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Cancer Health Assessments Reaching Many (CHARM): A clinical trial assessing a multimodal cancer genetics services delivery program and its impact on diverse populations

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Conflict of Interest

All authors report no conflict of interest.

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Abstract

Advances in the application of genomic technologies in clinical care have the potential to increase existing healthcare disparities. Studies have consistently shown that only a fraction of eligible patients with a family history of cancer receive recommended cancer genetic counseling and subsequent genetic testing. Care delivery models using pre-test and post-test counseling are not scalable, which contributes to barriers in accessing genetics services. These barriers are even more pronounced for patients in historically underserved populations. We have designed a multimodal intervention to improve subsequent cancer surveillance, by improving the identification of patients at risk for familial cancer syndromes, reducing barriers to genetic counseling/testing, and increasing patient understanding of complex genetic results. We are evaluating this intervention in two large, integrated healthcare systems that serve diverse patient populations (NCT03426878). The primary outcome is the number of diagnostic (hereditary cancer syndrome) findings. We are examining the clinical and personal utility of streamlined pathways to genetic testing using electronic medical record data, surveys, and qualitative interviews. We will assess downstream care utilization of individuals receiving usual clinical care vs. genetic testing through the study. We will evaluate the impacts of a literacy-focused genetic counseling approach versus usual care genetic counseling on care utilization and participant understanding, satisfaction, and family communication. By recruiting participants belonging to historically underserved populations, this

study is uniquely positioned to evaluate the potential of a novel genetics care delivery program to reduce care disparities.

Keywords

genetics; genetic counseling; hereditary cancer; family history; underserved populations

Background

Individuals with hereditary cancer syndromes have up to an 80% lifetime risk of developing cancer.[1-5] About 1-2 in 200 individuals have a variant associated with one of the two most common hereditary cancer syndromes—Hereditary Breast and Ovarian Cancer syndrome (HBOC) and Lynch syndrome (LS).[1-5] Identifying these patients prior to cancer diagnosis facilitates preventive and risk-reducing measures that decrease morbidity and mortality.[6-12] Family history assessment and genetic testing for patients at risk for HBOC are now recommended in primary care by the United States Preventive Services Task Force (USPSTF).[13, 14] Despite this and the increasing availability of genetic testing, not all clinicians are aware of or implement the current recommendations.

Historically underserved populations experience barriers to cancer genetics services. Providers are less likely to evaluate their family history and refer them for genetic counseling, and they are less likely to receive genetic testing when appropriate.[15-18] Patients in community practice settings are less likely to receive genetics services than those receiving care in other practice settings, such as academic medical centers.[18-25] Communication about genetics and genomics between providers and patients is suboptimal.[26-29] Further, low health and genomic literacy present barriers for many English-speaking U.S. patients, and these barriers are exacerbated in Spanish-speaking patients. [30-33] Interventions are needed to improve access to genetics services for hereditary cancer syndromes, with a focus on improving access for historically underserved populations.

The Cancer Health Assessments Reaching Many (CHARM) study is part of the Clinical Sequencing Evidence-Generating Research (CSER) consortium, funded by the National Human Genome Research Institute (NHGRI) with co-funding from the National Institute on Minority Health and Health Disparities (NIMHD) and the National Cancer Institute (NCI).[34] CHARM is evaluating a series of interventions to address healthcare inequities in cancer genetics services among diverse populations. We endeavor to provide evidence and experience that health systems can use to increase access to genetics services for patients from all backgrounds. CHARM is recruiting a population of English- and Spanish-speaking patients, enriched for individuals from historically underserved backgrounds, in order to study the critical interactions among patients, family members, health practitioners, and laboratories that influence implementation of streamlined genomic services in these populations. The CHARM design addresses multiple barriers to equitable care in the current medical genetics services delivery model by implementing a multimodal intervention with 12 components (Figure 1).

These components include a streamlined process for cancer risk assessment, genetics education, and consent for genetic testing through electronic tools. The electronic tools can be completed at the patient's convenience either at home on a personal electronic device or in a clinical setting on a tablet. Further, we have trained CHARM study genetic counselors to implement a new mode of literacy-focused communication in post-test genetic counseling sessions, which we have termed the Accessible, Relational, Inclusive and Actionable (ARIA) model of genetic counseling. [35] Here we detail our protocol for testing the effectiveness and efficiency of this comprehensive risk assessment, genetic testing, and genetic counseling paradigm in a diverse patient population.

Overview of experimental design

Setting

Recruitment of participants is taking place at Kaiser Permanente Northwest (KPNW), an integrated healthcare system in the Portland, Oregon, metropolitan area, and Denver Health (DH), an integrated safety net health system with nine sites in Denver County, Colorado. KPNW serves approximately 25% of the population of Southwest Washington and Northwest Oregon. About 38% of members are racial/ethnic minorities. We are focusing recruitment in three KPNW clinics with the highest proportion of patients from racial/ethnic minorities and/or living in a census tract with low socioeconomic status as determined using geocoded census tract information and defined as a person living in a census tract where >20% of households are below the poverty level and/or >20% have less than a high school education; we are also focusing recruitment on patients with a documented need for Spanish interpretation (approximately 2%) as well as patients who have EMR indication of a primary language of Spanish. However, any KPNW patient is eligible to complete the risk assessment if they are a current health plan member aged 18-49 years.

The DH health system contains a regional trauma center and provides preventive, primary, and acute health care to almost one-third of Denver County residents. DH has nine federally qualified neighborhood health centers with approximately 160,000 unique users, of whom approximately 81% are publicly insured or uninsured, 69% are racial/ethnic minorities and about 21% of the 18-49 year old demographic speak Spanish primarily or exclusively. DH is a health system serving a low-resource area, meaning that individuals at higher risk are less likely to be able to receive genetic testing, even when they have been identified as eligible, both due to access (DH does not offer genetic testing) and due to health coverage constraints. In order to close the recognized genetics care gap related to testing access at DH and to strive for health justice, recruitment at DH is focused on individuals identified as at potentially higher risk based on cancer screening uptake outside of clinical cancer-screening guidelines for the general population and those referred by their providers based on assessment of risk.

Study aims

The CHARM study has 4 overarching aims:

(1) Implement a hereditary cancer risk assessment program in 880 healthy 18-49-year-old adults at risk of a hereditary cancer syndrome in primary care settings, with stakeholder input, and offer exome sequencing to clarify risk.

(2) Evaluate and tailor for diverse populations the critical interactions in the program, including the consent process, choices for selecting additional findings, genetic counseling results disclosure approach, and participant and primary care provider response to results disclosure.

(3) Evaluate the clinical and personal utility of using exome sequencing to diagnose individuals with hereditary cancer syndromes and provide additional findings, including healthcare utilization and adherence to recommended care.

(4) Address pragmatic and ethical challenges to the integration of genomic medicine into clinical and health systems decision-making.

Inclusion and exclusion criteria

The CHARM study has inclusion and exclusion criteria at 3 different points: 1) to complete the risk assessment, 2) joining the genetic testing portion of the study, and 3) for family members to receive targeted testing for variant(s) identified by the CHARM study (Table 1).

Interventions

CHARM is a multimodal intervention, designed to increase uptake and retention at each step of the clinical genomic service pathway, from patient identification and risk assessment through result disclosure (Figure 1). The study processes are presented in Figure 2. To create accessible Spanish-language versions of our materials, materials were developed in English with input from Spanish speakers to ensure effective translation prior to further cultural adaptation and translation into Spanish. All English materials were subject to reduced literacy adaptation by the study team and then iterative review by a seven-member English-speaking patient advisory committee to ensure cultural competency and accessibility. Spanish materials were translated by Dr. Nangel Lindberg, a CHARM co-investigator who is a certified translator with over 30 years of experience in culturally-adapted translations of research materials. This experience includes English speakers of limited literacy and Spanish-speaking participants from diverse socioeconomic and cultural backgrounds. Dr. Lindberg’s translations and cultural adaptations were subject to review by a ten-member Spanish-speaking patient advisory committee who provided input on further cultural adaptations. To ensure accessibility of study materials for patients of all literacy levels, whenever possible we crafted materials at a maximum 6th grade reading level in both English and Spanish. Further, bilingual research staff are available in clinic and by phone to read all documents to the participant when needed. The KPNW IRB approved this study, and all collaborating IRBs ceded to KPNW except Dana Farber Cancer Institute and Columbia University, who approved the study separately.

Recruitment

We aim to enroll and complete clinical exome sequencing for 880 individuals at risk for hereditary cancer syndromes. In order to reach this target, we expect to recruit ~22,000 participants to complete the risk assessment portion of the study. This target assumes 10% of individuals who complete the risk assessment are eligible (namely, that high-risk individuals do not self-select to participate at higher rates) and that less than 50% of eligible participants elect to receive genetic testing through the study. Recruitment methods vary by site. As the primary recruitment method, KPNW uses one email followed by one text message for patients age 18-49 with upcoming visits at recruitment clinic sites. Secondary recruitment methods include one email followed by one text message for patients likely to be at higher risk for a hereditary cancer syndrome (see description of 'high-risk' below) and an in-person recruitment booth at select clinics. DH does not allow email or text message outreach for research purposes, so the primary recruitment approaches are a combination of postcards followed by a phone call for primary care patients who met criteria for being at potentially higher risk, and provider referrals for known high-risk patients (Figure 1; intervention 1). As a low-resource setting, DH does not provide genetic counseling or genetic testing outside of pregnancy and many patients cannot afford genetic testing via referral to a local university; therefore, we encouraged health care providers with suspected HBOC/LS patients to refer them directly to the study. As part of our efforts to reach Spanish-speaking individuals, we queried the EMR at both KPNW and DH to identify and perform outreach in Spanish to patients who regularly use Spanish interpretation services.

At both KP and DH, patients identified for outreach on the basis of being potentially higher risk are defined as those receiving cancer screening outside of general population risk screening guidelines (e.g., screening colonoscopy prior to age 50), those with an HBOC- or LS-related cancer diagnosis prior to age 50, those with a documentation of a family history of HBOC- or LS-related cancers, and any patient who received a referral to genetics services due to cancer but did not ultimately receive genetic testing.

Online Interactive risk assessment

We invite patients to complete an electronic patient-facing family history risk assessment for LS and HBOC (Figure 1; intervention 2). To increase accessibility, the electronic tool was optimized for display on multiple electronic device types, including mobile devices such as tablets and phones. Tablets are available at clinic recruitment sites for participants without access to these devices, and a phone number is provided on mailed recruitment materials for participants to call the study; bilingual study staff are available to complete the application over the phone for the participant. Following a single page consent for the risk assessment, participants answer questions about their personal and family history of LS and HBOC-related cancers. Additionally, we ask participants who do not screen at clinically significant risk based on family history about limited family structure or limited family history knowledge (Figure 1; intervention 3). The electronic tool, which we adapted for patient-facing use among English- and Spanish-speaking participants with limited literacy, leverages two clinically validated risk assessment algorithms (PREMM$_5$™ and B-RST™ 3.0) to assess participant risk for LS and HBOC, respectively.[38, 39] We created a third, unique

algorithm designed to assess limited family knowledge and limited family structure, as acknowledged in NCCN guidelines.[36, 37]

Participants are considered eligible for genetic testing through the CHARM study with any of the following: (1) B-RST score of high or moderate risk, (2) $PREMM_5$ score of ≥2.5% risk of LS genetic variant, or (3) a limited family history knowledge or family structure on the basis of the novel CHARM algorithm. Risk is automatically calculated from participant input, and all participants, regardless of eligibility, are immediately presented a summary of their risk assessment results and next clinical steps (Figure 1; intervention 4). We also inform eligible participants that they can request genetics services through their health care provider even if they do not enroll in the genetic testing portion of the study.

Online consent to genetic testing and study enrollment

In place of pre-test genetics education and counseling with a genetic counselor, patients who are eligible for genetic testing through CHARM are presented with an online education and consent application. The application informs participants about genetic testing and the study, describes their options for receiving genetic testing, and provides informed consent information (Figure 1; intervention 5).Although the genetics education and consent information is provided electronically, participants can download a PDF copy or request a paper copy from the study. We included custom illustrations[40] depicting key concepts about genetic testing and the CHARM study and incorporated pre-recorded audio voiceover options (in English and Spanish) for all written text in the online genetics education and consent module. In the education and consent module following determination of eligibility, participants are informed about and agree to (1) interest in genetic testing (generally), (2) obtaining genetic testing and cancer genetic test results through CHARM as well as being contacted for surveys and interviews; and (3) release of personal health information. Following the education and consent module for cancer genetic testing, we offer participants the option to receive additional findings (findings outside of the diagnostic genes for hereditary cancer risk) including medically actionable results for all participants and carrier results for some participants (Supplement 1). Participants can choose all, some, or none of the additional finding results.

A subset of English-speaking participants are randomized, block-stratified by site, to receive a decision aid that helps them decide if they want medically actionable additional findings, through completion of a seven-item values clarification exercise referred to as the Optional Results Choice Aid (ORCA). Based on responses to these items, participants receive summative guidance about the directionality of their responses, with a suggestion about what they might decide. (Figure 1; intervention 6).[41] Individuals who are randomized to not receive the decision aid complete the values clarification exercise questions on the baseline survey after their selection of additional findings.

Genetic testing: clinical exome sequencing

CHARM uses an exome-based panel (Figure 1; intervention 7), which includes the clinically relevant portion of the genome (about 5,000 of the 20,000 genes in the human genome). Following consent, participants receive a saliva self-collection kit by mail or in person

(Figure 1; intervention 8) and can return the kit via prepaid mail or by returning it to study staff. Sequencing is completed at a CLIA-certified laboratory at the University of Washington, using a predefined gene list for variant reporting (Supplement 1). We report pathogenic, likely pathogenic, and variants of uncertain significance in 39 genes association with a hereditary predisposition to cancer (diagnostic; Supplement 1). For participants who consent to receipt of additional findings, we report pathogenic and loss of function, likely pathogenic variants in 77 medically actionable genes, and, for a subset of participants, pathogenic variants in 14 carrier genes (collectively, additional findings). Appropriate first- and second-degree relatives of individuals with pathogenic and likely pathogenic variants in cancer genes or medically actionable secondary findings are eligible for cascade testing through the study. Participants with secondary carrier findings are provided information for their family members and partners for appropriate clinical follow-up.

Genetic variant interpretation

Sequencing results are interpreted by the CLIA-certified laboratory at the University of Washington that performs the sequencing. Variants are classified using the American College of Medical Genetics and Genomics recommendations for variant interpretation.[42]Variants classified as VUS in a cancer gene associated with the participant reported personal and/or family history are reported to study participants and documented in the medical record to facilitate future updates by the health system when variants are reclassified. Variant reclassifications during the course of the study result in participant notification and entry of an updated laboratory report into the electronic health record.

Results disclosure interventions

Some participants with a limited family history receive negative results by letter, provided in English or Spanish based on patient's preference for risk assessment and consent (Figure 1; intervention 9). For all individuals with positive results and for those individuals with negative results but at clinically significant risk on B-RST™ 3.0 or PREMM$_5$™, result disclosure is conducted by telephone by board-certified genetic counselors (Figure 1; intervention 10).

We randomly assign participants (block-stratified by site) to receive results by phone via one of two approaches: usual care genetic counseling or the ARIA model (Figure 1; intervention 11). Genetic counselors (n=2) in the ARIA arm received training (seven 1-hour sessions) and ongoing support through case reviews to use evidence-based techniques for effective communication with individuals of limited health literacy and effective approaches to working with Spanish-language interpreters.[35] Genetic counselors (n=2) in the usual care arm use traditional genetic counseling communication methods and were not privy to nor received any specialized training for the study. As part of their training, all genetic counselors receive education to support the competent provision of culturally responsive and respectful care, and the genetic counselors disclosing results through the study have ongoing training available at their institutions and through their professional organizations. Participants are informed via consent that we are evaluating different ways to communicate results, but they are blinded to the genetic counseling arm to which they are assigned.

English-speaking genetic counselors conduct counseling visits for Spanish-speaking participants in partnership with professional interpreters. We also developed and are evaluating a training course in exome sequencing for healthcare interpreters (Figure 1; intervention 12). We randomly assigned 24 interpreters into two groups: the intervention group receives the training prior to providing interpretation services for the study; the control group receives the training after completing the interpretations.

Following disclosure, all testing results and genetic counseling notes are documented in the medical record and deidentified data is deposited into ClinVar and AnVIL. Study genetic counselors facilitate follow-up care for at-risk participants by coordinating clinical hand-offs to clinicians within the participants' health care system.

Evaluation of Study Outcomes: Process and Outcome Evaluations

We will evaluate the implementation of each intervention in our genetics healthcare delivery model using a variety of process and outcome measures gathered through qualitative and quantitative approaches. In cancer-related genetic testing, miscomprehension – especially of VUS – in tested patients and their referring providers has been reported, and it has been shown in some studies that counselees' perception of risk, rather than their actual genetic risk status, is the driving factor in medical actions.[43-45] Thus, our assessments of patient-reported outcomes (e.g., understanding, satisfaction) as well as healthcare outcomes (namely, care utilization) will include the entire study sample..

Electronic tracking

All participant engagements with the study, including interactions with the online risk assessment and consent, are recorded electronically either automatically or manually by study staff in an integrated, secure study tracking system.

Surveys

Participants receiving genetic testing complete three surveys: a baseline survey and two follow-up surveys after results disclosure. Over half of the survey measures – such as subjective understanding of results, patient assessment of communication, and satisfaction of communication mode (each as a measure of genetic counseling mode success) – we collect from participants are from harmonized measures used across all six CSER consortium projects [46] (Table 2). We also ask participants about reasons for study participation, healthcare barriers, genetics communication, and genetics self-efficacy, family environment, and expanded demographics (e.g., formal education history, sexual orientation, gender identity, income, and insurance status). Additionally, we assess CHARM-specific outcomes such as decisional conflict and regret, satisfaction with information delivery about test results (i.e., participant satisfaction with genetic counseling mode), recall of test result as a measure of genetic counseling success, patient understanding of the utility of the test result, and quality of Spanish language interpretation. We invited potential participants who are eligible for genetic testing but decline to enroll and consent to complete a 'decliner' survey (Table 2). We administer surveys and capture all survey item responses via Research

Electronic Data Capture (REDCap) tools hosted at KPNW.[47, 48] We import participant baseline completion events into the secure study tracking system.

Fidelity of genetic counseling to the ARIA model or usual care

All counseling sessions are audio recorded and assessed to ensure fidelity to the two counseling approaches. We randomly assess a selection of audio recordings from each quarter, evenly distributed across the four genetic counselors. We developed a coding scheme to assess fidelity to each counseling approach and each recording is dual-coded.

Use of the electronic medical record (EMR)

At the time of identification for recruitment, potential participant demographic data available in the EMR is imported into the study tracking system for participants at KP; DH participants have demographic data added to tracking from the EMR at time of consent. When participants do not answer the demographics questions on the baseline or decliner surveys in REDCap, study analyses utilize data obtained from the study tracking system. Care utilization of participants in the genetic testing portion of the study and individuals eligible for, but who decline, genetic testing through the study will be drawn from procedure codes in the EMR and evaluated against recommendations provided by study genetic counselors.

Inferential statistical analysis

We will evaluate the risk assessment tool (interventions 2-4) in the following ways: (1) evaluate interrater agreement between genetic counselor family history data and the risk assessment tool (convergent validity); (2) determine predictors of time spent on the risk assessment tool using multivariable linear regression, and (3) index the overall agreement between accurate risk tool stratifications and risk stratifications produced from family history available in the EMR. We will determine whether the decision aid (intervention 6) improves informed values congruence using multivariable logistic regression. To compare the reportable findings yield between those with different family history knowledge and risk scores, we will use multivariable logistic regression (intervention 7). Comparing the yield between those with sufficient family history (standard thresholds=1) and those with incomplete family history (=0), 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. Using the projected sample size of 880 and assuming that 25% of participants qualify through incomplete family history data, and that 20% of participants who meet standard criteria have a reportable finding, the power is >80% to detect an odds ratio as small as 2. We will test for the superiority of the ARIA genetic counseling approach using ANCOVA (intervention 11). Using multivariable logistic and negative binomial regression, will compare uptake of recommended downstream risk-management and health care visits between (1) ARIA and usual care genetic counseling approaches (intervention 11) and (2) CHARM study interventions and usual care (wholistic evaluation). Regression analyses will be conducted in all participants and in those receiving reportable test results, exclusively. For all multivariable regression and ANCOVA analyses of participants in the genetic testing portion of the study, arm will be the independent variable and the randomization stratification factor of site (0=DH, 1=KP) will be the covariate. At a sample

size of 880, we have 80% power to detect a Cohen's d of .15 comparing patient reported outcomes from the two genetic counseling arms. Evaluations of non-randomized components of the multimodal CHARM intervention will be adjusted on the basis of measured covariates, including demographics and patient-reported data.

Quantitative evaluation of CHARM study Intervention

An overview of the CHARM study evaluation leveraging quantitative data is presented in Table 3.

Interviews

We are also using semi-structured qualitative interviews to assess participant, provider, and interpreter experiences with CHARM interventions at various points in the study (Table 4), including after risk assessment, after declining to join the genetic testing portion of the study, after consent to genetic testing through the study, immediately after result disclosure, and 6 months after result disclosure. These interviews assess participant, provider, and interpreter experiences with multiple aspects of the CHARM study intervention (Table 4). A unique codebook will be developed using inductive and deductive techniques for each set of qualitative interviews to identify common themes.[65, 66]

Discussion

In 2013, the USPSTF recommended family history screening for breast and ovarian cancer risk in primary care and recently reaffirmed that recommendation.[14, 67] However, these recommended screenings are under-implemented in current clinical practice, representing the first care gap for patients in the hereditary cancer genetics services delivery pipeline.[18-25] This care gap is wider for patients from medically underserved populations, who have a lower likelihood of both referral for genetic counseling and receipt of genetic testing when indicated.[15-18] The current genetics services delivery model may be thought of as a 'leaky pipeline,' especially for individuals who face systemic barriers to care access. Interventions are needed at multiple points to remove barriers created by the current structure and improve the equity of genetics services delivery. However, any intervention designed to increase appropriate referrals and genetic testing will contribute to an already strained genetics services delivery system.[68-74] The current genetics services delivery model is resource and labor intensive, typically requiring both pre- and post-test genetic counseling visits (often in-person), and there is a limited availability of genetic counselors to meet this demand. [68, 70, 71, 73, 74] As such, interventions need to both address the "leaky pipeline" and reimagine how genetics care is delivered in order to alleviate strain on the health system and make widespread genetic testing scalable even in low-resource areas. To address the issue of patients lost to follow-up at each step in the genetics services pipeline and to alleviate health system impact of increasing genetics referrals, the CHARM study is a evaluating a multimodal intervention acting at all stages of the current genetics services delivery model.

The approaches to genetic assessment used in CHARM allow for a healthcare system to potentially reach a much larger portion of the patient population to assess risk, because they

do not rely on contact with a healthcare provider (Figure 1, intervention 1). Similarly, a provider is not required to collect the family history data, because participants interact with a patient-facing risk assessment tool (Figure 1, intervention 2). The CHARM study also provides a way to expand eligibility for genetic testing on the basis of an assessment of limited family history knowledge or structure based on current guidance,[36, 37] which is more likely to impact patients from some historically underserved populations (Figure 1, intervention 3).[75-79] Through automated assessment and immediate communication of risk status, the study intervention seeks to provide guideline-adherent risk communication to participants, rather than relying on a provider to recognize risk from patient-provided family history during a medical appointment. Together, these interventions are designed to support systematic and efficient risk assessment and patient identification for referral (Figure 1, interventions 2-4). These barriers disproportionately impact medically underserved individuals and produce strain on the care system taxing already limited medical appointment time.[15-25]

With limited availability of genetic counselors and increased genetics services demand,[66, 69, 70, 72, 73] pre-test counseling and appropriate genetic test selection pose a bottleneck to genetic testing receipt. To address this bottleneck, our intervention delivers pre-test genetic testing education and consent in a web-based electronic patient-facing application (Figure 1, intervention 5) and also provides a decision aid designed to assist participants in selection of the receipt of medically actionable additional findings to be congruent with their values (Figure 1, intervention 6).

All participants in the study are receiving a large exome-based panel for cancer-related genes as well as medically actionable additional findings, which removes the need for patient-specific panel selection (Figure 1, intervention 7). However, a larger panel does introduce the possibility of additional reportable findings and may increase the identification of variants of uncertain significance or with unclear implications for the familial phenotype.

To reduce patient travel and time burden, a barrier that disproportionately impacts medically underserved populations,[80, 81] participants are able to self-complete a saliva collection kit at their convenience in their home and return it via prepaid postal envelope rather than needing to visit a clinical laboratory for a blood draw (Figure 1, intervention 8). Similarly, all participants receive genetic test results remotely by letter (Figure 1, intervention 9) or phone (Figure 1, intervention 10), which we anticipate will both reduce burden on the care system and remove the barrier posed by requiring travel to specialty centers. Further, the study is evaluating a novel genetic counseling approach (ARIA model) to address barriers to communication in limited-literacy populations (Figure 1, intervention 11). Finally, language barriers account for significant disparities in healthcare receipt, especially in genomics,[80] and the study is evaluating interpreter training methodology designed to ensure adequate communication of results by interpreters (Figure 1, intervention 12).

The multimodal intervention of the CHARM study provides a pathway to genetic testing that is scalable, removes the barrier of multiple appointments and repeated care system contacts, and reduces travel burden by making it possible to complete every step of the intervention outside of an in-person healthcare setting. All participant-facing materials were

culturally adapted and translated into Spanish at a 6th-grade reading level. Individually, each aspect of the CHARM intervention is designed to remove or reduce a systemic barrier to genetics services access and/or to alleviate stress on the healthcare system to make widespread genetic testing more scalable. Our study design will evaluate the success of each component of this multimodal intervention in terms of both patient and care system impact, starting from screening and ending with result disclosure. While eliminating disparities in genetics services delivery does not end at diagnosis of a cancer syndrome, the CHARM study represents an important step in evaluating evidence-based scalable strategies that address inequities in the current medical genetics services delivery model. The evidence generated will include data on adherence to appropriate care based on genetic test results. These results may also provide hypothesis-generating data on the equity in receipt of downstream care that can guide the design of future studies to close downstream healthcare gaps. As part of the CSER consortium, our study also will contribute important evidence about sequencing in underserved populations, including best practices for variant interpretation, results reporting, and ethical, legal, and social implications in these groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Genetics services process	Intervention	Evaluation method(s)
Identify individual	1. Outreach via email/text/postcard/phone	
Collect family history	2. Web-based patient-facing tool	
	3. Ask about limited family information	
Assess risk	4. Online automated risk assessment	
Education, consent & select test	5. Online pretest education and consent	
	6. Decision aid for additional findings	
	7. Preselect exome-based panel	
Sample collection	8. Self collection of saliva at home	
Results disclosure	9. Letter for some negative results	
	10. Phone genetic counseling	
	11. Literacy-focused genetic counseling	
	12. Training for interpreters	
Downstream care		

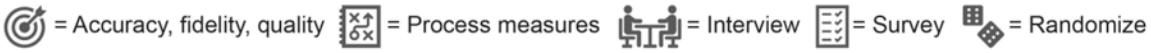

Figure 1. Multimodal CHARM intervention altering the current genetics services delivery model

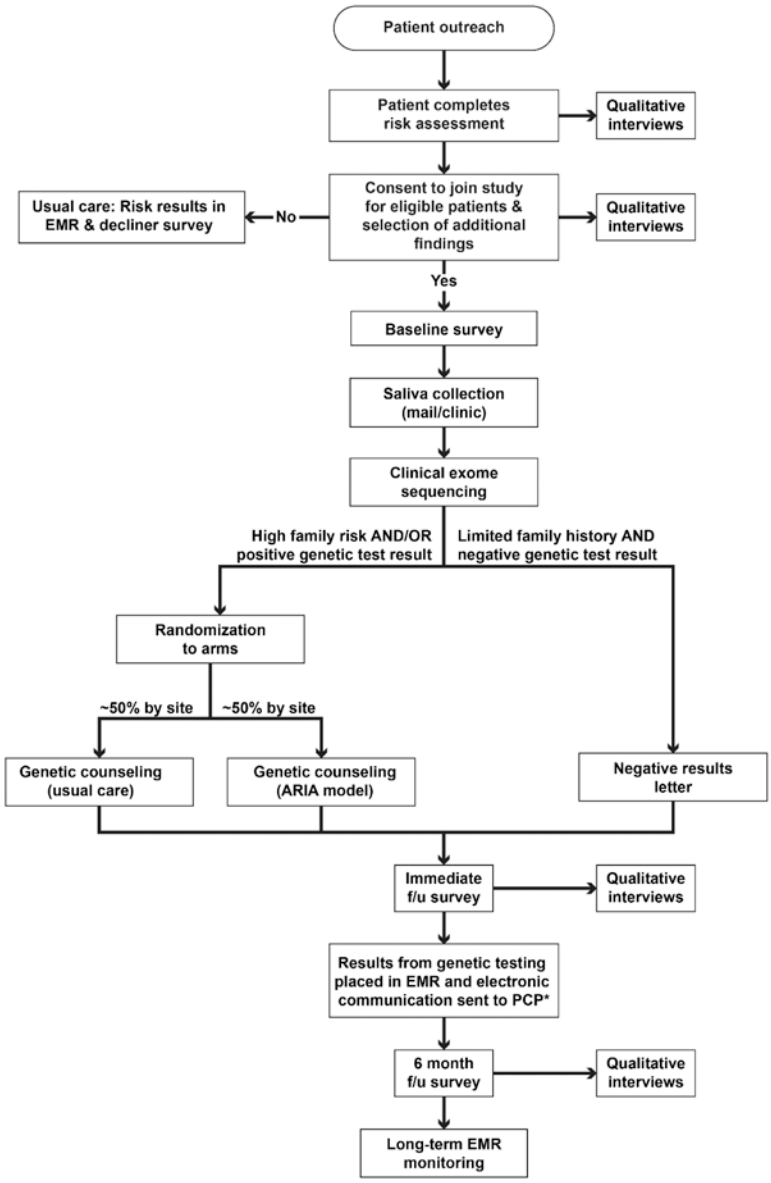

Figure 2. Study schema depicting patient-study interactions in the CHARM study.
Abbreviations: f/u =follow-up.

Table 1:

Inclusion and exclusion criteria for completing the risk assessment and obtaining genetic testing through the study and for family member genetic testing

	Study participants	**Family member genetic testing**
Inclusion	*Criteria to take risk assessment:* 1. KPNW or DH patient 2. Age 18-49 3. English or Spanish speaker *Additional criterion for genetic testing through study:* 1. Screen at risk for a hereditary cancer syndrome via the risk assessment algorithms OR have limited family structure or knowledge of family history[36, 37] 2. No disclosure on the risk assessment of prior testing for germline variants predisposing to LS or HBOC and no healthcare record of prior testing	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 additional finding. 2. Over the age of 18 3. English or Spanish speaker 4. Lives in the United States
Exclusion	*Criteria to take risk assessment:* 1. Not an English or Spanish speaker 2. Unable to provide informed consent 3. Patients that don't want their results placed in their medical record *Additional criterion for genetic testing through study:* 1. Does not screen at risk for a hereditary cancer syndrome via the risk assessment algorithms AND does not have limited family structure or knowledge of family history 2. Disclosure on the risk assessment of prior testing for germline variants predisposing to LS or HBOC or healthcare record of prior testing	1. Under the age of 18 2. Previous positive result for variant identified in CHARM participant 3. Not an English or Spanish speaker 4. Lives outside of the United States

Table 2.

Patient-reported outcome measures

Domain	Measure	Survey Timepoint
Reasons for participating	Novel[a]	BL
Concerns about participation	Novel[a]	BL
Barriers to genetic testing	Novel[a]	BL
Quality of life[49]	Short Form Survey 12 (SF12)[b]	BL, FU2
Health literacy[50]	Brief Health Literacy screening Tool (BRIEF)[b]	BL
Subjective numeracy[51]	Shortened Subjective Numeracy Scale (SNS-3)[b]	BL
Health-Related locus of control[52]	Multidimensional Health Locus of Control (MHLC)[a]	BL
Access to care[53]	Medical Expenditure Panel Survey Household Component (MEPS-HC)[b]	BL
Communication self-efficacy[54]	Adapted from Ask, Understand, Remember Assessment (AURA)[a]	BL
Genetic self-efficacy[55]	Adapted from Kaphingst et al.[a]	BL, FU1, FU2
Cancer/Genetics knowledge[56]	Adapted from Rose et al.[a]	BL, FU1, FU2
Distrust[57]	Health Care System Distrust Scale[b]	D, BL
Family environment[58]	McMaster family assessment device[a]	BL
Information engagement[59]	Health information orientation scale[a]	BL
Understanding of consent Religiosity	Novel[a] Multidimensional measure of religiousness/spirituality[a]	BL, FU1, FU2 D, BL
Satisfaction with communication mode	Novel[b]	FU1
Quality of interpretation	Adapted from IPC Interpersonal processes of care[a]	FU1
Subjective understanding of results	Novel[b]	FU1, FU2
Feelings about results[60]	Feelings About genomiC Testing Results (FACToR)[b]	FU1, FU2
Satisfaction with results	Novel[b]	FU1
Patient-reported personal utility[61]	Personal Utility (PrU)[b]	FU1, FU2
Family communication	Novel[b]	FU2
Understanding of utility of results	Novel[a]	FU1, FU2
Patient assessment of communication[62]	Adapted from Patient Assessment of cancer Communication Experiences (PACE)[b]	FU1[c]
Information seeking Version 1	Novel[b]	FU1[d]
Information seeking Version 2	Novel[b]	FU2[d]
Patient-initiated actions	Novel[b]	FU2

Domain	Measure	Survey Timepoint
Follow through on medical actions	Novel[b]	FU2
Recall of test result	Novel[a]	FU1, FU2
Satisfaction with information delivery	Novel[a]	FU1[c]
Decisional regret[63]	Decision regret scale[a]	FU1
Decisional conflict[64]	Decisional conflict scale[a]	BL
Decision aid knowledge questions	Novel[a]	BL
Values self-assessment	Novel[a]	BL[e]
Reasons for declining	Novel[b]	D

Abbreviations: BL = baseline, FU1 = immediate follow-up survey, FU2 = 6 month follow-up survey

[a]CHARM specific measures. Novel measures were created by study team members with relevant expertise and face validated

[b]CSER consortium harmonized measure[46]

[c]Administered only to participants with a telephone result disclosure

[d]Portions of these questions only administered to participants with a positive result

[e]Administered on BL survey only to participants who were not randomized to the decision aid arm. Those who were randomized to the decision aid arm responded to the questions during the consent process.

Table 3.

Quantitative CHARM study evaluations leveraging data from the CHARM tracking system, EMR, and/or participant reported outcomes on CHARM surveys

Intervention-specific evaluations			
Intervention(s)	**Process Evaluation(s)**	**Outcome Evaluation(s)**	**Clinical Trials Outcome**
1: Outreach via email/text/ postcard/phone	- Number receiving each outreach method, number of times contacted, number who engage with the online web tool - Non-responders and responder characteristics	- Response rate	N/A
2-4: Web-based patient facing tool; ask about limited family information; online automated risk assessment	- Proportion incompleters - Risk assessment outcomes	- Time spent on the tool - Accuracy of reported family history	N/A
5: Online pretest education and consent	- Proportion of eligible individuals consenting to genetic testing - Time spent on the consent module	- Time spent on consent	N/A
6: Decision aid for medically actionable additional findings	- Decision aid selections and choices for additional findings - Time spent on decision aid	- Informed, values-congruent decision making	N/A
7: Preselect exome-based panel	N/A	- Number and type of findings (P/LP/VUS) (descriptive)	**Primary study outcome** - Number and type of findings in genes related to hereditary cancer syndromes **Secondary study outcomes** - Number and type of findings in genes related to medically actionable hereditary conditions - Number and type of findings in genes related to common carrier conditions
8: Self collection of saliva at home	- Proportion of samples mailed	- Proportion of inadequate and successful first or second samples	N/A
9: Letter for some negative results	- Participant characteristics - Proportion of participants receiving a letter	- Understanding, utility, and satisfaction	**Secondary study outcomes:** - Participant understanding of recommended care - Participant understanding of genetic test results - Participant satisfaction with genetic counseling - Family communication - Personal utility
10: Phone genetic counseling	- Participant characteristics - Proportion of participants receiving genetic counseling by phone	- Understanding, utility, and satisfaction	
11: Literacy-focused genetic counseling (ARIA model)	- Characteristics of individuals in the two arms - Fidelity to the two counseling modes	- Understanding, satisfaction, assessment of communication	
12: Training for interpreters	- Interpreter characteristics and characteristics of participants utilizing interpreter services	- Quality and accuracy of interpretation - Interpreter knowledge and self-efficacy -	

Intervention-specific evaluations			
Intervention(s)	**Process Evaluation(s)**	**Outcome Evaluation(s)**	**Clinical Trials Outcome**
		Participant understanding and satisfaction	
Wholistic evaluations of study interventions			
Utilization	- CHARM participant characteristics	- Uptake and adherence to recommended downstream cancer prevention measures	**Secondary study outcome:** Healthcare utilization
Provider experiences with care of CHARM participants	- Provider characteristics	- Satisfaction and understanding	N/A
LGBTQ+ participant family communication	- Characteristics of LGBTQ+ participants in comparison to CHARM study population	- Family communication	N/A

Table 4.

Qualitative interview approach

Intervention(s) Evaluated	Interview Focus	Key domains	Time point
1: Outreach via email/text/postcard/phone 5: Online pretest education and consent Wholistic evaluations of study interventions	Participant feelings of respect during research procedures	-Respect in the clinical setting -Respect during recruitment and consent -Decision-making process -Trust in medical research	After consent and before result disclosure OR within 4 weeks of disclosure of negative result
2-4: Web-based patient facing tool; ask about limited family information; online automated risk assessment	Participant experience with risk assessment	-Reasons for incompletion or taking a long time to complete -Understanding discrepancies between risk assessment responses and family history disclosed to genetic counselor -Acceptability -Application design	After risk assessment
5: Online pretest education and consent	Participant experience with consent for study enrollment	-Decision making -Understanding of consent and data sharing -Information quality -Emotional response -Application design and flow of consent	After consent and before result disclosure
10: Phone genetic counseling 11: Literacy-focused genetic counseling (ARIA model) 12: Training for interpreters Wholistic evaluations of study interventions	Participant opinions of personal utility of genetic testing	-Impact on clinical care, affective state, cognitive state, and life planning -Social impact	3+ months after result disclosure
10: Phone genetic counseling 11: Literacy-focused genetic counseling (ARIA model) 12: Training for interpreters	Participant experience with result disclosure	(2 week interviews): -Familiarity with genetic testing -Understanding of test results and care recommendations -Perceptions of genetic counseling communication -Perceptions of Spanish interpretation -Uncertainty (6 month interviews): -Family communication -Communication with providers -Experience with downstream care	Within 4 weeks of result disclosure and 6 months after result disclosure
12: Training for interpreters	Interpreter experience	-Experience as an interpreter -Experience interpreting for study -Perceptions of genetic counselors' communication -Perceptions of interpreter training	After 2 completed interpretations
Wholistic evaluations of study interventions	LGBTQ+ participant experience	-Impact of LGBTQ+ identity on family relationships and family history sharing -Impact of LGBTQ+ identity on sharing of study results	After result disclosure
Wholistic evaluations of study interventions	Provider experience	-Provider understanding of result -Communication with patient -Plan to manage patient care	After medical encounter with participant OR 6 months post result disclosure

Intervention(s) Evaluated	Interview Focus	Key domains	Time point
		-Prior experience and uncertainty of some genetic results -View of risk assessment tool	