in prenatal, neonatal, pediatric, and adult primary care contexts for a broad range of evaluations. However, not all clinicians are aware of the current state of the science, and patients in community practice settings are less likely to receive these services. In addition, health disparities exist in access to and use of genomic applications for traditionally underserved populations. To address this health care inequity for genomic medicine, the National Human Genome Research Institute (NHGRI) launched the Clinical Sequencing Evidence-Generating Research (CSER) consortium to learn how to better deliver these services, and to provide the evidence and experience to ensure that health delivery systems provide equitable services to all patients.

This study is one of six sites funded by NHGRI's CSER consortium. The purpose of this consortium is to generate evidence on the clinical utility of genomic services in settings that serve diverse populations, study the "critical interactions" among patients, family members, health practitioners, and laboratories that influence implementation of genomic services, and to identify and address real-world barriers within healthcare systems.

Genomic services are a complex process that includes many more steps than just the testing itself. Figure 1 below from Scheuner and colleagues [1] demonstrates the steps in the three phases (preanalytic, analytic, postanalytic) of a genomic service. The "intervention" in our study includes all parts of a genomic service, not just the test.

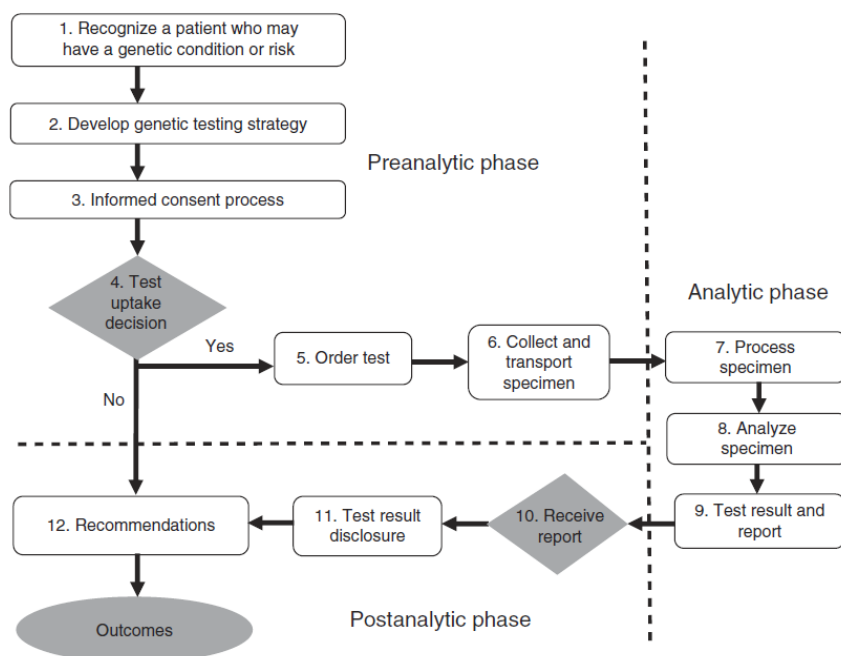


Figure 1. Steps in a genomic service.

The overarching premise of this research is that screening for hereditary cancer syndromes is a **medically necessary service of proven benefit and cost-effectiveness that is vastly underutilized in general, and especially underutilized in populations that are traditionally underserved, including both racial/ethnic diversity, as well as socioeconomic diversity.** We will leverage the evidence-based clinical recommendations for these disorders to advance the understanding of the utility of exome sequencing and genomic medicine in diverse and under-represented populations. Our decision to focus on hereditary cancer syndromes was driven by the needs of primary care providers in under-resourced settings who prioritize services that are both evidence-based and cost-effective.

Our specific study, CHARM (Cancer Health Risk Assessments Reaching Many) is similar to a “Program Project” given its large size/budget and broad scope. A Program Project grant supports a broadly based multi-disciplinary research program that has a central research focus. The central focus or theme of this research project is to investigate ways to reduce health disparities from differences in understanding and use of genomic services using the clinical context of hereditary cancer syndromes. The CHARM study includes multiple, inter-related projects, each with its own aims and hypotheses.

In the table below, we provide a high-level summary of the purpose and objectives of CHARM, but additional detail on the specific aims can be found in the grant application and analysis for these aims is described in the analysis section of the protocol.

PURPOSE		
<p>The <b>primary purpose</b> of this research is to investigate ways to reduce health disparities from differences in understanding and use of a genomic service for hereditary cancer syndromes.</p> <p>A <b>secondary purpose</b> is for clinicians and patients to gain experience with exome sequencing technology in the context of a well-established indication for genomic medicine (hereditary cancer syndromes) to better understand the needs of clinicians and patients, and to support more equitable use of exome sequencing for future indications.</p>		
OBJECTIVES		Grant Application Aims
Preanalytic Phase*	1) <u>Risk Assessment</u> : Adapt and implement existing, clinically validated tools (PREMM and B-RST) to identify individuals who may have a genetic condition or risk for use in populations with a range of literacy levels and into Spanish.	Aim 1A
	2) <u>Consent Process</u> : Design, implement, and assess a contextualized consent process to support informed decision-making in two steps about a) whether to have the genetic test, and b) whether to participate in research.	Aim 2A
	3) <u>Decision Aid</u> : Evaluate a novel decision aid for selecting optional categories of additional findings.	Aim 2B
Analytic Phase*	4) <u>Analyze Specimen</u> : Perform the genetic test and interpret sequence variants.	Aim 1B
Postanalytic Phase*	5) <u>Test Result Disclosure</u> : Conduct a pragmatic randomized controlled trial to compare traditional genetic counseling to modified genetic counseling.	Aim 2C
	6) <u>Systems to Support Recommendations</u> : Assess the impact of genetic testing on primary care providers and systems developed to help them manage patients at high risk for inherited cancer.	Aim 2D Aim 4A
	7) <u>Adherence to Recommendations</u> : Evaluate downstream impacts of genetic testing results, including healthcare utilization, family member cascade testing, and personal utility.	Aim 3A-D Aim 4B

\*The phases of the Steps in a genomic service are not the same as our Phase I and Phase II protocols submitted to the IRB.

### 3. Background

**Hereditary syndromes greatly increase cancer risk.** Individuals with hereditary cancer syndromes have up to an 80% lifetime risk of developing cancer. Indeed, about 1-2 in 200 individuals carry a variant associated with one of the two most common hereditary cancer syndrome—Hereditary Breast and Ovarian Cancer (HBOC) and Lynch Syndrome (LS) [2-6]. Identifying these patients is important because there are both preventive and risk-reducing measures available for both conditions [7,8] and research unequivocally shows that these interventions reduce morbidity and mortality[9,10,7,11-13].

**Despite recommendations for risk assessment, major care gaps persist in identifying at risk individuals.** Our studies have shown that less than 5% of individuals with a diagnosis of colorectal cancer (CRC) were tested for LS, despite the fact that 34% met criteria for genetics referral and testing [14]. Similarly, our preliminary data show that about 94% of individuals with LS remain unidentified. This highlights a care gap in diagnosing individuals prior to developing cancer. Under-diagnosis of hereditary cancer syndromes remains a substantial care gap despite few barriers to access.

**Populations may experience barriers differently.** The proliferation of genetic services may exacerbate health disparities [15]. With limited access to healthcare, for example, using information from genetic services may be aspirational for many Americans [16]. Indeed, large studies have shown that non-white racial/ethnic minorities face significant barriers to receiving genetic services [17]. Obtaining genetic services may impose too great a burden on low-income populations who may have difficulties keeping medical appointments due to inflexible working hours and transportation barriers[17-20]. Medical care like genetic services that require multiple office visits, extensive medical assessment, or primary care referrals are particularly vulnerable to access barriers[21]. Even when access is improved, testing may provide little benefit when patients experience significant barriers to follow-up services (e.g., mammography or risk-reducing surgeries) [22]. Insurance coverage for preventive interventions is variable and exacerbates health disparities by preventing some patients from receiving recommended follow up care [15].

**Minority populations are more likely to receive ambiguous test results.** In addition to reduced access to care, laboratories may experience difficulties when interpreting sequence variation for non-white individuals. This is because some populations, such as those with African ancestry, have greater genomic variation that is also less well understood. This is complicated by the fact that racial and ethnic minorities have been under-represented in genomic research and clinical genetic testing. As such, variants identified in individuals with ancestral diversity are more likely to be of unknown significance [23,24]. Resolving these issues will require research and clinical testing to include these populations in greater numbers. Exome sequencing may be a cost-effective approach to improve the diagnostic yield once testing is initiated.

**Objective 1, Risk Assessment:** Our prior work, and that of others, has demonstrated that family history information is often not collected or is not adequately collected for all patients [25,26]. We will adapt clinically

validated family history collection tools for use in populations with low health literacy or in languages other than English with input from patient stakeholders in Phase I of our study (planning/development). In Phase II of our study, we will use these adapted tools to systematically capture family history information and conduct risk assessments.

**Objective 2, Consent Process:** Prior work has demonstrated that even when risk assessments are performed in sufficient detail, they do not always generate an appropriate referral to medical genetics [27-29]. We will design, implement, and assess a consent process to support informed decision-making and increase appropriate referrals.

**Objective 3, Secondary Findings & Decision Aid:** Our program will offer optional, secondary findings for study participants. We would like to study: 1) ways for people to select which secondary findings that they want, 2) responses of individuals from more diverse settings and populations, and 3) reactions of providers from more diverse settings. Participants will have the choice of whether to receive optional results. We developed and will evaluate a novel decision aid for selecting these optional categories of additional findings. After approval of study mod 27, any participant that consents will no longer be given the option to receive carrier results. After approval of study mod 37, we will implement the decision aid so that half of people (randomly selected) see the original version for category selection and half of people see the new decision aid.

**Objective 4, Analyze Specimen:** We have partnered with the University of Washington to provide clinical sequencing and interpretation. We will also provide patients with information related to other medically actionable findings and carrier status that have evidence for medical impact and actionability. Carrier results will be removed from interpretation for participants who consent after approval of study mod 27.

Our testing for primary findings is a common part of medical care. Indeed, Kaiser Permanente offers a cancer gene panel for hereditary cancer syndrome testing. The genes that we are including are primarily on that panel or another panel offered by major clinical genetic testing providers. Professional guidelines recommend offering medically actionable secondary findings as part of standard care when exome sequencing is performed, and they have been well studied in prior research studies, including our study conducted at KP.

The University of Washington is a clinical provider that meets regulatory requirements of CLIA and CAP certification, which is what governs most genetic testing that is offered clinically in the US, including the tests that are used by the Medical Genetics department at KPNW. The University of Washington conducts clinical sequencing using an exome platform, regardless of the “test” that is ordered.

**Objective 5, test results disclosure:** Despite having a client-centered model of care, [30] research has documented barriers to communication in genetic counseling practice. These barriers include: “oral literacy demand”, [31] dominance of informational (compared with psychosocial counseling) dialogue, [32] and limited effort to provide relevance to patients [33]. Our modified “communication-focused” approach will consider principles and evidence-based strategies for effective communication with low health literacy (LHL) populations including: recognizing and adapting to limited literacy; limiting to patient-relevant information; avoiding

jargon;[34] assessing comprehension with teach-back;[35] using proven risk-communication strategies;[36-38] and a more directive approach[39]. Traditional counseling will follow the information-focused practices documented in the literature.

**Objective 6, Systems to support recommendations:** Even when patients are identified as having a pathogenic mutation for a hereditary cancer syndrome, it is challenging for both patients and providers to adhere to clinically recommended medical management. (Mittendorf, publication in progress , Grant 5R01CA140377-05I PI: Katrina Goddard) Providers note the lack of easily accessible information in the EMR about care recommendations for these patients [40], and patients lament the lack of automated reminders for recommended surveillance [41]. We will work with KPNW staff and providers to create a consensus statement on the standard of care for these patients. We will then facilitate the creation of a smartset to make medical management easier for the patient's PCP. The care guidelines that are created will be heavily informed by interviews we will conduct with PCPs that have patients with high-risk risk assessment results.

**Objective 7, Adherence to recommendations:** While the clinical utility of genomic services for hereditary cancer syndromes are well established in better served populations [42], we will document how their utility may differ for underserved populations. We will also assess personal utility, which may be an important aspect of benefit for populations with more limited access to health care.

#### 4. Study Design

We expect half of eligible patients to decline participation in our study. These individuals (decliners) will be our usual care group, if they do not specifically opt out of review of their EMR data. We will passively observe the usual care group through EMR prospectively for one year. All enrolled study participants will receive genetic testing for hereditary cancer syndromes including Hereditary Breast and Ovarian Cancer (HBOC) and Lynch Syndrome (LS) and other cancer genes. In addition, enrolled study participants can choose to receive optional additional results for other genetic conditions that are medically actionable or carrier status (carrier status eliminated for participants consenting after approval of study mod 27) for conditions that can be passed on to their children. After approval of study mod 37, during the consent process, English-speaking participants will be randomized 1:1 into two arms to receive or not receive the decision aid, stratified by site and using permuted blocks. One arm will have the usual consent information about secondary findings, and the other arm will have the decision aid. Those who enroll into the study will be randomized to receive traditional or modified genetic counseling for results disclosure. Participants who qualify based on limited family history and have negative test results will not be randomized into a genetic counseling arm and will receive their results by mail if they consented after approval of study mod 27.

We are amending the protocol phase II in study mod 27 to make 2 changes to the study design. 1) We will no longer give participants the option of receiving carrier status results after mod 27 is approved. 2) Participants that consent after mod 27 is approved who qualify to join the study based on limited family history will receive their results via a letter if all results are negative. Both of these changes will allow us to reduce the workload on the laboratory and genetic counselors so we can complete recruitment

sooner. This will allow for more participants to have complete (6 months) of follow-up before the study ends.

## 5. Study Population

### a. Number of Subjects

We expect to conduct the risk assessment tools with approximately 15,000 people at Kaiser Permanente Northwest (KPNW) and approximately 6000 Denver Health (DH). Of those, we expect about 800 people at KPNW and 300 people at DH will be eligible and consent to join the research study (50% consent rate), for a total of about 1100 enrolled participants (Note: our recruitment goal for analyses is 880). ~250 participants will be randomized into the two arms used for the decision aid activities.

We also will perform chart review and review EMR data on all KPNW patients that have had genetic testing for HBOC and LS. For analyses involving these subjects, we will exclude individuals in the Research exclusion database and the Genetics exclusion database.

### b. Inclusion and Exclusion Criteria

The inclusion criteria for the risk assessment are as follows:

1. KPNW or DH patient
2. Age 18-49
3. No known prior testing for familial mutations predisposing to LS or HBOC (based on participant report)
  - a) For patients that we outreach to because they are at a priori high risk for LS or HBOC, we will review a CHR data file providing information of known genetic testing results of KPNW patients to identify high risk patients who may benefit from the testing available in this study. Those patients who had comprehensive panel testing will be excluded from outreach efforts.
4. English or Spanish speaker

For the decision aid portion of the study, only English-speaking participants will be randomized into the two groups for those activities. Given that the launch of the decision aid will not happen until around November 2019, we will not have a large enough sample size of Spanish-speaking participants recruited during the study period to find significant results for that subpopulation during analysis.

For the genetic testing portion of the study, there is one additional inclusion criterion:

5. Screen at risk for a hereditary cancer syndrome via the risk assessment tools algorithms OR have insufficient information about their family history (e.g., because they are adopted)

The exclusion criteria are as follows:



1. Participant self-reported prior testing for LS or HBOC or identified previous comprehensive testing via the CHR data file for patients who are known to be at higher risk for LS or HBOC.
2. Not an English or Spanish speaker
3. Unable to provide informed consent
4. Patients that don't want their results placed in their medical record

Information on the creation of the CHR data file regarding genetic testing results of KPNW patients:

Members of the Genomic Strategy and Implementation Team within the KP National Quality department are working together with members of KP's Center for Effectiveness & Safety Research (CESR) project team to develop a database of genetic testing and results across all KP regions. This working group has approached external vendors (Ambry, Genedx, Invitae, Myriad and Fulgent) who perform clinical genetic testing services for inherited cancers as part of patient care and asked them to send to KP electronic data on genetic tests and results for KP members from all 8 regions. This database was designed by the working group, which is composed of members of both the Quality department and the CSER project. The data is received and maintained by personnel in the Quality department. Future plans indicate that other vendors (Quest, ARUP, Mayo, Consyl, Genomic Health) will be sending data to KP National Utility for Care Data Analysis (UCDA) as they can house and provide data for all KP regions and the KP sites will extract the data.

Patients will be screened for eligibility to join the study via the online risk assessment tools. We will use two risk assessment tools (PREMM and B-RST). The U.S. Preventive Services Task Force (USPSTF) has given conducting risk assessments for HBOC a 'B' recommendation, which means USPSTF recommends the service and there is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial. For B ratings, it is recommended by USPSTF that these services are provided. Of note, one of the tools we are using, B-RST is included in USPSTF's recommendation. Additionally, under the Affordable Care Act, health systems are required to provide services that receive an A or B grade recommendation from USPSTF. KP is currently implementing a similar risk assessment tool (Progeny) as part of KP's quality improvement activities across all KP regions (Kristen Janes, personal communication). Although we would have liked to use the same tool that KP is implementing, it is not available on the timeline needed for this study, and it is also not intended for a low literacy population, so we had concerns about the complexity of the Progeny tool given the goals of this research to be more inclusive. KP also has an internal practice guideline on the offer of genetic counseling and genetic testing services for hereditary cancer syndromes, which we have referred to in developing this study protocol. We did not find a similar internal practice guideline for DH.

To screen eligible via these tools, patients' results on the PREMM and B-RST algorithm must indicate one of the following:

- B-RST – determined to have greater than average risk for a hereditary breast and ovarian cancer syndrome based on the clinically validated algorithm.
- B-RST – there is insufficient information about their family to determine if they have greater than average risk for hereditary breast and ovarian cancer syndrome than most people (e.g., adopted or not many women in the family).

- PREMM – determined to have greater than a pre-determined threshold for Lynch Syndrome based on a clinically validated algorithm (The cut-off for PREMM score is  $\geq 2.5\%$ ; this was decided based on clinical validation and input from the developers at DFCL, one of our study collaborators).
- Limited Family History – there isn't enough information about cancer in their family for the screening questions to be helpful (e.g. adoption). Eligibility via limited family history is determined via answering the additional questions (Survey 3 in risk assessment tool). The first question qualifies a patient for the study if someone in their family has had a formal diagnosis of HBOC or LS, but the patient themselves has not been tested for the variant. The second question qualifies a patient for the study if they are adopted. The third question qualifies a patient for the study if they answer "no" to family history knowledge about both sides of the family. The final question will qualify a patient for the study if their answers to first- and second-degree relatives surviving beyond age 45 sum to less than 2 for either side of the family, in accordance with NCCN guidelines for limited family history/structure.

While diversity is not part of the eligibility criteria, as explained further below, some recruitment methods that do not occur in person (i.e., by mail, phone, or text) will only be used for individuals that meet the following diversity definition:

- Racial/ethnic minority
- Medicaid/Medicare insurance
- Low SES based on census (below poverty level; less than high school education)

#### Eligible Patients that do not enroll:

We will follow patients who are eligible but choose not to enroll through the electronic medical record throughout the study. Patients who are eligible and go through the consent process and decide they do not want to be in the study (e.g. choose a decliner option) will be able to choose to opt in or opt out of having their medical record reviewed. Additionally, if a patient is at one of the recruitment clinics with recruitment staff present and the patient does not want their medical record reviewed, they can inform CHARM recruitment staff of their decision in-person and their decision will be recorded. If the patient is going through the process online and does choose an option to have their medical record reviewed, we plan to include them in medical record review (see p. 11 "Modifications to Consent Process" for more detail).

The risk assessment will collect medical record numbers primarily so that we can include the result of the risk assessments in their medical record. However, this will also enable us to not intentionally reach out again to someone who is ineligible or declines.

#### Family Members of Study Participants:

Family members of study participants who are enrolled in the study and are found to have a variant (pathogenic, likely pathogenic, and VUS in select cases) that is associated with a hereditary cancer syndrome, or a pathogenic variant for a medically actionable secondary finding, will be eligible for genetic testing through the study.

We will offer to test certain types of family members (e.g. first and second degree relatives) who

are also at-risk for pathogenic or likely pathogenic variants in genes associated with hereditary cancer syndromes or pathogenic variants in genes associated with medically actionable secondary findings. We may offer family testing to participants with a VUS in a cancer-related gene; this will be determined on a case-by-case basis. Family members will sign a different consent form than regular study participants. Family members do not have to be KPNW or DH patients.

Family member inclusion criteria:

1. First or second degree relative of a study participant with a pathogenic or likely pathogenic variant in a gene for a hereditary cancer syndrome or a medically actionable secondary finding. Family members of participants with VUS in a cancer-related gene will be invited on a case by case basis.
2. Over the age of 18
3. Speaks English or Spanish

Family member exclusion criteria:

1. Under the age of 18
2. Known personal pathogenic mutation
3. Speaks a language other than English or Spanish

**c. Vulnerable Populations**

Children	Exclude	Only participants age 18 and older will be recruited.
Pregnant Women	Exclude	Pregnant women may be approached. We will not specifically target pregnant women for recruitment. Results are unlikely to impact pregnancy management as the pregnant woman would have to opt to receive carrier information, test positive for a genetic condition that could be passed on to the fetus, also have their partner tested, and receive this information during their pregnancy.
Neonates of uncertain viability	Exclude	
Prisoners	Exclude	
Decisionally Impaired Adults	Exclude	We will not target decisionally impaired adults in our recruitment. If we learn that someone who is decisionally impaired has consented for the study (online), we will withdraw them from the study.
Non-English Speakers	Include	Non-English (Spanish) speakers will be approached by Spanish-speaking recruiters/translators and provided Spanish language recruitment and consent materials. We will not recruit individuals who only speak languages other than English and Spanish. [In Phase 1 of the study, Spanish speakers will help develop materials in Spanish that are appropriate for a low literacy population.]
Low Literacy and Low	Include	People of low literacy and low economic status may be

Socioeconomic Status		<p>invited to join our study. We will not specifically target low literacy people for recruitment, although low literacy is likely correlated with some of the factors in our diversity definition. Our study is being inclusive of all literacy levels and socioeconomic statuses. We anticipate that some of our participants may have lower literacy. Materials have been developed so that they can be understood by a lower literacy population. Materials will be reviewed by research staff specializing in communications targeting low literacy populations. Patient groups have also reviewed documents to provide feedback to make documents more understandable.</p> <p>If a patient in person discloses that they have trouble reading, they will be offered headphones and helped with the tablet so that it reads the text aloud.</p>
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#### d. Setting

Recruitment of subjects will take place at KPNW and DH. While in-person recruitment will take place at the specific clinics listed below, we will additionally be using recruitment methods that are not in-person for DH and KPNW patients that receive care at any clinics in the DH and KPNW health system via mail, email, phone, and text.

Denver Health (DH) was established in 1860 and is an integrated safety-net health system and regional trauma center providing preventive, primary and acute health care to almost one-third of Denver County residents. Denver Health has nine federally qualified neighborhood health centers with approximately 150,000 unique users, of whom 81% are publicly insured or uninsured. Denver Health's study personnel will recruit primary care patients through mail, phone and on-site in-person recruitment and may assist patients through the consent process in-person at their participating clinics. Participating Denver Health clinics for in-person recruitment include: Webb FIM, Park Hill and Westside. These locations were chosen for in-person recruitment because they serve 1) a diverse population; nearly all of the members at these clinics meet one component of our diversity definition but the clinics differ in the populations they serve (i.e. one clinic serves majority Hispanic patients, another clinic serves mostly Hispanic and black patients, the third clinic serves both Hispanic and black patients), 2) a Spanish-speaking population (inclusion criteria: Spanish or English), and 3) some locations have existing relationships with study staff. [Note: Diversity is not an inclusion criterion for our study; all patients that meet our inclusion criteria will be eligible to join our study and we will implement recruitment training and measures to reduce unconscious bias and the appearance of bias when recruiting in-person. See Recruitment on p. 14 for more details].

In-person recruitment at KPNW will take place in 3 clinics: Rockwood, Gateway, and North Lancaster. These locations were chosen for in-person recruitment because they are three clinics in the greater Portland metro area that serve a diverse and Spanish-speaking patient population. [Note: Diversity is not an inclusion criterion for our study; all patients that meet our inclusion criteria will be eligible to join our

study and we will implement recruitment training and measures to reduce unconscious bias and the appearance of bias when recruiting in-person. See Recruitment on p. 14 for more details].

Additionally, we will use recruitment methods that are not in-person for KPNW and DH patients via mail, email, and phone regardless of the KP or DH clinic where they regularly receive their care.

We will add study and contact information to the CHR public website, section 'CHR studies now recruiting' to provide the option to the public to get informed about CHARM.

We also have the following sites working on the project:

Site	Role
Seattle Children's Hospital	<ul style="list-style-type: none"> <li>• Create consent form/process and plan for consenting participants (Stakeholder feedback on consent form included in Phase 1). Assist with implementing plan</li> <li>• Assist with developing and integrating plan for recruiting and screening participants with the plan for consenting participants (Stakeholder feedback on recruitment materials and risk assessment tools included in Phase 1).</li> <li>• Conduct interviews (e.g. post consent interviews)</li> <li>• Analyze and report on qualitative data</li> <li>• Contribute data to project reports, presentations, and manuscripts. Lead manuscripts related to stakeholder engagement.</li> </ul>
University of Washington (UW)	<ul style="list-style-type: none"> <li>• Participate in the development of the gene list (for targeted sequencing) and clinical results reports (Note: The gene list was developed in the planning and development Phase 1 of the study but did not require patient advisor or community member feedback).</li> <li>• Receive and process samples, perform CLIA-certified/CAP-accredited sequencing for study subjects; annotate and analyze DNA sequence data, classify variants</li> <li>• Lead the pathogenicity classification of genes</li> <li>• Disseminate sequencing results to appropriate study sites/team members</li> <li>• Participate in disclosure of sequencing results and provide genetic counseling to study participants</li> <li>• Analyze sequence data for manuscripts and reports</li> <li>• Post sequence data and submit variants to federal databases</li> <li>• Contribute to project reports, presentations, and manuscripts, including leading manuscripts related to laboratory findings</li> </ul>

Columbia University	<ul style="list-style-type: none"> <li>• Assist with interview guide development, cognitive interviews, code development for qualitative analysis, and analysis of qualitative data</li> <li>• Participate in the genetic counseling qualitative assessment</li> <li>• Contribute data to required project reports, presentations, and manuscripts</li> </ul>
University of California San Francisco (UCSF)	<ul style="list-style-type: none"> <li>• Participate in the development of intervention study materials, especially with respect to literacy, culture, and language. Lead the development of standard versus modified counseling and post-result disclosure interview guides.</li> <li>• Conduct post-disclosure interviews with study participants according to protocol; code and analyze qualitative data</li> <li>• Lead qualitative study of results disclosure (genetic counseling) from patient and provider perspective; evaluate standard versus modified counseling</li> <li>• Contribute to project reports, presentations, manuscripts, including consortium-wide manuscripts, and dissemination activity meetings.</li> </ul>
Kaiser Permanente Colorado (KPCO)	<ul style="list-style-type: none"> <li>• Work closely with DH staff to facilitate the implementation of all aspects of the study protocol related to recruitment at DH.</li> <li>• Contribute data to required project reports, presentations, and manuscripts</li> </ul>
Emory University	<ul style="list-style-type: none"> <li>• Provide access to B-RST tool upon receipt of a one-time license fee for KPNW which allows continued use for research activities</li> <li>• Provide expert consultation on the adaption of B-RST tool for our study population</li> <li>• Assist in troubleshooting and testing the performance of the updated tool</li> <li>• Analyze and interpret study data after B-RST tool is implemented</li> </ul>
Dana Farber Cancer Institute	<ul style="list-style-type: none"> <li>• Provide access to PREMM tool (upon receipt of annual access fee from KPNW)</li> <li>• Direct the adaptation of PREMM tool for our study population</li> <li>• Maintain calculation algorithms for PREMM tool based on adaptations</li> <li>• Assist in troubleshooting and testing the performance of the updated tool</li> <li>• Analyze and interpret study data after PREMM tool is implemented</li> </ul>

All sites except Dana Farber Cancer Institute and Columbia University will be ceding reliance to the KPNW IRB. Denver Health is affiliated with the Colorado Multiple Institutional Review Board, housed at the University of Colorado Denver. Since the overall research program will be coordinated from KPNW, with Denver Health being one of 2 recruitment sites, DH will seek COMIRB's approval to cede review and continuing oversight to KPNW IRB. The review and continuing oversight by KPNW IRB will meet the human subject protection requirements of the University of Colorado's Institutional Review Board.

#### **e. Recruitment Methods**

Subjects will be screened for eligibility to join the study via the risk assessment tools. The main way to complete the risk assessment tool will be via a website. The website can be accessed from anywhere there is WIFI (e.g. at home, or in-clinic on a tablet).

We plan to recruit/assess eligibility for the study via 4 methods at KPNW and DH (See Figure 2):

1. **Via text/phone/mail/email to all patients with an upcoming appointment at DH or KP in-person recruitment clinics** We will identify patients via EMR in target clinic(s) that have a scheduled appointment in primary care in ~14 days. We will:
  - a) Send link to risk assessment
  - b) Follow-up with phone call in ~3 days for those who meet diversity definition and don't complete risk assessment. We may contact a select number of patients if the volume is high.
  - c) For any patients that meet eligibility criteria to join the study after completing the risk assessment, they can consent online or they can stop by our recruitment booth at their upcoming appointment. If they consent online we can either mail them a saliva kit or meet them at their appointment to collect the sample.
2. **In-person recruitment by study staff at DH and KP recruitment sites to all patients present when recruitment staff are present.** A study recruitment booth that will be set up at recruitment clinics. Patients can both walk up to us, and we will initiate conversations with patients as they walk by the booth, such as "Hi, are you interested in learning more about cancer that runs in families?". Recruitment staff will say this line to any patient that walks by the booth, unless they are clearly outside of the age range.

In addition, we will provide unconscious bias training via KP Learn ([Unconscious Bias: How It Affects Our Decisions and Behaviors](#)) to recruitment staff at KPNW and emphasize the importance of not creating the appearance of bias in the recruitment setting. We will advise our partners at Denver Health to offer this or a similar training to their recruitment staff, as well.

Patients can complete the risk assessment tool or consent form on their own with a study tablet after approaching the booth or with study staff if assistance is needed. If a patient needs assistance completing the risk assessment tool or consent form, study staff will assist them privately (e.g., recruiters to ask patient if they are okay with talking in the area, recruiters will use quiet voices, recruiters will utilize quiet areas away from patient traffic or quiet areas where there is a barrier to imply or provide privacy (screen/wall/stanchion) including conference rooms and clinic administrative areas if possible, recruiters can provide an option to participants to call to speak with someone later).

3. **Postcard mailing to DH and KP patients that meet our diversity definition;** Mail postcard to patients who meet diversity definition regardless of the KP or DH clinic where they usually receive their care (e.g. not restricting to in-person recruitment clinics) that includes a link to risk assessment online.
4. **Via text/phone/mail/email to DH and KP patients that have indications in the medical chart that they may be at high risk** (any KP/DH patient; not restricted to in-person recruitment at clinics). Outreach to known increased risk patients regardless of the KP or DH clinic where they usually receive their care (e.g. not restricting to in-person recruitment clinics), such as patients with mammography or colonoscopy at ages younger than recommended for the general population, or people that have a documentation of a family history of cancer in the EMR. We

will not include results of genetic tests found in the EMR to identify this increased risk population; it is part of our exclusion criteria to exclude people who have a known mutation, however that will be reported to us when the complete the risk assessment tool and will not be pulled from EMR review. For patients who we outreach to because they are known to be higher risk, we will exclude those patients who have documented comprehensive panel genetic testing in the CHR testing data file.

There is no chronological order for our recruitment approaches. All four of these approaches can happen at the same time.



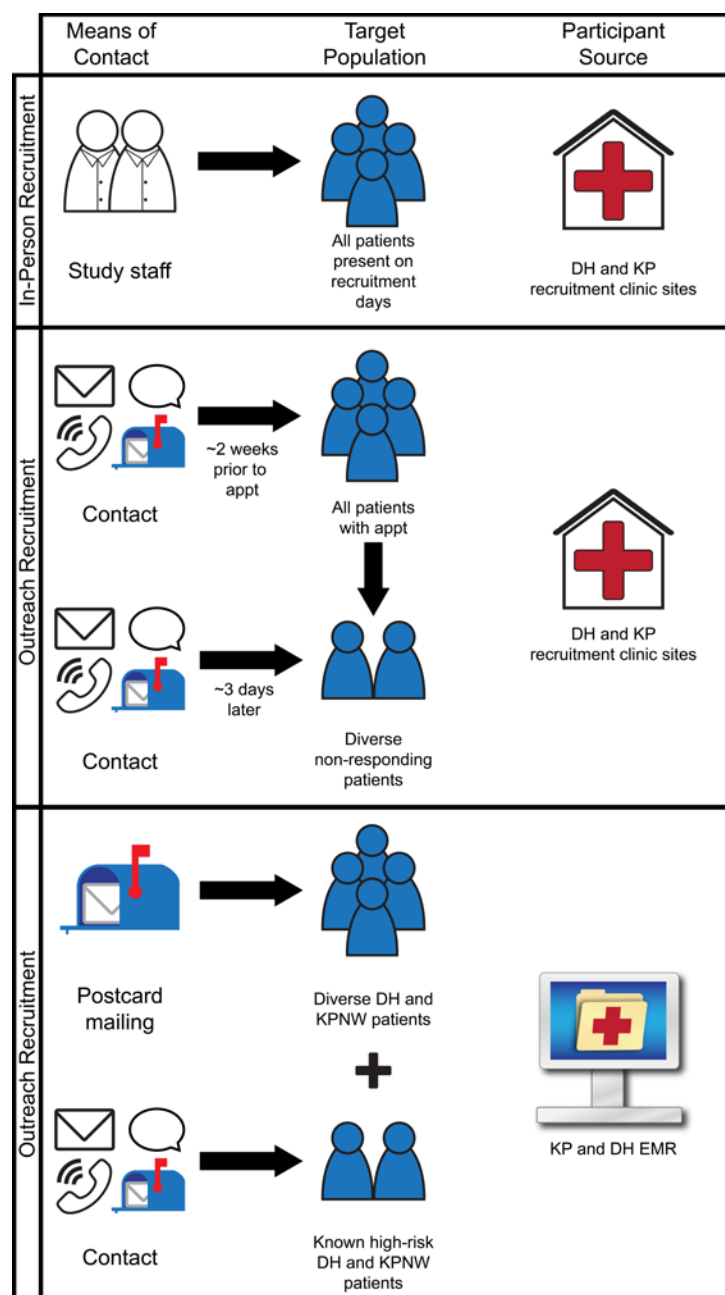


Figure 2. Recruitment Approaches

We anticipate needing to be flexible with recruitment methods, and we will use a combination of methods (mail, text, email, phone call). The study postcard and brochure will be available to patients at any point in recruitment, however the postcard is intended as a method to get patients to the risk assessment tool and the brochure is intended for patients who are high risk or have limited family history who are eligible to enroll into the study. We anticipate in-clinic patients will be called back for

their appointments, at which point the postcard or brochure (depending on where they are in the recruitment process) could be provided so they could follow up with the study team. We may also put up signs in primary care clinics. We will have a recruitment booth where patients can approach members of the study team. Any additional materials needed for these recruitment purposes will be submitted to the IRB for approval before use.

We will not reach out to patients more than 4 times via a combination of mail, text, email, or phone call to complete the risk assessment tool. There will be no additional follow-up for passive refusers. For patients that consent to complete the risk assessment tool and screen eligible but do not actively decline study participation, we will contact them up to 6 times via a combination of mail, text, email, or phone call due to their high risk/limited family history status.

The recruitment staff will be a combination of research assistants, patient navigators, project managers, and study clinicians. Throughout the course of the study, the PIs for this study will verify that all recruitment staff are listed in the eIRB (including personnel at collaborating institutions as noted in Other\_Study\_Staff Excel spreadsheet attachment). The PIs will additionally verify that all listed staff have completed their CITI training, although it is noted that the collaborating institutions manage the required trainings for their research staff).

We have included language in the consent that we may contact participants in the future about other studies. We anticipate there may be additional studies in the future, including studies with the CSER consortium (sites funded under this collaborative agreement).

#### **f. Consent Process**

We will have two consent processes: consent prior to the risk assessment and, for those eligible after completing the risk assessment, consent to join the study. Patients will review all elements of consent, except provide their signature (it is an online tool), prior to completing the risk assessment tool.

If, per the risk assessment tool, eligibility criteria are met (See section b. Inclusion and Exclusion Criteria and e. Recruitment for more info), patients will be directed to information about genetic testing and the research study consent process. Patients will be directed to this information via the website. This information can also be provided in paper form, if requested.

Eligible patients will be invited to participate and provided opportunity to ask questions of study staff (in-person at the clinic or by phone). The consent process includes information about who to contact if they have questions, and how to withdraw if they change their mind about participation. Starting after the approval of study mod 37 and around November 2019, half of English-speaking participants will have the decision aid incorporated into the optional additional results section of the consent form.

At KPNW, patients who are at high risk who choose not to enroll in the study can self-refer to the Genetics Department for an assessment and possible genetic testing via clinical care. At DH, the patient's PCP can refer them to genetic counseling and testing.

Spanish-speaking research staff will be available when needed, and consent forms (online and on paper) will be available in both English and Spanish. The consent process will include an opportunity to ask questions and clarify implications of the genetic testing being performed through the study.

Because our target recruitment population includes patients of limited literacy and low-SES, we strive to keep all documents and discussions at a maximum 6<sup>th</sup> grade reading level whenever possible (this effort includes stakeholder feedback that was part of Phase 1). We will also provide custom illustrations to depict key consent concepts for online consent forms (also developed with stakeholder input in Phase 1) and audio voiceover of all written text in the consent form (online)

### ***Modifications to the Consent Process***

Family history risk assessment information will be collected to determine eligibility for genetic testing via the study; the majority of people (about 80-90%) who complete the risk assessments will not be eligible for genetic testing. We will use modified versions (e.g. modified for literacy level, clarity, and ease of administration online during Phase 1) of the B-RST tool (to assess risk for breast and ovarian cancer) and the PREMM model (to assess risk for colorectal and other Lynch-related cancers) to determine if the family history provided by the subject is suggestive of a hereditary cancer syndrome. The subjects will provide the information either through an online risk assessment tool themselves or verbally to study staff (and recorded online by study staff).

We proposed a staged consent process to allow the patient to focus on the decisions sequentially. Individuals will provide consent for completion of the risk assessment tool during the first stage. For the risk assessment consent, we are asking for a waiver of signature, as we expect that most people will complete this online and will click the “I agree” button to continue to the tool after reading the consent.

Completion of the risk assessment tool will determine eligibility to join the study and will occur prior to the remaining stages of consent.

For individuals who, after they complete the risk assessment tool, are eligible but decline to participate in our study, we will include questions on the decliner pages about whether or not they agree to having their medical record reviewed. Additionally, if a patient is at one of the recruitment clinics and recruitment staff are present and the patient would like to opt out of having their medical reviewed, they can inform CHARM recruitment staff of their decision in-person. Their response will be recorded in the study tracking system. However, if the participant completes the risk assessment tool online but does not advance to the decliner page of the online tool and does not make their selection to opt-in or opt-out of medical record review, we will not follow them. The test information, consent, and HIPAA are roughly 5 pages of text to read. Participants could close their browser at any point during this process, after they complete the risk assessment, not return, and not select an option for medical record review. Study staff do plan to follow-up with all eligible participants that do not decline and do not consent to see if they are interested in joining the study. At that time, study staff can further confirm their option of medical record review if they decline participation in the study. Participants lost to follow-up (passive decliners) will have their medical record reviewed if they did not make their preference known about EMR review. This research cannot be practicably carried out without a waiver of consent.

***Non-English Speaking Subjects***

We will only recruit English and Spanish-speaking subjects. We are not recruiting subjects in any other language. Participants must be able to speak English or Spanish as noted in our inclusion/exclusion criteria. We will have a Spanish consent process for Spanish-speaking subjects. At least one recruitment staff member will be a Spanish speaker and will be able to answer questions these subjects may have. All recorded audio that accompanies the consent will be recorded in both English and Spanish. Spanish-speaking certified interpreters will be used for genetic counseling when indicated.

A Spanish-speaking study staff member will conduct the consent process and, for Spanish patients not proficient in English, a certified interpreter will be used for the genetic counseling session. Any follow-up interviews with Spanish-speaking participants will be conducted by a Spanish-speaking study team member.

***Assent of Children and Parent Permission***

Children will not be recruited for this study.

***Adults Unable to Consent/Decisionally Impaired***

We will not target decisionally impaired adults in our recruitment. Recruitment staff will not be trained to assess impairment and will use common sense as is typically done in studies. If a patient does not understand, we will not pursue recruitment. If a patient can complete the risk assessment tool, we will assume they are not decisionally impaired. If we are informed by a provider or healthcare proxy that a decisionally impaired adult has consented for the study, we will withdraw them from the study.

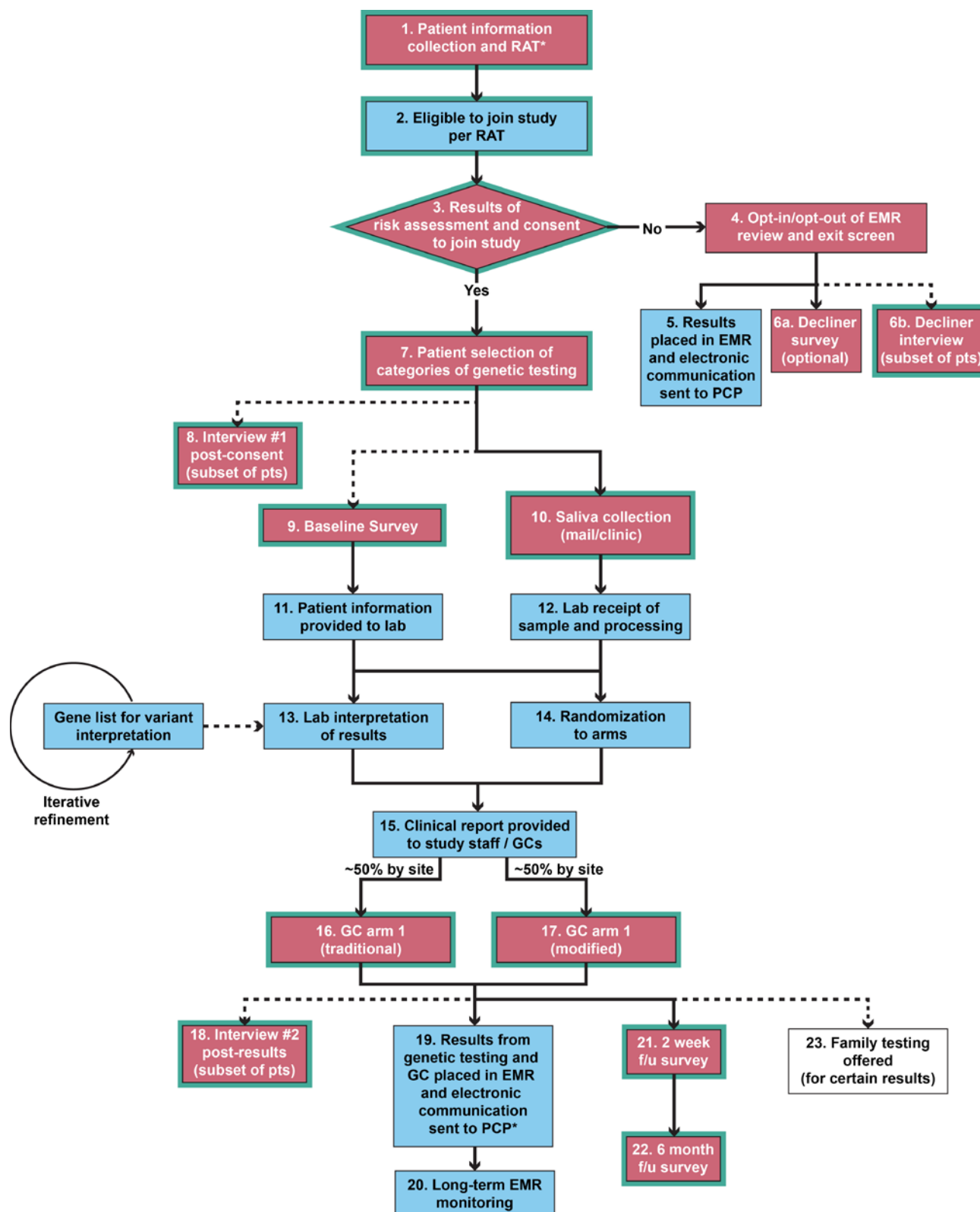
We will enroll participants who have varying levels of literacy. We will provide audio for the consent. For illiterate patients (who self-identify or it becomes clear to recruitment staff during the consent process) we will have a third party (not study staff) participate in the consent process (e.g. family member or available clinical staff).

***HIPAA Privacy Rule Authorization – if study will use or disclose Protected Health Information (PHI)***

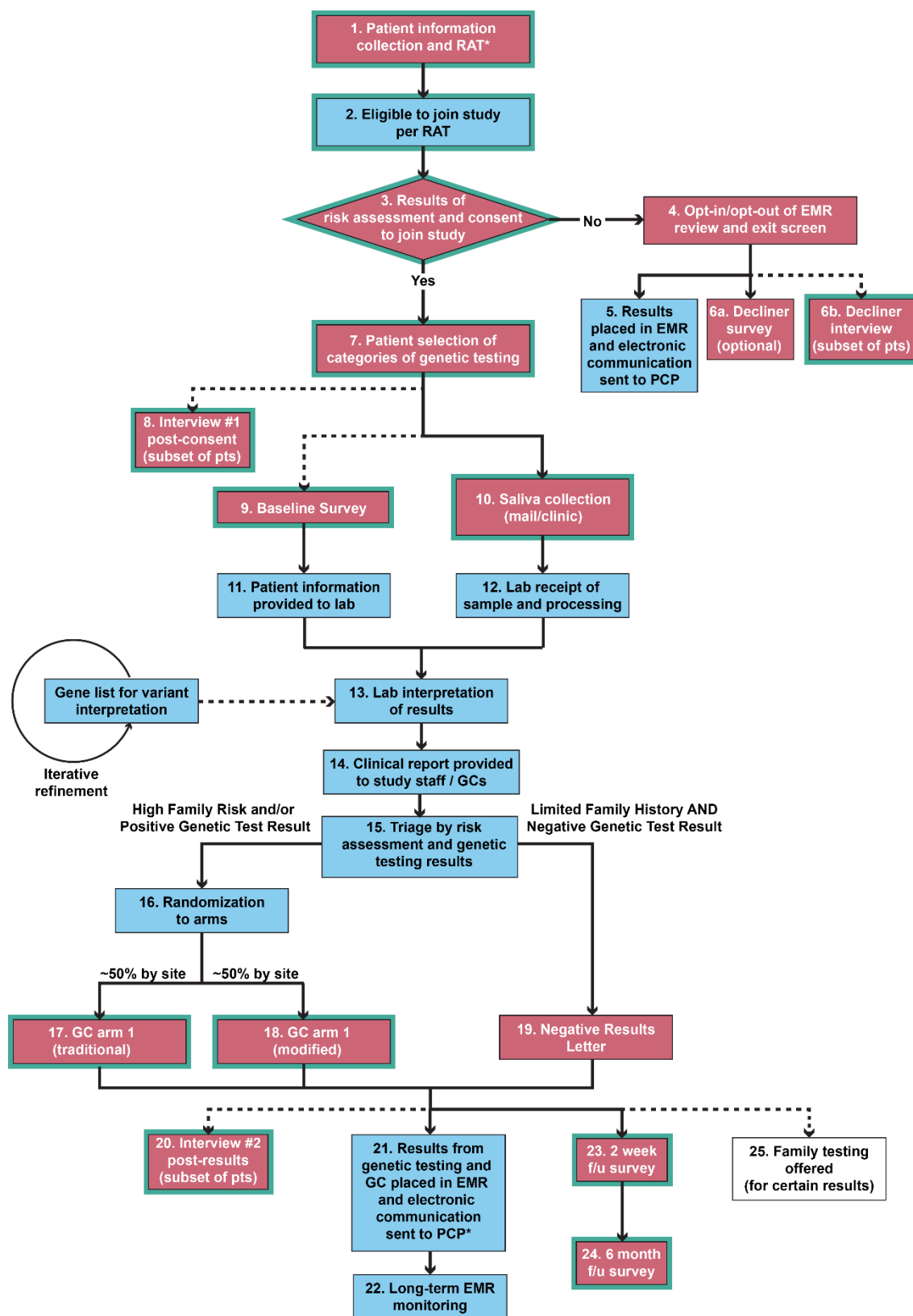
After signing the consent form or checking the appropriate field on the online form, participants will receive a HIPAA Authorization form to review and agree to.

## 6. Study Procedures

### Figure 3a

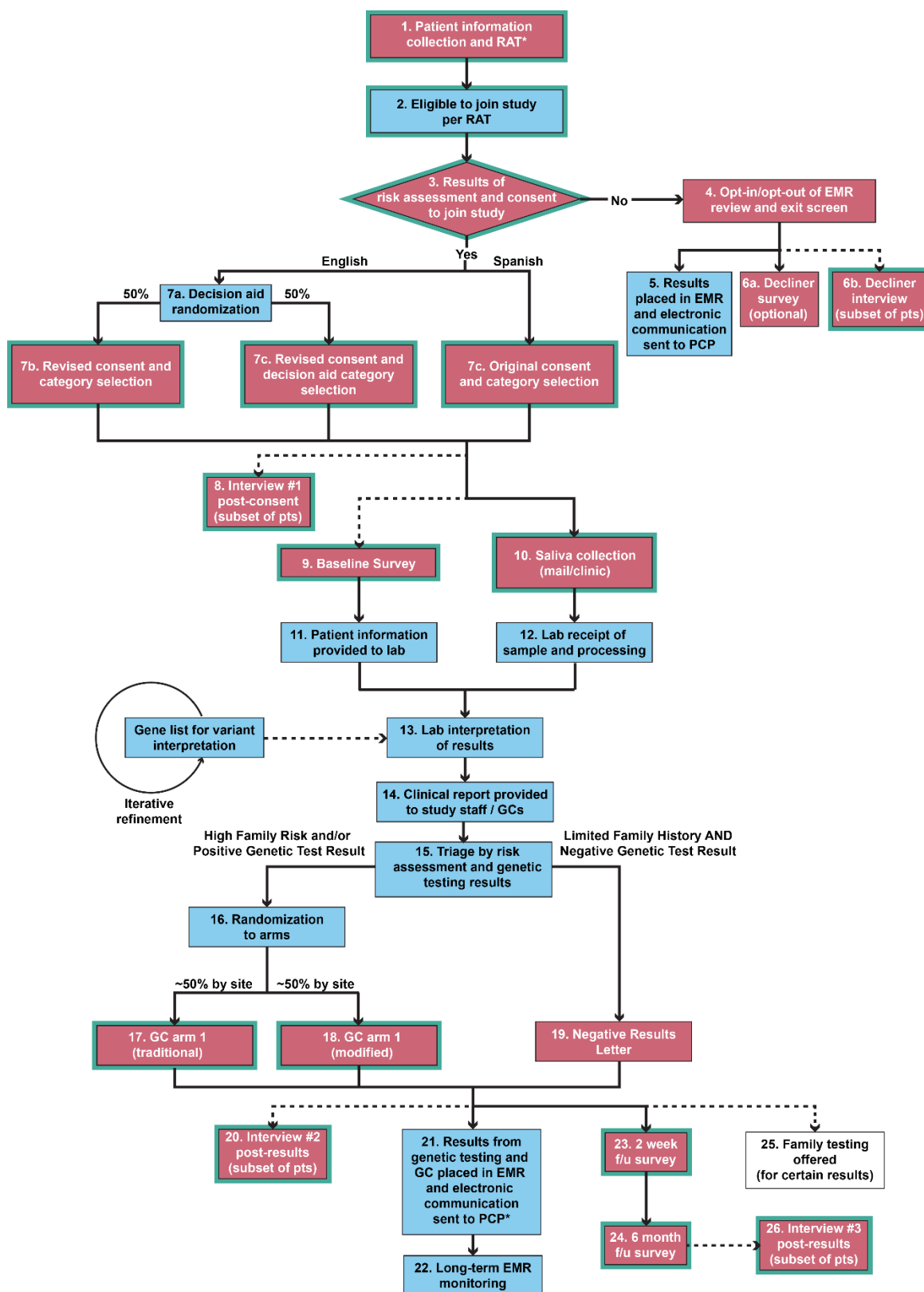


**Figure 3b**





**Figure 3c**



**Figure 3a** – Overall Study Procedures and Work Flow prior to approval of study mod 27

**Figure 3b** - Overall Study Procedures and Work Flow after approval of study mod 27

Legend: Patient and study processes from eligibility. Pink boxes represent processes involving patient interaction. Blue boxes represent boxes involving automated or manual study processes. Boxes with thick borders represents activities where study staff will send reminders to patients/participants to complete activities. Dotted lines to activities mean that the activity will not happen for every participant. RAT = risk assessment tool. GC = genetic counselor.

\* Patients lost to follow-up, that do not receive genetic counseling, will still have their results placed in the EMR.

Figure 3c - Overall Study Procedures and Work Flow after approval of study mod 37

### Additional Information related to Risk Assessment Tool

The participants will receive the results online after they complete the online risk assessment tool, and they will have the option to print it if they have access to a printer. They may also call study staff and request a copy to be mailed to them. We will provide paper printouts of the results to patients who complete the risk assessment in clinic with study staff.

Results shared with participant from these tools are not a score nor a percentage or a statement about risk (high risk/low risk).

[Note: The algorithms themselves are proprietary information; the tools have been adapted for lower literacy, clarity, and ease of administration on a website, but the algorithms have not changed].

Patients are not eligible for proceeding with the study if they have average/typical amounts of these cancers in their family history, which is expected to be ~90% of patients that complete the risk assessment.

We may recruit patients who appear to be at increased risk for hereditary cancer syndromes based on information in their medical chart. We will reach out to the patients that meet this 'increased risk criteria' regardless of the KP or DH clinic where they regularly receive their care (e.g. not limited to in-person recruitment clinics). Increased risk includes factors such as mammography or colonoscopy at ages younger than recommended for the general population in the EMR, or people that have a documentation of a family history of cancer in the EMR. We may make effort to invite at-risk patients using the recruitment methods described below (Section on Recruitment) to complete the risk assessment as part of our study. We will not include results of genetic tests found in the EMR to identify this increased risk population; it is part of our exclusion criteria to exclude people who have a known mutation. Known mutations will be reported to us via the risk assessment tool and will not be pulled from EMR review.

Patients that have not completed the risk assessment tools via in-person recruitment may receive invitations to participate in the study regardless of the KP or DH clinic where they regularly receive their care.

### Eligible Participants

After a participant is deemed eligible (Box 2, Figure 3a&b) through the completion of the risk assessment tools and/or through the determination of a limited family history knowledge, the participant will be provided the option to consent (Box 3, Figure 3a&b). For patients that are eligible for the study but decline enrollment (usual care group), they will be presented with the option to have their medical record reviewed or not on the decliner pages (See. P. 19-20 for more details). Additionally, we will invite decliners to complete a short, voluntary survey to obtain information on why they do not want to participate in the study and demographic characteristics (Box 6, Figure 3a&b). For those that do not opt-out of medical record review, we will follow these individuals through the EMR to determine what actions they take, if any, that are related to the result of their risk assessment and overall healthcare utilization.

As a condition of participation in the study and part of the consent process, the participant must consent to diagnostic testing for genes associated with hereditary cancer (Box 3, Figure 3a&b). After completing the consent process, study participants will also be able to make choices about which types of optional results they would like to receive as secondary findings in addition to the hereditary cancer syndrome genetic test results (Box 7, Figure 3a&b). Secondary findings are results that are not associated with the reason the test was ordered. All of the secondary findings are optional. Participants can choose two types of secondary findings, medically actionable and carrier status (carrier status will be removed after approval of study mod 27). Medically actionable conditions are conditions for which preventative measures and/or treatments are indicated. Carrier status results are related to the risk for disease in offspring and are relevant for participants who are reproductive age and/or for participant family members who are considering having children. Prior to approval of study mod 27, the participant can also choose what kind of carrier status secondary findings they want to know by selecting lifespan limiting, serious, and/or unpredictable carrier status results. All participants (regardless of decision aid randomization) will receive similar information describing secondary findings. Participants that are randomized to the decision aid will additionally be required to respond (on a 4-point Likert scale from 'strongly agree' to 'strongly disagree') to a series of relevant values-based statements interspersed within the information describing secondary findings. The end of the decision aid information will additionally include illustrative quotes for conveying the feelings or values that would lead some individuals to make their decisions about receiving secondary findings (with one quote supporting receiving the findings and one quote supporting declining receipt of the findings). Lastly, the decision aid will use a sum of the responses to the value statements to provide summative guidance at the end; this guidance states that the participant's answers suggest he/she would want to receive (or not receive) the secondary findings. The guidance also acknowledges that the participant may make a contrary decision (to what the answers suggest) based on other factors.

### Sample Collection

Participants will be asked to provide a saliva specimen (Box 10, Figure 3a&b) after consenting to the study. Study staff will provide the saliva collection kit necessary for the donation of saliva by either handing it to the participant at the clinic or by mailing the saliva kit to the participant. Participants who are approached at the clinic will have the option of completing the donation and providing it to study staff before leaving the clinic. Participants can also complete the sample donation at their home and mail it to the UW lab with mailing materials provided in the sample collection kit. Samples collected at the clinics may be batched together and sent to UW by study staff.

The laboratory will be provided information required for variant interpretation at the lab (Box 11, Figure 3a&b). This includes participant identifiable information (such as full name, DOB, and medical record number), information about their preferences for learning of medically actionable secondary findings, and their personal and family histories of cancer which will be extracted from their answers to the risk assessment tools. This information is needed for the laboratory to accurately interpret the DNA sequence information. Specimen labels will include two pieces of identifiable information (such as name, study ID, HRN, or DOB). Because the results of the genetic test will be placed into the medical record and potentially used by providers for subsequent downstream care, it is critical that we follow standard clinical procedures, which includes the use of PHI, for labeling samples and reports to ensure that downstream care is delivered to the right person. We will also conduct quality control procedures after the clinical report is placed in the medical record, to ensure that the right report is in the right person's medical record. In past studies we have observed reports that were placed in the wrong medical record during our QC process. We feel it is less likely that downstream care would be delivered to the wrong person if their name and medical record number are clearly labeled on the report.

#### Lab Receipt, Genomic Testing, and Variant Interpretation

The lab will enter the receipt of samples in a centralized study tracking system once received.

Genomic testing will be completed in a CLIA-certified laboratory and involve clinical exome sequencing (described below, Box 12, Figure 3a&b). The lab will be provided participant demographic and family history information (Box 13, Figure 3a&b) and will interpret variants in the cancer diagnostic genes and optional medically actionable secondary finding genes based on participant selection. We expect that the number of genes on the cancer diagnostic list and the secondary finding list will change, with IRB approval, over the course of the study as we learn more about gene/disease associations over time (see Section 6. *Developing Gene Lists to Inform Variant Interpretation* below for further information). Adding genes to genetic panel tests based on new evidence is standard of practice in clinical laboratory genetics. For example, the University of Washington Department of Laboratory Medicine hereditary colorectal cancer gene panel Coloseq™ increased from 7 to 26 genes from 2011 to present (<http://tests.labmed.washington.edu/COLOSEQ>, [43]). Positive findings will be validated using clinical standards.

We will perform “clinical exome sequencing”, which includes the “clinically relevant” portion of the genome, or about 5000 of the 20000 genes in the human genome (not the same thing as “whole exome sequencing” which includes most of the 20000 genes). However, results will only be reported on a subset of ~127 genes to the participant. *The IRB should refer to the list of genes (“KP and DH - Gene List”) for the exact genes we are including in our return of results as we do not want to be out of compliance if at some point in the future the number of genes in the protocol does not exactly match the number of genes in the gene list.*

This subset of ~127 genes will be referred to as the “genetic test” and will include the cancer diagnostic genes and optional medically actionable secondary finding genes. The cancer diagnostic gene list currently includes ~40 genes associated with an elevated risk of different cancers including breast, colorectal and/or ovarian cancer. The secondary finding gene list currently includes ~101 genes total;

~87 genes associated with medically actionable conditions and ~14 genes associated with carrier status, but carrier genes will be removed for participants consented after approval of study mod 27. The remaining genetic information will be available for secondary uses by 1) request through dbGaP or other NIH database; 2) a yet to be determined process for collaboration with the CSER consortium and 3) for participants from KPNW, through the ABC process.

*Note on the Development of the Gene Lists*

The cancer diagnostic and medically actionable secondary finding gene lists were developed by a work group of study personnel including clinical geneticists, a laboratory molecular geneticist, and genetic counselors with clinical and laboratory expertise in hereditary cancer and the return of secondary finding results. (The gene list was developed in planning and development Phase 1 of the study, but did not require patient advisor or community member feedback).

Diagnostic cancer genes with an established association to hereditary cancer were chosen. These genes are tested for clinically as standard of care in patients who are deemed to be at an elevated risk for hereditary cancer based on their personal and/or family history of cancer. Additionally, hereditary cancer genetic testing via multigene panels is rapidly replacing targeted single gene testing as standard clinical practice [44-46], and is the current practice at KPNW. Considering genetic testing for diagnostic cancer genes in appropriate patients is supported by national recommendations and peer reviewed literature. Examples of such recommendations and guidelines for genetic testing in patients being evaluated for hereditary cancer can be found below:

- The National Comprehensive Cancer Network (see '*Genetic/Familial High-Risk Assessment: Breast and Ovarian*' and '*Genetic/Familial High-Risk Assessment, Colorectal*')  
[https://www.nccn.org/professionals/physician\\_gls/default.aspx#detection](https://www.nccn.org/professionals/physician_gls/default.aspx#detection)
- The National Society of Genetic Counselors (NSGC) and American College of Medical Genetics and Genomics (ACMG)  
<https://www.ncbi.nlm.nih.gov/pubmed/23188549>  
<https://www.ncbi.nlm.nih.gov/pubmed/25394175>
- Other peer reviewed literature  
<https://www.ncbi.nlm.nih.gov/pubmed/20948872>  
<https://www.ncbi.nlm.nih.gov/pubmed/29465928>  
<https://www.ncbi.nlm.nih.gov/pubmed/24523625>

The medically actionable secondary finding gene list was developed based on the recommendations of the American College of Medical Genetics and Genomics (ACMG) and peer-reviewed publications on the return of secondary findings from genomic sequencing. The ACMG recommend the interpretation and return of pathogenic variants in 59 genes associated with medically actionable conditions when this sequence data is available from a genomic test [47]. Our medically actionable secondary finding gene list includes the non-cancer, adult onset conditions on this list of 59 genes. The additional ~51 medically actionable secondary finding genes on our list are associated with conditions that are typically rarer than those recommended by the ACMG. Pathogenic variants in these genes were returned as secondary findings as part of a previous NHGRI funded translational genomics research study. See [48] '*Supplemental Digital Content 1: CSER site Narratives, University of Washington – NEXT Medicine Project*' for a description of the development of this list as well as '*Supplemental Table 4: UW NEXT Medicine Study Medically Actionable Genes*' for the full list of secondary finding genes for that project.

This expanded list of genes has also been used in published peer reviewed research exploring the return of medically actionable secondary findings [49,50]. As noted above, we expect that this gene list to change, with IRB approval, over the course of the study as genetic knowledge evolves.

Although we currently return only pathogenic variants in secondary findings, we would like to expand to also report expected pathogenic variants, which are a subset of likely pathogenic variants. This change will make our study processes consistent with clinical ACMG guidelines. At the time of implementing this change, no subjects with findings for expected pathogenic variants had been identified within our study population.

Carrier status secondary finding genes were selected based on disease frequency and the ability of exome sequencing technology to identify known pathogenic variants in these genes. The decision to include only 14 carrier status genes was based on balancing the burden of variant interpretation for study personal with the need to include several conditions in each category of carrier status results (lifespan limiting, serious, or unpredictable disorders). These genes will not be reviewed for participants consenting after approval of study mod 27.

### Genetic Counseling

Prior to approval of study mod 27, all patients that receive genetic testing will receive post-test genetic counseling, regardless of their results. Half of the counselors will provide traditional counseling throughout the study, and half will provide the modified counseling throughout the study. This protocol figure is presented as Figure 3a

Following approval of study mod 27, most patients that receive genetic testing will receive post-test genetic counseling, regardless of their results. Half of the counselors will provide traditional counseling throughout the study, and half will provide the modified counseling throughout the study. Participants that qualify for the study because of limited family history AND who have negative results will receive their results via letter if they join the study after ~July 8, 2019 (Box 19, Figure 3b). This set of participants will not be randomized. This protocol figure is presented as Figure 3b.

Based on randomization (see Randomization section above), patients will be counseled by one of two methods (Boxes 16 and 17, Figure 3a; Box 17 and 18, Figure 3b). The two genetic counseling methods (traditional and modified) will have some common elements, including the common informational and psychosocial elements.

The following is what the two types of counseling have in common:

#### **1. Informational elements:**

##### **Pathogenic, likely pathogenic and VUS result**

- a. describe the condition caused by the gene change
- b. review medical management recommendations
- c. obtain additional family history relevant to result
- d. discuss importance of sharing results w/family members (pathogenic and likely pathogenic)

- e. identify who else in the family should consider genetic testing, as well as the availability of family member genetic testing through study or clinically
- f. next steps for study
- g. clinical downstream care

#### **Normal result**

- a. discuss possible explanations (not genetic, variant not found, gene not tested, etc.)
- b. review medical management recommendations
- c. next steps for study
- d. clinical downstream care

## **2. Psychosocial questions:**

Both genetic counseling methods will include questions that gauge how the patient is feeling about their result and if they are feeling unsettled or worried about their test results. They will also be asked who they might share their result with and how they would explain their result and next steps to their family.

Otherwise, the two genetic counseling methods will be conducted in accordance with the following guidelines and will differ in the following ways:

### **Traditional Protocol**

Genetic counselors will provide counseling per **usual care practice** specific to each genetic counselor. No training will be provided to the counselors delivering the traditional counseling. All genetic counselors participating in this study are board certified and licensed in the state of Washington when required (there is no licensing for genetic counseling in the states of Oregon or Colorado). The genetic counselors that are currently on the study (May 2018) have a range of experience from 5-23 years. Traditional genetic counseling is ideally tailored to the participant's knowledge and psychosocial response. This type of genetic counseling typically includes education about inheritance patterns, penetrance, variable expressivity, and genetic variability [51,52]. The use of at least some genetic terminology (see 'Terms' in Table 1) and a non-directive approach is considered standard practice in the field. Genetic counselors in the traditional arm will not be instructed to follow the communication techniques outlined for the modified arm. Therefore, we expect that the traditional counseling will include the use of more technical genetics terminology, and more technical information about genetics concepts and genetic testing. In addition, the traditional protocol will not include the technique of "teach-back" to check for patient understanding, but rather will likely include questions such as "Do you have any questions?" or "What questions do you have?" to check for patient understanding. Participant cancer risk estimates will be conveyed using percentages and could include number needed to treat and relative risk formats. Genetic counselors may also provide patients with publicly available materials typically used with patients, such as pamphlets from the Hereditary Colon Cancer Foundation.

### **Benefits/harms**

The main potential harm associated with standard of care traditional genetic counseling is inducing short term anxiety or emotional distress in participants due to discussion of disease risks and inheritance of genetic conditions in a family; however beneficial outcomes of genetic counseling cited in the literature



include increased knowledge, understanding and satisfaction, as well as decreased anxiety in the long term [53-56].

Returning negative results via a letter is common, and the participants that receive the letter will not have any known risks for a hereditary cancer syndrome. They will still have the option to call the study for genetic counseling.

### **Modified Protocol**

Modified genetic counseling will incorporate evidenced-based techniques designed to increase comprehension for patients of limited health literacy. These techniques were developed and tested in other areas of Medicine (e.g. primary care) [35,57,58] and have been adapted for the genetic counseling context for patients of limited health literacy and others who may be unfamiliar with genetics or have difficulty understanding the complex information delivered through traditional genetic counseling for other reasons. This approach is based on the Universal Precaution Principle which provides for communicating in a manner that anyone can understand [59]. Counselors providing the modified protocol will undergo training in these specific techniques, which will include role plays and other opportunities to practice.

Modified genetic counseling will use a more directive than non-directive approach, including the following:

1. Use of plain language (See Table 1 below)
  - a) Use specific alternative words/phrases for technical terms
2. Use of active instead of passive voice
3. Assessment of comprehension
  - a) Use teach-back technique for any educational components to ensure patient comprehension [unless participant is actively engaged and asking questions that demonstrate understanding]. E.g. after explaining that a family member is also at risk, use teach-back to get the participant to demonstrate enough understanding to explain to the family member that they should discuss risk with a doctor.
4. Provide “patient relevant” information only and avoid providing too much information. Limit information to what the patient needs to remember and be able to do later.
  - a) e.g. do not explain how genetic testing works (genetics 101; sequencing, like a spell check etc.) unless patient asks;
  - b) e.g. do not explain how genetic counselor came to recommendation or decision unless patient asks;
  - c) e.g. focus on actionable recommendations (information the patient needs and what the patient can/should do to address risk in self and family)
  - d) e.g. focus on what you want the participant to remember and be able to do later
5. Use evidence-based risk communication strategies
  - a) e.g. use frequencies instead of percentages; present statistical information using absolute risk rather than using relative risk or number needed to treat formats)
6. Minimize uncertainty

a) e.g. use concrete language that is clear about what is certain and what is uncertain.

**Table 1. Examples of alternative plain speak language for genetic terms**

<b>Term</b>	<b>Modified</b>
Hereditary	Runs in the family (or passed down from parent to child)
Sporadic Cancer	Regular Cancer
Multifactorial Cancer	Cancer with more than one cause or cancer that happens for more than one reason
Mutation/variant	Change or broken/faulty/nonworking.
Negative Result	Normal Result
Pedigree	Family History/Family Tree
First degree/third degree	Close or distant blood relatives
Risk	Chance that ____ will happen
Risk factors	Reasons why people get sick (smoking and lung cancer)
General Population	Most people
Variants of Uncertain Significance	Test results that are unclear
Surveillance	Close observation with frequent exams or watching carefully for any signs with regular visits to the doctor
Genetic factors	Things passed through the family
Genetic information	Things passed through the family
Genetic material	Things passed through the family
Hereditary factors	Higher chance of having a medical problem/ type of cancer because of something you were born with, passed down from parents
Pathogenic/likely pathogenic variant	Gene changes that increase chances of getting cancer
Recessive	Conditions that affect family members, including children. Not usually in every generation of a family.
Hereditary breast and ovarian cancer syndrome	Higher chance of getting breast cancer and ovarian cancer than general population
Inherited in dominant way/ Dominant inheritance	Each generation in a family has people with the condition
Later onset	Happens after 50 years old
Not informative	Did not give an answer
Ascertainment bias	Studies from a group of people that aren't the same as the people in this study
Medically actionable	Results that change medical care
Cancer predisposition condition	Higher chance of getting cancer than general population
Manage risk –Additional surveillance through lifetime	Lower chances of getting cancer/increase chances of finding cancer early by getting tests every year
predispositions	Higher chance
Sequencing	Looked at the gene/read through the gene

### Benefits/harms

There are no known harms associated with the modified genetic counseling approach that are different than the traditional genetic counseling approach. The goals of informing participants and providing psychosocial support which are central to traditional genetic counseling are also included in the modified protocol. In pilot-testing at University of California San Francisco (the site leading this work) of the modified protocol, no harms to patients have been observed, while the benefits of more time for psychosocial counseling and increased comprehension have been observed (publication in progress; Susan G Komen for the Cure grant #

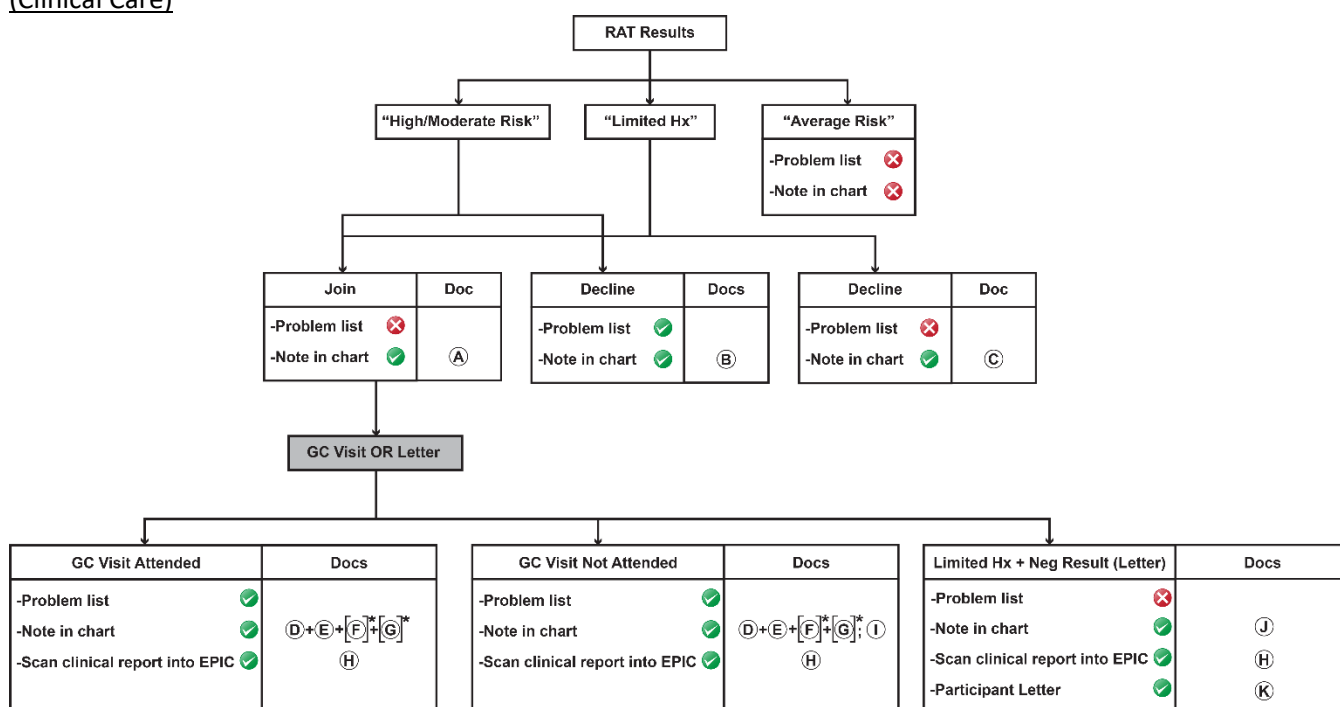
IIR12221854; PI: Galen Joseph).

### Evaluation of genetic counseling approaches

All study staff who perform genetic counseling as part of the study will share their input with the study team on how the participants are responding to the two modes of genetic counseling. This could occur by sharing input in writing, during team meetings, or one-on-one discussions. We have developed a process for maintaining fidelity to the intervention which will involve listening to audio recordings of the counseling sessions, reading transcripts of the counseling sessions, and discussing this information with the genetic counselors and other members of the research team.

See section 7.b for additional information on genetic counseling.

### Uploading Data to the Participant's Medical Record and Sharing Results with Providers in the EMR (Clinical Care)



**Figure 4** –Patient Results in the Medical Record

Legend – green check mark means the info will get placed in the chart; red X means it will not. The legend for the document letters (A through I) is explained in the in box below):

Letters in Boxes from Figure 4	Document Name in eIRB
--------------------------------	-----------------------

A - Note in Chart [High/Mod Risk/Limited - Joined]	N/A. Study staff, including CRSS staff at KPNW will document the participants consent in their EMR per standard processes
B - Note in Chart [High/Mod Risk - Decline]	KP and DH - Results - Provider Letter - Study Decliners - At risk
C - Note in Chart [Limited - Decline]	KP and DH - Results - Provider Letter - Study Decliners - Limited Family History
D - Note in Chart [Yes GC Visit and No GC Visit]	KP and DH - Results - EMR Smartphrase - Overall Template
E - Note in Chart [Yes GC Visit and No GC Visit]	KP and DH - Results - EMR Smartphrase – Hereditary Cancer Syndrome Genetic Test Results
F - Note in Chart [Yes GC Visit and No GC Visit], only if ppt said yes to getting carrier results	KP and DH - Results - EMR Smartphrase - Carrier Status Genetic Test Results
G - Note in Chart [Yes GC Visit and No GC Visit], only if ppt said yes to secondary findings	KP and DH - Results - EMR Smartphrase - Secondary Finding Genetic Test Results
H - Scan clinical report into Epic [Yes GC Visit and No GC Visit],	KP and DH - Results - Clinical Report - Exome Results
I - Note in Chart [No GC Visit - Lost to F/U]	KP and DH - Results - Provider Letter - Study Ppts - Lost to Follow-up
J – Note in Chart [Limited Hx + Neg result]	KP and DH – results – EMR Smartphrase – Negative Addl Questions
K – Participant Letter	KP and DH – Results – Participant Letter – Screen Negative Additional Questions

Please refer to Figure 4 regarding study information that will be entered into the participant’s medical record. It will include information such as the results of the risk assessment including updating family history in the chart, the clinical report from the testing laboratory, and any medical recommendations for the study participant based on their results.

Our initial plan is to not put the average risk PREMM and B-RST results for participants in the patient’s medical record as a chart note (See Figure 4 – “Average Risk”). This is due to multiple factors, including Kaiser Permanente’s and Denver Health’s Epic teams needing to facilitate this work if it is to happen, potential intellectual property concerns with the developer of the tools, and clinician request to not clutter the EMR with information that is not actionable.

The genetic test results and recommendations will be available to the primary care provider in an electronic communication. In most cases, this information will be entered after the participant completes genetic counseling and has had an opportunity to discuss their results with a clinical genetic counselor, or they have received a negative letter in the mail. In some circumstances, we may not be able to successfully reach the study participant for a genetic counseling session, and the information will

be entered in the absence of genetic counseling. In these circumstances, an electronic communication will be sent to the participant's primary care provider and an additional recommendation will be added to the participant's medical record for genetic counseling. Providers will be given contact information for the study and referral information for additional genetic services.

The Return of Result protocol for Denver Health CHARM participants includes phone outreach and communication with the participant's primary care provider. In the rare event of an abnormal genetic result with medially actionable consequences with the failure of all other forms of outreach, Denver Health CHARM research staff may outreach directly to the participant at their last known address, as happens in routine clinical care. In that event, both the research assistant and the care navigator together would drive to the home during business hours, assess the safety of the neighborhood, and if safe, knock on the door /ring doorbell and outreach to the participant. A card or note with the study information and a request for the participant to outreach to the CHARM staff may be left at the address in the event the participant is not located. The CHARM study staff will update the CHARM Tracking database as well as our DH REDCap recruitment database. Information to this effect will additionally be sent to the participant's primary care provider by a study clinician (Sonia Okuyama or Katy Anderson) and the participants electronic medical record will be updated with the study results are per study protocol.

Genetic counselor clinical judgement will be used when creating electronic communication such as chart notes, updating the problem list and family history sections of EPIC; Figure 4 is a guideline only. For example, we plan to review the problem list and family history sections of the EMR at these timepoints (green check marks) but depending on what is already present in these fields, we may or may not make changes or edits.

In addition, if participants were eligible to join the study, their risk assessment tool results will be available to the primary care provider in an electronic communication ('Chart notes' in Figure 4).

We acknowledge that there may be burden on primary care providers to follow up with patients, although we will be giving providers information to help with the expert recommended follow up and study staff will do what they can (answer questions, be available for additional information) to help minimize this burden.

### Survey data

Participants will be asked to complete 3 surveys: a baseline (BL) survey before results disclosure/genetic counseling (Box 9, Figure 3a&b), a follow-up (FU1) survey about 0-2 weeks post result disclosure/genetic counseling (Box 21, Figure 3a; Box 23, Figure 3b) though allowing participants to reply up to 4 weeks, and second follow-up (FU2) survey approximately 3-7 months post result disclosure/genetic counseling (decision on timing will consider consortium guidance) (Box 22, Figure 3a; Box 24, Figure 3b). The BL survey will assess domains such as sociodemographics, self-reported health and quality of life, psychosocial outcomes (e.g., health literacy and numeracy), perspectives of genetic testing, and satisfaction and understanding of the consent visit. After the approval of IRB study modification #41 and with implementation of the decision aid around November 2019, we will move to 2 baseline survey

versions. We will be using one baseline survey for participants randomized to the decision aid arm and one baseline survey version for participants randomized to the usual care arm. Both baseline surveys will contain knowledge questions and questions assessing decision conflict (regarding the decision to receive optional secondary findings), as part of the decision aid assessment. We will also add Values Self-Assessments to the baseline survey for the usual care arm. Values Self-Assessments are part of the Consent and PRA Process – Web Pages of the decision aid arm, approved with study modification #37. Only those participants enrolled after the beginning of randomization (i.e., receiving the decision aid and revised usual care versions of the consent form) will also receive the revised baseline survey (DA version or UC version, respectively). Spanish-speaking participants will receive the same Spanish version of the baseline survey, without modifications.

With study modification #41, we are moving ‘Locus of Control’ questions towards the end of the baseline surveys, past the demographic section. The FU1/FU2 surveys will also assess additional domains such as satisfaction and understanding of the genetic counseling sessions/letter, impact of genetic testing results, decisional regret (regarding the decision to receive optional secondary findings—FU1 only; which is being submitted with study modification #41) and personal utility. Only English-speaking participants enrolled after the beginning of randomization will also receive the revised FU1 survey.

For patients that are eligible for the study but decline enrolment (usual care group), we will invite a portion of them to complete a short, voluntary survey to obtain information on why they do not want to participate in the study and demographic characteristics.

We will collect name and address in order to mail a \$10 gift card to Fred Meyer as a thank you for the participant’s time. We will not share their address with anyone else.

### Interviews

A portion of participants will be interviewed after consent (Box 8, Figure 3a&b) and after result disclosure (Box 18, Figure 3a; Box 20, Figure 3b).

#### *Post-Consent*

Our recruitment targets for the post-consent interviews is approximately 75 patients (roughly 50% will be study participants that agreed to continue in the study after receiving their risk assessment tool results and the other 50% will be patients that are eligible for the study but decline enrollment (usual care group)).

The post consent interview will occur within approximately 2-4 weeks of becoming eligible to continue in the study. Questions will address domains including satisfaction with the consent process and research interactions, understanding of the study and results, and decision-making factors.

Criteria for identifying post-consent interviews include: mix of English and Spanish-speaking participants, mix of DH and KP participants, and demographic information to ensure demographics of interviewees reflects study population.

#### *Post-Results*

Our recruitment targets for the post-results interviews (Post-Result Disclosure = Post-RD) is up to 100

patients (about 2/3 will occur as soon as possible after participants complete their FU1 survey and about 1/3 will occur approximately 6 months after they receive their results. Questions will address domains including pre-study familiarity with genetic testing, their experiences with the study, understanding of their genetic counseling results and recommendations, and impact of use of interpreters for Spanish-speaking participants. Our selection criteria are described below, although we may modify them based on scientific need (i.e. if we don't have 10 patients with VUS results, we will shift those recruitment targets to another group of participants).

#### Selection Criteria for Post-RD1

- Didn't refuse to participate when GC mentioned they may be contacted for an interview
- Didn't participate in a personal utility interview
- Test results (25 positive test results cancer (including likely pathogenic), 5 negative test results for everything, and 10 VUS test results cancer; 10 positive for secondary)
- Completed FU1 survey
- To the extent possible given the test results goal, include a diverse sample (SES, literacy, age, DH/KP, language, gender) race/ethnic minority; geocode with less than 20% w high school educ)
- To the extent possible given the test results goal, include Modified and Trad arm participants in relatively equal numbers

#### Selection Criteria for Post-RD2

- Didn't refuse to participate when GC mentioned they may be contacted for an interview
- Didn't participate in a personal utility interview
- Test results (e.g. 15 positive or VUS for Cancer and 10 positive for Secondary)
- Participated in RD1; if can't recruit enough, include those who did not participate in RD1

#### *Additional interviews*

In addition to the post-consent and post-results interviews described above, we will also conduct some additional interviews. Participants in these additional interviews will be informed that these are in addition to the interviews described in the original consent and that they will get additional compensation for doing them.

The first set of additional interviews will be on the general topic of respect. Our recruitment target for these interviews is roughly 40 patients (roughly 50% study participants and 50% patients who are invited to take the risk assessment tool and either (a) do not complete the risk assessment tool or (b) complete the risk assessment tool and are eligible for the study but decline enrollment).

These "respect" interviews will occur within approximately 1-6 months of becoming eligible and/or being invited to the study. Question domains will include reflections on interactions with the study team, views on respect in healthcare and research settings, and trust in researchers and medical professionals.

Criteria for identifying the "respect" interviewees include: mix of English and Spanish-speaking participants, mix of DH and KP participants, and demographic information to ensure demographics of interviewees reflects study population. We may ask participants at the end of the post-consent

interview if they are willing to be contacted for another interview; if they decline, they will be excluded from these interviews. We will also exclude individuals who decline the post-consent interview.

The second set of additional interviews will be on the topic of personal utility and will address the ways that participants perceive genetic testing to provide benefits and/or cause burdens and harms. These interviews are part of an administrative supplement project with several other sites across the CSER Consortium. Overall, this sub-project aims to interview 60 adult patients and parents of pediatric patients who receive genetic testing results across 6 CSER sites (Baylor College of Medicine; HudsonAlpha Institute for Biotechnology; Icahn School of Medicine at Mt. Sinai; Kaiser Permanente Northwest; University of California, San Francisco; University of North Carolina at Chapel Hill). All interviews with CHARM participants and transcription thereof will be managed by our study team. Only de-identified transcripts and combined demographic data will be shared with collaborators at other sites.

At KPNW, we will conduct semi-structured interviews with approximately 10 CHARM participants. The enrolled CHARM participants to be interviewed are adults only and their age ranges from 18 to 49 years. Questions will cover such topics as background information about their study participation, the experience of receiving results, and how this information made an impact in their life. Criteria for inclusion are that the participant received sequencing results from the CHARM study within the past 2 months to 2 years. To the extent possible, we will aim to have race/ethnicity representative of the CHARM study population and a balance of gender. We will also include participants with a diversity of sequencing results, including: diagnostic or secondary monogenic findings; carrier findings; pharmacogenomics; variants of uncertain significance; and “negative” or no findings.

#### Health System Data

We will follow all participants that have completed the consent process via their medical record up until the end of the study period (Box 20, Figure 3a; Box 22, Figure 3b). This may involve both electronic queries and chart review to ascertain information such as about healthcare encounters both directly related to genetic results (i.e. genetic counseling, screening visits and procedures) and indirectly related (i.e. mental health visits, visits with PCP). See Table 2 in Section 7 (Data Analysis) for more information on data points to be collected.

#### Testing of Family Members

First and second degree relatives will be offered genetic testing if the study participant has a pathogenic or likely pathogenic variant in a cancer-related gene, or a pathogenic variant a gene for a medically-actionable additional finding (Box 23, Figure 3a; Box 25, Figure 3b). Family members of study participants that have a VUS in a cancer-related gene may be offered testing, but this will be determined on a case-by-case basis. Family member or partner testing will not be offered to participants who have a pathogenic variant in a carrier status gene. Family members will be contacted by the study participant by letter, email, or text message. Family members who decide to proceed with testing will provide written informed consent, and they will be tested only for the known familial variant and not receive clinical exome sequencing. These family members will receive genetic counseling for results disclosure by a member of the study team.



## 7. Data Analysis

### a. Analysis Plan

All analyses and subanalyses may utilize data collected as part of participant or study team interactions within study tracking databases, including the tracking system and REDCap.

Family History and Yield of Reportable Findings. To test the hypothesis that participants with incomplete or reduced family history (relaxed threshold for the risk assessment) will have a lower yield of reportable findings than participants with sufficient family history information (standard thresholds), we will use multivariable logistic regression to compare the yield between those with sufficient family history (standard thresholds=1) and those with incomplete or reduced family history (=0), and include a propensity score as a covariate. The propensity score will be used to account for the likelihood that individuals with incomplete knowledge of their family history or reduced thresholds for family history are likely to be younger, have fewer social connections in their family, or have less access to healthcare than those who have sufficient family history. A significant odds ratio that is greater than one would support the hypothesis that those with sufficient family history information have a higher yield of reportable findings. For analyses and subanalyses related to family history data, we may use risk assessment and consent data recorded in the tracking system and/or differences in family history report recorded by GCs during result disclosure.

Effectiveness of the Modified Genetic Counseling Approach. To test the hypothesis that participants who receive the modified genetic counseling will demonstrate a greater understanding of how to interpret genetic testing results, more satisfaction with the genetic counseling encounter, and improved communication with family members than participants who receive standard genetic counseling, we will model survey data for these domains using an independent-samples t-test to compare the two groups. If the assumptions for this analysis are not met (e.g., domain scores are heavily skewed), we will use an equivalent nonparametric analysis. We will examine whether demographics, socioeconomic status, and health insurance modify the effect of the counseling on the outcomes using a series of multiple regression analyses; one for each outcome and moderator. The regression will include an indicator for arm, the moderator, and a term representing the product of the arm and moderator (i.e., the interaction term). A significant effect for the interaction term would suggest moderation and will be followed up with graphs of the simple effects to interpret the nature of the effect modification.

Genetic Counseling Approach and Healthcare Utilization. To test the hypothesis that participants in the modified genetic counseling groups will utilize fewer follow-up visits with genetic counselors and fewer visits with PCPs to discuss their genetic testing results compared to participants in the standard genetic counseling group, we will model differences in utilization using negative binomial regression. We will construct separate outcomes using EMR data that measures each category of utilization across the 12-month period following randomization. To test the hypothesis that participants with a reportable finding (pathogenic, likely pathogenic, or VUS) in the modified genetic counseling group will adhere better to recommended screening over the 12-month follow-up period compared to those in the standard genetic counseling group, we will use logistic regression to estimate the differences in receipt of recommended screening services.

Study Participation and Healthcare Utilization. To test the hypothesis that study participants will use more healthcare services than the usual care group during follow-up we will use a two-part model. In the first stage of the model we will use logistic regression to look at how many people use a service at all. In the second part we will look at the number (count) of visits for those who use any of a service. This later part is typically analyzed using negative binomial regression, but it can be examined with several different approaches, therefore we will formally test which model that has the best fit.

Genetic Testing Result and Healthcare Utilization. We will test a series of 4 hypotheses related to the results of genetic testing and healthcare utilization. The first 2 hypotheses are: 1) that participants with a reportable finding will initiate recommended care compared to the time period prior to results disclosure/genetic counseling and 2) that participants without a reportable variant will either not start additional services (which are not recommended for them) or discontinue recommended care related to their family history compared to the time period prior to testing. To test these hypotheses, we will compare the rate of recommended uptake in the year prior to results disclosure/genetic counseling to the year following using generalized estimating equations (GEE) with a logit link and binomial distribution to account for the pairing of observation periods within persons. The independent variables will include a dummy indicator for time [prior year (0) vs post year (1)], a dummy indicator for result [no findings (=0) vs at least one reportable variant (=1)] and a product term of time and group to represent the interaction. A significant product term would indicate a difference in uptake of recommended care. An  $OR > 1$  for those with a reportable finding would indicate that they are more likely to increase their level of recommended uptake while an  $OR < 1$  for those without a reportable finding would indicate they decreased their level of recommended uptake. The next 2 hypotheses are: 3) that participants with a reportable finding at KP will use recommended care more often compared to participants at DH and 4) that participants with a reportable finding who are racial/ethnic minorities or have low SES compared to participants without these characteristics will use recommended care less often. To test these hypotheses, we will use logistic regression to determine whether there are differences in the uptake of recommended actions by the groups of interest (KP vs. DH and diverse vs. not diverse). We will develop propensity scores for each comparison model to account for confounding. A significant OR for group after accounting for the propensity score would indicate that there is a difference in the uptake of recommended actions between the groups.

We will also review genetic testing and healthcare utilization among all KPNW patients that have received genetic testing for HBOC or LS to assess uptake of recommended actions after genetic testing results have been received, as well as actions that might not be recommended, such as among individuals with a VUS result. We will also describe demographic and clinical characteristics (e.g., personal cancer history) of those who receive genetic testing and patterns of testing for these conditions at KPNW.

Genetic Testing Results and Personal Utility. To assess the personal utility of exome sequencing, survey responses will be modelled using multivariable logistic regression, assessing each time point independently. Predictors will be factors such as sex, age, cancer history, race/ethnicity, socioeconomic status, insurance status, and healthcare setting. We will assess how patient perspectives on personal utility vary with the type of study results including primary findings (pathogenic, likely pathogenic, VUS, or none reported) and additional findings for carrier status or other medically actionable conditions. We will use GEE models to assess changes in survey

responses over time while accounting for correlation in responses for each participant. We will use a conservative two-tailed p-value of .01 to account for multiple testing.

#### Decision Aid analyses.

##### Informed values-choice congruence

Our primary endpoint is informed values-congruence. A high-quality decision, the goal of decision aids, is ideally informed by knowledge of the options and is “value congruent,” defined as the match between the chosen option and the patient’s values. We will classify someone as having “informed values congruence” if they are classified as value congruent AND are considered to have ‘adequate knowledge.’ Any other combination will have participants classified as not having informed values-congruence.

We will determine whether those who received the web-based decision aid differ in informed values-choice congruence from those who received usual care web-based information by using multiple logistic regression. The binary indicator of informed values-choice congruence will be the dependent variable, and binary indicators of arm (0=usual care web-based information, 1=web-based decision aid) and the randomization stratification factor of site (0=Denver health, 1=KP) will be the independent variables. A significant odds ratio > 1 would provide evidence for the effectiveness of the web-based decision aid in resulting in greater informed values-congruence.

#### Secondary outcomes

We will use the same analytical approach for the secondary binary outcomes of values congruence, decision to opt-in, and adequate knowledge. For the continuous secondary outcomes of knowledge level, decisional conflict, decisional regret, and time spent on the web platform, we will use multiple linear regression to compare the two arms. The independent variables will be the same as described for the logistic regression model. We will use a two-tailed  $\alpha=.05$  for all analyses. All analyses will be carried out using the intent-to-treat principle by including all participants in analyses and their original arm assignments.

#### Applicable Power Analyses:

Family History and Yield of Reportable Findings. The projected sample size is 880, and we expect 25% of participants will have incomplete family history. Assuming 20% of participants who meet standard criteria have a reportable finding, the power is >80% if the yield is <11.9% in the group with incomplete family history.

Effectiveness of the Modified Genetic Counseling Approach. The projected sample size is 880 with 50% in each counseling group. For the secondary analyses examining whether there is a difference in the change in outcomes from baseline to follow-up, and assuming an autocorrelation of .70, we will have over 80% power to detect a Cohen’s d of the difference in change of .15.

Genetic Counseling Approach and Healthcare utilization. We assume a sample size of 880 participants and anticipate a 20% reportable primary finding rate. Using data from preliminary studies at KPNW, we calculated that people with a family history of cancer charted in the EMR had 6.8 outpatient visits per year. We assume power=.8 and a two-sided  $\alpha=.05$  and a 12 month

follow up period. Because we were unable to find estimates of the baseline annual screening, we assumed an annual screening rate of 50% among adults aged 18-49 with a pathogenic or likely pathogenic result. With the same assumptions as above, and using logistic regression, we will be able to detect odds ratios  $\geq 2.39$ .

Study Participation and Healthcare Utilization. We project a sample size of 1760 for the primary comparisons. Using data from age-eligible members at KPNW who had a charted EMR indication of family history of cancer, we calculated the mean number of outpatient visits (6.8) and the proportion of patients receiving colonoscopies (.027) over a 12-month follow-up period ending June 2016. All calculations assumed power=0.8 and a two-sided  $\alpha=.05$ . We have power to detect odds ratios  $\geq 2.02$  for the occurrence of a colonoscopy over 12 months following results disclosure/genetic counseling.

#### Decision Aid.

##### *Informed values congruence*

For the 8 true-false knowledge assessment questions we estimate that 75% of participants in the usual care group vs. 95% of participants in the decision aid group will achieve an “adequate” knowledge score (6 or more out of 8 (75%) questions and one in each of the 4 domains correctly). We estimate that 80% of participants in the usual care group will have values-choice congruence; this is because the population is biased toward wanting to receive genetic information; their values responses and their choice will likely reflect this. We estimate that 99% of participants in the decision aid group will have values-choice congruence. This is because the decision aid enables them to identify their values before deciding whether to receive the secondary findings; it also provides summative guidance from their values responses, guiding them toward a values-congruent decision. Overall, we estimate that 75% of participants in the usual care group vs. 89.5% of participants in the decision aid group will have informed values-choice congruence.

Assuming a rate of informed values-congruent decisions in the usual care arm of 75%, and assuming that 93% of participants continue to complete the baseline survey (N=216) and a two-tailed alpha level of .05, we will have 80% power to detect an odds ratio for arm of at least 2.84. That is, we will be powered to detect a 14.5% or larger difference between the usual care (75% informed values congruence) and web-based decision aid arms (89.5% informed values congruence). Power calculations were performed with PASS 15.

#### Quality Control Procedures:

#### SURVEY DATA:

While we will implement surveys using a variety of modalities, our preferred approach is web-based instruments. The surveys will be developed and conducted using RedCap. The completion of surveys will be tracked using a CHR-developed tracking system. Because we prioritize data completeness, we will also conduct surveys on paper or verbally (read aloud by study staff and with participant’s verbal response entered by study staff into the web-based instrument) to increase participation. We will use double entry for data obtained on paper to minimize errors.

We will include survey reminders for study participants at encounters with study staff and provide incentives to increase the response rate. Before any analyses are carried out, we will audit the data for quality and completeness, including missing data patterns. We will evaluate distributions to ensure that they meet the assumptions of planned analyses (described above), including the detection and review of outliers (another potential indicator of entry error).

#### EMR DATA:

The EMR systems at KP and DH provide comprehensive medical histories. Manual chart review will augment EMR data; we will abstract data from physician notes, scanned reports, or other uncoded fields in the EMR. See Table 2 below for data points on the types of information that we will use from the EMR and specific examples of variables within those categories. All members of our analysis team have experience with extracting similar data from the EMR and working with multi-institutional data sets. We will run frequencies on EMR variables to audit the data for quality and completeness, including missing data patterns.

**Table 2: EMR and Chart Review Data Points**

<b>Data Points</b>	<b>Applicable to:</b>
age, language	Screening/Eligibility
race, ethnicity, sex/gender, insurance, census variables (income and education)	Screening/Eligibility: Inclusion/Exclusion criteria
early screening and more frequent screening (mammography, colonoscopy; dates), family history indication of cancer or diagnosis codes for personal or family cancer history (e.g. renal/bladder, endometrial, breast, colorectal, prostate, ovarian, pancreatic, or cancer), additional screening modalities (breast MRI, breast biopsy; dates), incomplete referrals to genetic counseling	Screening/Eligibility: High Risk (more likely to screen eligible)
phone, address, email, home clinic, PCP, name, DOB, MRN, marital status, date of last visit, dates of upcoming visits	Screening/Eligibility: Contact Information/Identifiers
<i>captured in screening/eligibility criteria above</i>	Enrolled Participants and Usual Care (Decliners): Demographics
type of encounter (PCP outpatient, genetic counseling, mental health, etc.), number of visits, dates and timing of visits, diagnosis codes, procedure codes and chart review (mammography, colonoscopy, prophylactic breast surgeries, oophorectomy, hysterectomy, endoscopy, ovarian cancer screening procedures, endometrial cancer screening procedures, etc.) diagnosis codes relevant to genetic results/findings; receipt of genetic services outside of study and results, recommendations and indications for care (chart review), costs associated with services	Enrolled Participants and Usual Care (Decliners): Healthcare Encounters

comorbid conditions, ICD codes for summary risk measures (Charlson), medication use, benefit structure/insurance status, tobacco use, family characteristics	Enrolled Participants and Usual Care (Decliners): Propensity score methodology
Prior genetic testing for HBOC and/or LS and related care (e.g. genetic counseling, screening tests, prophylactic surgery)	All KPNW members

## b. Disclosure of Results with Subjects

Results originating from the CLIA-certified laboratory will be disclosed to individual participants and entered into their medical record. The purpose of entering the information into their medical record is to ensure the provider receives the results and is aware of medical recommendations based on their patient's results.

Secondary findings during exome sequencing are possible. As described above, participants will have the choice to learn of secondary findings including medically-actionable conditions (not related to cancer) and carrier status results (for those consented prior to approval of study mod 27) in addition to learning results related to hereditary cancer syndromes. An example of a secondary finding that could occur is that a gene that is tested for carrier status could be found to have two pathogenic variants for a particular individual, in which case they would be at risk of being affected with the condition. This happened in our last study for a gene related to hereditary deafness, and the person was found to have some hearing loss that might have been explained by this finding. This was a true secondary finding. This study will not release other kinds of secondary findings or interpret variants absent from the study gene list.

Genetic test results will be scanned into the participant's medical record by KP and DH research staff after results disclosure/genetic counseling session with the participant by UW and KP genetic counselors. Additionally, any medical recommendations for the study participant based on those genetic test results will be shared with them and entered into their medical record. If we are unable to contact the participant after at least 6 contact attempts via a variety of means (text, phone, mail, email) we will place the test results into the medical record so the patient's provider can access them. We will include a chart note that the patient has not received the results from the study team.

## c. Data and Specimen Banking

Specimens will not be used for future research.

Genomic data (both raw data and variant files) will be stored indefinitely and available for future research via dbGaP or other federal databases. Access to data in these databases will be managed according to the processes and procedures of dbGaP or other federal databases. Access to KPNW genomic data for future studies will be governed by the CHR Advisory for Biospecimen Committee (ABC). Data will also be shared with the CSER consortium (process for sharing in development).

## 8. Privacy, Confidentiality, and Data Security

Specimens: Saliva specimens collected from study participants.

- a. Who: Staff responsible for recruitment (coordinating the collection of the saliva sample), mailing, receipt, processing, and testing of samples will have access to the samples.
- b. Where: Samples will be collected at KPNW, Denver Health, or at the participants home. Samples will be sent to UW and stored at UW. Specimens will be destroyed at end of study.
- c. Type of Data: Fully identifiable labels on each specimen containing full PHI (see "Sample Collection" under section 6 for information about how specimens are labeled)
- d. Transfer protocol: Materials will be sent through regular USPS mail or through a mail courier

Genomic Data: Genomic data generated at UW will be sent to KPNW and stored indefinitely (see section 7.c for more information).

- a. Who: Study staff responsible for managing genomic data, interpreting or analyzing the data, or managing the data long term will have access to these data
- b. Type of Data: Fully identifiable
- c. Transfer protocol: Data will be sent from UW to KPNW using the CHR secure transfer site or an encrypted external hard drive will be mailed to KPNW.
- d. Storage security: Stored on an encrypted, external hard-drive stored in a locked room and within the key-card controlled areas of CHR/Denver Health buildings or a folder within the file share network with restricted access.

Genetic Reports: Clinical Reports created by the UW staff, which will be the record uploaded to the patient's EMR (see attached documents in the eIRB for the template). The clinical lab at UW uses the GeneInsight report writing system. There are two components: 1) GeneInsight Lab, and 2) GeneInsight Clinic. Reports are written in the Lab module, and then sent to the Clinic module for dissemination to providers.

- a. How data will be collected: Data contained in the clinical reports is generated from testing and interpretation at UW.
- b. Type of Data: Fully identifiable
- c. Security: GeneInsight is a HIPAA-compliant, web-based system, hosted by Sunquest. Limited staff at UW will have access to the Lab system, on an as-needed basis. To access clinical reports through GeneInsight Clinic, UW staff will create one CHARM account, to which all reports will be sent. This account can only be accessed, via web browser, with the specified login/password credentials. All data is encrypted "in transit" and "at rest". Study personnel will only have access to the Clinic account. UW staff will provide the login credentials to necessary study staff to the Clinic account when the study is ready to begin issuing and disseminating reports.
- d. Transfer protocol: Study staff identified as requiring access to the clinical reports will be given permission to log onto the UW system and download a PDF version of the clinical report. When new reports from the study are posted, UW will send a generic email notifying study staff to log-on and check for new clinical reports.

Tracking System: The study tracking system will track study activities and will be accessible to study staff located at the collection sites and UW.



- a. Storage location: This tracking database will be developed, housed, and maintained by KPNW
- b. How data will be collected: Data will be data entered into the tracking system or imported from other study systems. Both KPNW and DH patients will be tracked in the tracking system. Recruitment staff will be trained on the tracking system.
- c. Type of Data: Fully identifiable data is needed to ensure study staff have data available necessary for study activities. For instance, full name and other identifiable information is required for UW to develop the clinical reports that will be disclosed to study participants. Study staff also need contact information to contact participants to disclose results, ask participants to complete surveys, respond to questions, etc.
- d. Security: The tracking system application is hosted by CHR in their data center on fault-tolerant server clusters running Windows Server operating system. Separate clusters are used for the database and web servers, Microsoft SQLServer 2014 R2 and Microsoft Internet Information Systems 8.5, respectively. The data center is restricted via card-reader access and limited to only key personnel. All application requests on the web servers are secured via 256-bit SSL encryption for data in transit. Access to the participant tracking application is restricted via account authentication and uses group management to assign permissions. Access to specific site participants can be restricted to only staff from the specified site. Accounts use single session cookies for tokens and are automatically logged out after 30 minutes of inactivity.

#### Web (Risk Assessment Tools/Consent):

- a. Who: Study participants or study staff assisting the participants with surveys from all collections sites that will be involved in the data entry of data. These data will be entered via tablets at the collection site clinics, computers at sites, or via participants' own devices. KPNW staff that are involved in the management of the data, data cleaning, and creation of final datasets will also have access to the data in this system
- b. Where: KPNW
- c. What Identifiers: Fully identifiable information
- d. Other Security Measures: The web application for screening tools and consent is hosted by CHR in their data center on fault-tolerant server clusters running Windows Server operating system. Separate clusters are used for the database and web servers, Microsoft SQLServer 2014 R2 and Microsoft Internet Information Systems 8.5, respectively. The data center is restricted via card-reader access and limited to only key personnel. All application requests on the web servers are secured via 256-bit SSL encryption for data in transit. The screening tools do not use account authentication to restrict use, as the tools need to be accessible to participants in a clinic setting. No data collected via the screening tool is viewable after a session is completed. Access to the screening data is limited to users of the tracking system and key data center staff. All data is secured via encryption in transit.

#### Surveys:

- a. Who: Study participants or study staff assisting the participants with surveys from all collections sites that will be involved in the data entry of data. KPNW staff that are involved in the management of the REDCap survey, data cleaning, and creation of final datasets will also have access to the data collection tool
- b. Where: External REDCap survey
- c. What Identifiers: Fully identifiable information.



- d. Other Security Measures:
  - i. REDCap Security:
    1. REDCap is a HIPAA-compliant, web-based application for collecting and managing research data. It is created and supported by the REDCap Consortium at Vanderbilt University and it is used at over 1,000 sites world-wide. Additional information about REDCap can be found at the following link:  
<http://www.project-redcap.org/>
    2. CHR runs its own private instance of REDCap, which is housed at CHR. REDCap is hosted on a web server which is located in the CHR computing center. This web server uses an SHA 2 SSL certificate to encrypt the data transferred between the server and the end user's web browser. The database backend of REDCap is located behind the CHR firewall. Both web and backend servers are protected and are monitored for any unusual or malicious activity.
  - ii. Restricted Access to the REDCap survey
    1. REDCap uses user rights settings that uniquely identify each user and log their activities. These internal security settings determine the access and privileges of the signed in user.
    2. The PM or PI from each collection site will request access to the REDCap survey on behalf of their study staff by contacting the KPNW Project Director, Project Manager or the REDCap Manager. KPNW staff will instruct study staff how to create an account and will grant them access to the survey. If employees leave the project, the collection site PM or PI will be responsible for contacting the KPNW PM who will revoke access to the instrument.
    3. REDCap users will need to create an account username and password, which will be required when logging onto the REDCap survey

Genetic Counseling Sessions, Interview Recordings and Transcripts:

- a. Who: All participants will have their genetic counseling sessions recorded (to allow study staff to prep for follow-up interviews). A portion of study participants will be interviewed over the phone after the consent and results disclosure/genetic counseling process by CHARM study staff.
- b. Where: Phone calls will be recorded; transcripts of recordings will be created.
- c. What Identifiers: Study ID will link participant to transcript and recording. Fully identifiable information may be on the recording. We will de-identify the transcripts as much as possible.
- d. Other Security Measures:
  - i. Recordings will be stored on limited access study fileservice.
  - ii. Recordings and transcriptions of recordings will be shared among study staff at necessary sites via secure file transfer mechanisms.

## 9. Provisions to Monitor the Data to Ensure the Safety of Subjects

We believe that this research is minimal risk to participants. Project staff will review calls and voicemails from study participants and alert study team (PIs, Project Director) of any unexpected safety events immediately. Survey data entered by study staff will be double-entered to identify mistakes in data

entry. For paper risk assessment tools completed in clinics, recruitment staff will review the forms for completeness and accuracy. Study analysts will identify and work with the team to resolve inconsistencies in data accuracy and quality.

We will report any protocol deviations to the IRB. A protocol deviation/AE/SAE reporting log will be on the website so any events can be tracked and reported to the IRB within the required timeframe. We plan to review study processes at regular all-team meetings and submit any necessary protocol changes to the IRB.

## **10. Risks and Benefits**

### **a. Risks to Subjects**

By answering these family history questions, some people may learn the cancer in their family tree is more than average, and they may be offered genetic testing using saliva (spit) and/or additional medical care to reduce cancer risks.

There are limitations to the clinical exome sequencing and the clinical knowledge of genetic testing continues to grow. The results for each participant are limited to what was tested and the clinical impact of their result could change over time. Participants with normal results may not understand that they may have another gene that was not tested and be falsely assured by their results. Participants with a genetic variant may worry about their test results. They also might find it difficult to talk with family members about their results.

Data is being shared across many sites. It is possible that unauthorized release of confidential health information will occur. We have safeguards in place to prevent this from happening.

Some content areas covered in the surveys might cause a participant to feel distress. Many of the survey questions are validated measures. Participants can complete the survey in private and participants can refuse to answer any questions.

While there are currently laws (GINA) in place to protect discrimination from genetic testing results, if those laws change it is possible that having a positive result could impact a person's ability to get life insurance, or health insurance.

The healthcare institutions (KP and Denver Health) also are assuming some risks. It is possible that results could be scanned into the wrong participant's EMR, leading to incorrect care if the provider does not confirm the patient's name on the report.

### **b. Potential Benefits to Subjects**

Participants in this study will learn more about their personal and families' risk of cancer. They will learn if they have a gene variant for Hereditary Breast and Ovarian Cancer syndrome and Lynch Syndrome. They may also learn if they have a gene variant for other conditions of medical

significance or if they have a gene variant that they could impact their child's health (if they choose to get these results). We expect 10% of study participants to have one of these gene variants. All participants will be informed of their results by a genetic counselor and be able to ask questions. Participants may be reassured by their results and the information they receive from the genetic counselor. It is possible that because of participation in this study, participants will make behavioral and clinical decisions that could prevent cancer or detect cancer earlier; their family members may also be impacted similarly.

## **11. Costs to Participants**

Study related genetic testing and genetic counseling will be provided at no cost to the participant. Any downstream medical care that is recommended because of the test result (e.g. mammography, colonoscopy) will be subject to the participant's medical benefits. This is discussed in the consent.

## **12. Compensation to Participants**

Participants will be compensated for their time and inconvenience. After approval of study modification #40, we will change the incentive for completing follow-up survey 1 and 2 from \$10 to \$25 aiming to increase survey response rates. Participants will receive a \$25 gift card for each survey completed (2 week follow-up, 3-6 month follow-up). They will receive an updated survey cover letter/email indicating the correct reimbursement amount. Consent, recruitment email/letter, and the follow-up surveys 1 and 2 will also reflect this change. Participants will also be compensated with a \$30 gift card for completing the baseline survey and returning the completed saliva kit. Some patients will be invited to complete interviews after consent (\$20) and/or after result disclosure (\$20), for a total maximum of \$120 per participant. Compensation is described in the consent.

We will also compensate eligible participants who decline participation in the study \$10 for completion of the decliner survey.

In addition, participants who complete a "respect" interview will receive an additional \$20.

## **13. Resources Available**

All test results will be disclosed by trained genetic counselors. Genetic Counselors who will be providing the modified genetic counseling approach will receive additional communication-focused training.

## **14. Drugs or Devices**

Our study does not meet the criteria as a device needing FDA approval.

## **15. Multi-Site Coordination**

The KPNW IRB will be the IRB of record for the sites listed below:

Denver Health  
Seattle Children's Hospital  
University of Washington  
Columbia University  
University of California San Francisco (UCSF)  
Kaiser Permanente Colorado (KPCO)  
Emory University

We have a study website that uses the CHR Project Management template. All study staff have a login, and all final IRB-approved study materials will reside there. Approved modification documents will be added as well, and older versions of materials will be archived to mitigate version control issues. The study project manager, with the assistance of the study project director, will ensure all documents are loaded to the study website in a timely manner and an email is sent out to study team members to let them know of the new documents. In addition to study documents, a protocol deviation/AE/SAE reporting log will be on the website so any events can be tracked and reported to the IRB within the required timeframe. Study team members will be advised to notify the PIs and Project Director of any protocol deviation or adverse event.

Manual of Procedures (MOPs) will be developed and followed to ensure sites are conducting all aspects of the study appropriately. Data will be shared according to local security policies as identified by Risk Assessment Mitigation Processes at applicable sites. The study team has many workgroups and team calls throughout the month to communicate any IRB issues, study progress, or data needs. The study funder requires quarterly reports, which all sites will contribute to as needed.

## **16. Community-Based Participatory Research**

As previously approved in the design phase (Phase 1) for this study, we will be talking with local underserved community members as well as DH and KPNW patients. Additionally, we will regularly be meeting with clinic representatives at both Kaiser Permanente and Denver Health to ensure our implementation and recruitment is going smoothly and meeting the needs both of the study and patients/providers.

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