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Promoting Guideline-Based Cancer Genetic Risk Assessment for Hereditary Breast and Ovarian Cancer in Ethnically and Geographically Diverse Cancer Survivors: Rationale and Design of a 3-arm Randomized Controlled Trial

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Abstract

Background: Although national guidelines for cancer genetic risk assessment (CGRA) for hereditary breast and ovarian cancer (HBOC) have been available for over two decades, less than half of high-risk women have accessed these services, especially underserved minority and rural populations. Identification of high-risk individuals is crucial for cancer survivors and their families to benefit from biomedical advances in cancer prevention, early detection, and treatment.

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Methods: This paper describes community-engaged formative research and the protocol of the ongoing randomized 3-arm controlled Genetic Risk Assessment for Cancer Education and Empowerment (GRACE) trial. Ethnically and geographically diverse breast and ovarian cancer survivors at increased risk for hereditary cancer predisposition who have not had a CGRA are recruited through the three statewide cancer registries. The specific aims are to: 1) compare the effectiveness of a targeted intervention (TP) vs. a tailored counseling and navigation (TCN) intervention vs. usual care (UC) on CGRA utilization at 6 months post-diagnosis (primary outcome); compare the effectiveness of the interventions on genetic counseling uptake at 12 months after removal of cost barriers (secondary outcome); 2) examine potential underlying theoretical mediating and moderating mechanisms; and 3) conduct a cost evaluation to guide dissemination strategies.

Discussion: The ongoing GRACE trial addresses an important translational gap by developing and implementing evidence-based strategies to promote guideline-based care and reduce disparities in CGRA utilization among ethnically and geographically diverse women. If effective, these interventions have the potential to reach a large number of high-risk families and reduce disparities through broad dissemination.

Keywords

Hereditary Cancer; Genetic Counseling; Assessment Risk

1. Introduction

Implementing genetic counseling (GC) and testing for hereditary breast and ovarian cancer (HBOC) predisposition into clinical care is crucial for guiding precision prevention, early detection and cancer treatment.[1–7] The high risks of breast (~60–70%)[8–11] and ovarian (up to 44%)[8, 10] cancer among women with a deleterious mutation in genes such as in *BRCA1* or *BRCA2* can be reduced below the general population risk through cancer prevention and early detection options. [12] Although national care delivery guidelines[13–18] for cancer genetic risk assessment (CGRA) have been available for approximately two decades, less than half of high-risk women have had genetic counseling and/or testing. [19–21] High-risk women, particularly those who are medically underserved, are often unaware of their risk, CGRA availability and the genetic testing process, and risk reduction options. Compared to non-Hispanic Whites (NHW) and urban dwellers, Hispanics and other underserved minority populations as well as rural dwellers have lower levels of awareness and utilization of HBOC genetic services as well as fewer discussions with health providers about these services,[22–26] [27] [26, 28–30]. Identification of persons at increased risk for HBOC is crucial for cancer survivors and their families to benefit from biomedical advances in cancer prevention, early detection, treatment and survivorship. Further, widespread dissemination and adoption of national guidelines for CGRA is needed to achieve a population-level reduction in cancer morbidity, mortality and health disparities.

Surprisingly little work has been conducted to address this translational chasm. Previous studies have iterated the need for interventions that increase guideline-concordant cancer genetic care. The Genetic Risk Assessment for Cancer Education and Empowerment (GRACE) Project is addressing this translational gap by developing and implementing

strategies to increase the reach of evidence-based and potentially life-saving cancer risk communications and clinical genetic services. The trial's overarching goal is to test the effectiveness of two remote strategies to increase guideline-based CGRA for HBOC: a low intensity mailed targeted print (TP) intervention, TP plus a multicomponent personalized counseling and navigation intervention (TCN), or Usual Care (UC). We hypothesize that, compared to UC, CGRA (genetic counseling with or without genetic testing) uptake will be highest among women participating in the TCN arm, followed by women participating in the TP arm at 6 and 12 months after cost barriers are removed. The study will examine underlying theoretical mediating and moderating mechanisms through which each intervention promotes CGRA and perform an economic evaluation to estimate the potential cost-effectiveness of the two interventions compared to each other and usual care from the societal and payer perspectives.

Findings may influence population health care delivery models and policy level decisions. If successful, these interventions have the potential to reach tens of thousands of high-risk cancer survivors and ultimately, their family members through broad dissemination and to reduce the public health burden of HBOC. This paper describes the study's rationale and intervention protocol. We also summarize the community engaged research that informed the study design and data from the feasibility randomized trial that preceded our ongoing definitive trial.

2. Scientific Rationale

2.1. Conceptual Framework

Theory-based interventions that address multiple determinants of behavior have the highest likelihood of promoting healthy behaviors.[31, 32] Given the complexity of genetic risk communication and behavior change it is often necessary to combine constructs from several theories or models that have been effectively used in prior research.[33–38] The Extended Parallel Process Model (EPPM), [39, 40] Health Action Planning Approach (HAPA)[41, 42] and the Ottawa Decision Support Framework (ODSF)[43] are the primary theories that guide the content and structure of tailored messages, the selection of measures, and the proposed analyses. The study's conceptual framework is depicted in Figure 1.

The EPPM provides a framework for communicating risk messages in a way that helps people channel emotions and cognitions toward the desired behavior change.[39, 40] The model is based on elements of Protection Motivation Theory,[44] Theory of Planned Behavior[45, 46] and the Health Belief Model.[47, 48] Briefly, EPPM focuses on channeling fear in a positive direction aimed at controlling the danger (e.g., getting CGRA) rather than controlling the fear (e.g., derogating the message). Fear is aroused when individuals feel threatened (threat or risk appraisal process); they believe they and/or their family members are at risk for HBOC and a second cancer (perceived risk) and consider it a life-threatening disease (perceived severity). Individuals are more likely to obtain a CGRA if they believe that CGRA is effective in reducing HBOC risk (response efficacy) and have high levels of confidence in their ability (self-efficacy) to obtain CGRA. One way to bolster self-efficacy is to help patients overcome barriers towards action. This may include cues to action (e.g.,

provider or other network member recommendations) or other factors (e.g., demographics, psychosocial and cultural factors).[49, 50]

While the EPPM focuses on strategies that promote motivation and intention to engage in health behavior, the HAPA recognizes that a substantial number of individuals are already motivated to engage in the health behavior and form goal intentions, but fail to carry out those intentions.[41, 42] According to the HAPA, successful behavior change involves both a pre-intentional motivational phase in which intention is formed and a post-intentional volitional phase in which intention is translated into action. To this end, the HAPA attempts to bridge the “motivation/intention–behavior gap” with a planning component that helps with implementation. Implementation intention suggests that patients are more likely to carry out an intended action if they identify when, where and how they will do so and are reminded about their intention.[42, 51–54] Finally, consistent with ODSF’s conceptualization of decision support interventions, a central goal of cancer risk-related communication and behavior change counseling in this study is to facilitate informed decision-making about CGRA and prevent adverse psychosocial outcomes.[43, 55]

2.2. Targeted Generic Print Interventions

People from diverse age, socioeconomic, and racial/ethnic groups cite print educational communications as a preferred method of delivering information,[56–62] including information about CGRA. This strategy was also endorsed in our community engaged preliminary work described below. Generic print interventions are designed to appeal to large groups of people and are often targeted to a specific subpopulation (e.g., cancer survivors at increased risk for HBOC). [63] They can address key theoretical determinants (e.g., informational needs, threat/risk and efficacy beliefs and barriers) in an attempt to motivate health behavior. A generic print intervention targeting breast and ovarian cancer survivors may provide a low-cost, convenient, and effective public health approach to promote guideline-based CGRA. Disadvantages of targeted interventions are that they may not be viewed as personally relevant compared to tailored interventions.[64] To our knowledge, there are no randomized trials that have tested the effectiveness of this approach with promoting CGRA.

2.3. Tailored Interventions

In contrast to targeted print, tailoring uses motivational strategies of personalization, individualized feedback and content matching on theoretical and social determinants.[63, 65, 66] There is an increasing body of evidence that shows that if implemented effectively, tailored interventions result in more significant effects than targeted interventions on cancer prevention behaviors among average and high-risk individuals; however, this has not been effectively tested in the context of promoting HBOC CGRA guideline-based care.[38, 64, 67–69] Compared to targeted interventions, tailored communications are more likely to be perceived as personally relevant, heighten cognitive preconditions for health message processing and augment message impact by modifying behavioral determinants of the desired outcomes; however, they are often more expensive. [65, 70] Furthermore, tailored print and computerized interventions have been shown to be more effective than targeted print but, from a public health perspective, may have limited reach in medically underserved

populations who may not have internet access, or be able to complete mailed questionnaires that are required to deploy the intervention.[36, 71, 72]

One solution is to use health coaches to deliver telephone-based tailored interventions where they briefly assess and intervene on key theoretical constructs.[73] Theoretically-guided tailored health messages delivered in a motivational interviewing (MI) style have an advantage over targeted messages, especially when there is significant variability within the targeted audience on key determinants of the intended outcome (e.g., risk perceptions, knowledge, perceived benefits, decision uncertainty, self-efficacy, motivation, barriers). Telephone interventions have the potential to reach large numbers of people, particularly those in low socioeconomic strata and those who reside in rural areas where internet access may be limited. Further, telephone interventions that include barriers counseling plus active patient navigation have been effective relative to print information alone in medically underserved populations.[61, 72, 74–76] Calls can be followed by tailored letters that summarize the call and remind patients of their action plan.[33] In our TCN intervention, as part of their training, health coaches cultivated competency skills, thus enabling them to address behavioral, sociocultural, system-level and logistical barriers and facilitators (e.g., provider and family/friend support).

Provider knowledge about hereditary cancer risk and recommending CGRA to patients can be powerful predictors of guideline concordant care.[34, 77] Yet knowledge about cancer genetics is limited among healthcare providers,[78, 79] [80]which may help explain widespread deficiency in the identification of individuals and risk-appropriate care for women at high risk for HBOC.[81] Despite limited knowledge and time constraints, healthcare providers are generally receptive to educational opportunities. [80, 82, 83] TCN participants' providers (primary care and/or oncology provider) are mailed a letter that informs them that their patient meets the criteria for a genetics referral along with the participant's personalized letter (with the participant's permission). This provider-level intervention component serves as a cue to action for the provider and may also help to improve patients' motivation to utilize CGRA services.

2.4. Motivational Interviewing

While the content of the remote TCN approach relies heavily on the EPPM and HAPA, the delivery style is based on MI, an evidence-based conversational strategy.[84, 85] The contribution of MI is to encourage the participant to engage in and respond positively to the risk information. There is evidence that MI reduces defensive responses (message rejection, paralyzing fear, low response efficacy/fatalistic beliefs) after receiving fear-arousing cancer information and effectively motivates people to engage in preventive behavior. [33, 38, 85–88] MI is also culturally responsive because counselors/coaches can incorporate the social context into the interaction.[89, 90] Finally, MI has a substantial literature base among Hispanic populations and may be particularly well suited to minority and underserved populations.[91, 92]

3. Methods

3.1. Overall Study Design

GRACE is a randomized 3-arm trial designed to examine the impact of a personalized remote intervention that includes evidence-based risk communication and behavior change techniques with navigation and a low-intensity mailed educational brochure on promoting CGRA uptake. Breast and ovarian cancer survivors who meet the criteria for genetic counseling about HBOC are recruited from three statewide cancer registries (Table 1). They are randomly selected and recruited from the Colorado (CO), New Jersey (NJ), and New Mexico (NM) cancer registries according to their institutional procedures. The design and reporting of the trial is informed by the CONSORT Statement.[93, 94] Women are randomized to one of three study arms: UC, mailed TP, and TCN. Group assignment occurs after completion of the baseline interview. The interventions take place approximately 2-weeks after completion of the baseline survey. Follow-up surveys are conducted at 1 month (to assess mediating factors), 6 months and 12 months after randomization for the UC arm, and 1 month, 6 months and 12 months after the interventions for TP and TCN arms. The 3 arms will be compared with regard to uptake of genetic counseling at 6 months (primary outcome) and 12 months (after removal of genetic counseling related cost barriers), and other outcomes including genetic test uptake, and psychosocial and decision-making factors.

This trial is funded by the National Cancer Institute, was approved by the institutional review boards of the University of New Mexico, the Colorado Department of Health, and Rutgers University and is registered with clinicaltrials.gov (NCT03326713). All authors are responsible for the design and conduct of the study and meet International Committee of Medical Editors (ICMJE) criteria.

3.2. Randomization

At the end of the baseline interview, participants are randomly allocated to one of the three study arms. Randomization is accomplished by a computer-generated random number list. Randomized blocks with a size of 9 will minimize predictability of upcoming subjects' treatment assignments, while providing approximate balance between study arms and within the ethnic and geographic sampling strata.[95]

3.3. Interventions

3.1.1. Formative Research, Intervention Development and Feasibility Trial—

The TCN intervention was adapted from a remote multi-component intervention that was found to be effective in promoting colonoscopy among persons at increased risk for familial colorectal cancer who were recruited from five statewide cancer registries.[33, 36, 38] We believe that adding active patient navigation to this type of intervention will more effectively address disparities and lingering sociocultural, logistical and other barriers, especially for medically underserved women. We used an interactive process that engaged the target population and key stakeholders to identify perceptions about CGRA, get input into the study design, develop our intervention strategy and risk messages, develop culturally sensitive print materials, and craft the intervention prototypes. In 2014-2015, we conducted a survey of 213 high-risk Hispanic and non-Hispanic cancer survivors who underwent genetic

testing and had uninformative test results, and their close female relatives. We observed a high level of interest in multiplex testing for HBOC (84%); interest did not significantly differ between Hispanic and NHW women ($p=0.50$). Respondents indicated a strong preference for print HBOC informational materials and interactive (live) health coaching over web-based or DVD information, especially Hispanic women.

Using Learner Verification (LV), [96–98] participants reviewed and provided feedback on the draft intervention materials and messages (November 2015–January 2016). Initially, we conducted three focus groups with 13 Hispanic (Spanish and English-speaking) and non-Hispanic women with a personal history of cancer who met the criteria for a referral but had not had CGRA. Common barriers to CGRA included lack of knowledge, navigation assistance (interactive coached assistance to overcoming barriers), fear, concern about potential out-of-pocket expenses and no previous family history. Many women reported lack of knowledge about what would happen during a CGRA, misunderstanding how CGRA (i.e., genetic counseling) was separate from genetic testing, a belief that CGRA was not applicable to them or their biological relatives, including sons if they did not have daughters, and a lack of awareness that CGRA can help with decision-making to manage personal and familial risks. Once informed about CGRA, virtually all women agreed that increased knowledge of their genetic risk would be beneficial to themselves and their close biological relatives, and endorsed our population recruitment and intervention approach (study of tailored and targeted approaches), emphasizing its high significance and impact. They felt that the targeted and tailored interventions were culturally sensitive and would be appealing to all ethnicities.

Participants provided critical feedback on the intervention prototypes. Regarding the mailed generic brochure, they recommended increasing the emotional appeal and emphasis on how CGRA could benefit them as well as their family. Participants suggested a brief, “to-the-point (tri-fold)” tri-fold brochure, fewer and simpler statistics that would improve readability and extend the reach to those with less education and lower numeracy levels. They recommended that we retain the culturally sensitive photos, a testimonial, offer interventions in English and Spanish, and better define genetic counseling/CGRA and how it is different from genetic testing. As one woman said: “My assumption was I’m getting set up to be tested. Not being set up for an appointment for a screening [sic-genetic counseling session] ...it just hit me now.” Because ethnicity/race may not be accurately reported to cancer registries and many people identify as biracial/cultural, participants agreed that one pamphlet could be culturally sensitive for the target population for this study rather than one for each ethnicity/race, state, rural/urban). Spanish-speaking focus group participants expressed language and United States citizenship status as barriers to getting CGRA. Spanish-speaking women also reported greater difficulty communicating with providers about getting their needs met, including the need for information about hereditary cancer and CGRA. Overall, participants agreed that offering study materials and live interactions (i.e., telephone-based health coaching sessions) in English and Spanish was desirable.

Women strongly endorsed a telephone intervention that includes provision of knowledge about CGRA (benefits and process), interactive coaching (motivational strategies) and navigation for those who need it as opposed to tailored print materials alone. They felt a

conversation with a health coach first, followed by a 3-page tailored summary letter (that includes graphics and a testimonial) would be effective, as shown in our prior research.[38] Participants also emphasized the strengths of the personalized aspect of the letter's content, including an action plan, and pictures and names of the PI and genetic experts. They felt it would reinforce key topics discussed during the call. They also provided input into graphics/pictures, colors, organization and wording of generic and tailored materials, and suggested having web versions available to retain a "permanent record" and share with key social network members via email.

Following the feasibility trial, we held a community advisory board (CAB) meeting in April 2017 to assess feedback from six women from the target population or key community stakeholder on our recruitment strategy, recruitment materials, and intervention materials for the definitive trial. CAB members recommended increasing incentives for study participation, emphasizing the noninvasiveness of the study during recruitment, putting language about hereditary cancer in targeted print materials into layman's terms, and omitting the word "cancer" during recruitment calls to avoid unintended release of medical diagnoses to other household members. CAB members also emphasized the importance of cultural sensitivity, particularly with regard to Spanish translations of study materials capturing colloquial speech and understanding that fear of immigration and customs enforcement may keep some Hispanic women from participating or revealing information about themselves. These suggestions were implemented in the ongoing definitive trial.

3.3.2 Feasibility Trial—We conducted a pilot randomized controlled trial to assess the feasibility and acceptability of the intervention and obtain an effect size estimate. Thirty-four high-risk women were recruited through a statewide cancer registry and randomized to UC, TP, or TCN. Evidence-based behavior change strategies, the Extended Parallel Process Model, and the Health Action Process Approach to bridge the intention-behavior gap guided the TCN intervention. Telephone surveys elicited perceptions about CGRA and the intervention. Women in the TP (mean=4.10, SD=0.15) and TCN arms mean=4.38, SD=0.28) reported high satisfaction (possible responses ranged from 1-5 rating with 5 being very satisfied) with the interventions with no observed differences between the two study arms. CGRA uptake at six months post-intervention was observed for 30% of women in the TCN arm, 8% in the UC arm, and 0% in the TP arm ($P<0.05$). Financial and insurance concerns were the most frequently reported barriers to obtaining CGRA.

4.4. Intervention Arms

4.4.1. Usual Care—A usual care arm (treatment as usual) is included to assess GGRA uptake in the absence of intervention.

4.4.2. Targeted Print—Participants randomized to this arm are mailed an educational brochure within one week of completing the baseline survey. English or Spanish brochures are mailed according to the participant's language preference. This brochure addresses important evidence-based theoretical targets: CGRA guideline (knowledge), threat appraisal (to validate or raise risk perceptions, HBOC seriousness), response efficacy (benefits and expectations about CGRA), self-efficacy (CGRA resources, insurance reimbursement,

assistance for those with financial challenges) and possible actions to take (make an appointment and discuss with provider). Please see supplementary materials for the state-specific brochures.

4.4.3. Telephone Counseling & Navigation—Within one month of the baseline survey, a health coach (see section 4.4) conducts a 20–40 minute (depending on participant needs) telephone counseling session with women randomized to this arm. The intervention is offered in English or Spanish, depending on the participant's preference. Because theoretically-based tailored messages are generally more effective than generic messages in producing behavioral change,[36, 99] the psycho-education and navigation session is individualized according to each participant's perceptions of threat and efficacy as derived from the EPPM,[33, 38] and according to personal factors such as HBOC and CGRA awareness, family history, cultural factors (e.g., ethnicity, language preference, familism, fatalism, family history), psychological and logistical concerns, knowledge, and barriers to CGRA that arise during the phone call. Before the session commences, the coach accesses an electronic folder containing the participant's personal information (e.g., age, preferred language, rural or urban residence, cancer type, summary scores of measures collected during the baseline survey (genetic self-efficacy, hereditary breast and ovarian cancer knowledge, health literacy, cancer worry, CGRA intentions, fatalism) and a graph delineating the woman's scores on CGRA efficacy and threat perception measures. The coach reviews this information prior to the session and uses it during the session. The threat and efficacy perception scores provide the coach with an overall idea of what EPPM construct(s) and other factors they should focus on in their discussion with each woman. Prior to the telephone session, participants receive the same brochure that the TP arm receives. After the phone call, participants receive a tailored follow-up letter. Tailoring variables includes demographic, clinical, and patient-reported data derived from the cancer registry data (age, type of cancer diagnoses) and during the survey or phone call (ethnicity, family history, primary care provider or oncology specialist), threat and efficacy appraisals, concerns (e.g., family member's risk and/or risk of second cancer, family orientation), top two CGRA facilitators and barriers, and action plan. The letter also includes images tailored to the individual's age, self-identified ethnicity, and family composition.

Both the health coaching/navigation telephone session and tailored letter incorporate evidence-based communication and behavior change approaches designed to raise the participant's perceptions about the threat (to herself and at-risk family members), arouse emotions and manage fear, enhance positive beliefs about CGRA (response efficacy), increase self-efficacy by addressing barriers and facilitators, and motivation to get CGRA. [23, 100–109] The health coach uses an MI style to help participants explore their reasons for getting CGRA, resolve ambivalence/decisional conflict, and develop an action plan. The outline of the telephone counseling and navigation intervention is summarized in Table 2 and the intervention is provided in the supplementary materials.

4.4.4. Intervention Standardization and Fidelity—Best practice guidelines are employed to ensure and monitor intervention fidelity.[110–113] Health coaches receive training regarding the overall study and intervention delivery protocols. This includes: the

overall study protocol, overview of process and content of genetic counseling/CGRA, CGRA referral guidelines, theoretical aspects of the intervention including MI, and facts about obtaining health insurance. Training will also include general telephone communication strategies and issues, scope of practice (e.g., not providing health or medical information beyond their scope of work and training), strategies specific to patient navigation (including obtaining health insurance). Initial training consists of 1.5 days of lecture, discussion, case-based learning, role-playing and practicing tailored counseling and navigation sessions followed by weekly booster training sessions lasting 1 hour each for the first two months, then every other week for the next three months and then monthly until the interventions are complete.

An intervention fidelity checklist and implementation manual are used to help ensure intervention fidelity (see supplementary material). Each TCN coach conducts at least 3 audio-recorded pilot TCN sessions with analogue patients until competency is achieved. Audio-tapes of the analogue and research participant TCN sessions are reviewed by designated staff and the certified motivational interviewing specialist (SW) to assess adherence to the theoretical components of the intervention and levels of motivational interviewing competency using an intervention fidelity checklist and Motivational Interviewing Treatment Integrity Coding Manual[114], respectively. By referring to the study-specific TCN protocol checklists, the first 5 TCN sessions of each counselor are reviewed and then at least 10% of randomly selected sessions are reviewed thereafter to determine whether the coach adhered to the TCN intervention and receive performance feedback regarding motivational interviewing. Deviations from the protocol are assessed and additional training is done as needed. Health coaches complete intervention checklists during and after the sessions, similar to what we have used in our prior research to help ensure intervention fidelity. [38, 115]

4.4.5. Expanded Access to CGRA for All Women in All 3 Study Arms—Our study is likely to raise HBOC risk perceptions and may increase psychological distress, especially in women who have access barriers such as concerns about out-of-pocket expenses for genetic counseling, travel and logistical barriers as well as language barriers. Hence, after the 6-month survey, the study covers the costs for genetic counseling for women in all 3 study arms who indicate on their survey that they desire genetic counseling. The study facilitates access to telephone, web-based (e.g., Skype) or in-person counseling within the next 3 months based on participants' mode preference. Following the 6-month survey, women in the usual care arm are mailed the TP brochure and are informed in a letter that the study covers the cost of genetic counseling if they wish to have it done within the next 3 months. Participants in the TP and TCN arms are mailed a similar letter indicating that the study will cover a genetic counseling session within the next 3 months, and to call study staff within the next 3 weeks if they would like to proceed with the counseling through the GRACE Project.

4.6. Measures

Surveys are administered at baseline (T1) then at 1-month, 6-months and 12-months following the intervention for the TP and TCN arms and the baseline survey for the UC arm.

Surveys are administered via telephone or the internet. Our key outcomes (i.e., genetic counseling and testing uptake, costs) are described below; patient reported secondary outcomes and potential mediating variables are described in Table 3. Interviewers are blinded (as much as possible) to the treatment condition for all follow-up interviews.

4.6.1. CGRA—Participants who have genetic counseling by a cancer risk specialist (genetic counselor, nurse or clinical geneticist) and/or genetic testing for hereditary cancer within 6 months of the intervention (or baseline survey for UC arm) will be considered “completers” of CGRA. Those reporting that they had CGRA are asked to sign a medical release to verify self-reports. This approach is feasible and has been successful in our[38, 116] and others’[117, 118] prior work. We track the type of provider (e.g., physician, genetic counselor) who provided counseling and document their genetics training via the documentation form. Using the same strategy, we also assess genetic counseling utilization at the 12-month follow-up. For those who had genetic counseling, we will assess genetic counseling mode (i.e., in-person, telephone or internet-assisted. We will also assess whether the counseling was done in the participant’s preferred language and whether a language translator was used during the genetic counseling session. Through the medical record release signed by patients, self-reported genetic testing (including type of test and test result) is verified immediately following the 6-and 12-month follow-up assessments.

4.6.2. Cost Data—The incremental cost of implementing the interventions will be measured from a payer and societal perspective. The payer in this case would be the entity responsible for funding the cancer registry considering patient ascertainment and intervention implementation; therefore, we will estimate recruitment costs, intervention development and delivery costs and downstream costs up to 1-year post intervention. Implementation costs will include labor (e.g., registry and study staff, MI trainer, health coaches) and non-labor (e.g., printing, mailing, costs of CGRA and genetic tests, telephone charges, patient-related travel time). We focus on costs of replicating delivery of the intervention and the immediate down-stream consequences (e.g., obtaining CGRA and genetic testing). Health coaches record time and resources used to deliver the interventions on participant encounter forms; these forms are compiled to calculate the average time per participant. The societal perspective in theory includes all goods and services consumed as a result of the intervention, including the payer costs and patient costs: deductibles, copayments, and cost-sharing for direct medical goods and services in addition to direct non-medical goods and services such as transportation to appointments, and indirect, or opportunity costs incurred as part of the intervention.[119] We will use micro-costing techniques as recommended by the US Panel on Cost-Effectiveness in Health and Medicine[120] and utilized in our past research on the costs of behavioral interventions.[37, 121, 122] Costs will be estimated via direct elicitation from participants and medical records to assign fixed price weights. As part of the 1-month, 6-month, and 12-month surveys, participant time, travel, and resource utilization is ascertained and standardized price weights are applied to generate a total cost per participant that will be compared across arms. We have used these methods successfully in previous studies.[37, 121, 122]

4.6.3. Covariates—The following factors are assessed as covariates: 1) sociodemographics include age, gender, education, household income, financial status, marital status, rural-urban community area code,[123] living biological children, health insurance status, country of origin/Puerto Rico, years lived in the U.S mainland; 2) Medical history: personal/family history of cancer, age of diagnosis, cancer stage, bilateral breast cancer, two or more HBOC-related cancers, triple-negative breast cancer, health status, co-morbidity index; 3) Acculturation: Short Acculturation Scale[124]; 4) Family and friends' social support and encouragement to obtain CGRA[38, 125, 126]; 5) Family orientation: The Familism Scale;[127] 6) Brief Fatalism Scale;[128, 129] 7) Health System Distrust; [130] 8) health literacy;[131, 132] 9) Receipt of a physician/provider recommendation for CGRA; and 10) Primary health care provider who received the TCN participant's tailored letter.

4.7. Data Analysis

We will account for missing data in key study outcomes using multiple imputation and intent-to-treat (ITT) approaches. Multiple imputation under the Missing at Random assumption will be applied using a Markov Chain Monte Carlo method[156], given the expected pattern of non-monotonic missing data. A post hoc approach will address the influence of missing not at random (MNAR) and the effect of attrition on outcomes of interest. Sensitivity analyses will be performed to assess alternative multiple imputation techniques upon the extent of MNAR influences. Multiplicity will be adjusted for the primary outcome analysis using the Holm's adjustment procedure.[157] All tests will be two-sided. The effect sizes and 95% confidence intervals (CIs) of all outcomes using both ITT with multiple imputed data and per protocol will be reported regardless of statistical significances.

The proportion and its 95% CI of CGRA uptake for each arm will be calculated using the exact binomial distribution. Logistic regression modeling will be employed with the main covariate of arm (UC, TP, and TCN) to estimate an odds ratio (OR) along with a 95% CI. We will also compare the 3 study arms with regard to medical record verified CGRA uptake by 12 months after offering to cover the costs of genetic counseling following the 6-month survey for those who desire but did not access counseling. Evaluation of the incremental effect will be assessed by comparing the difference of the primary outcome between changed intervention arms (UC to TP/TCN; TP to TCN).

We will compare cognitive and affective intermediate endpoints among women in the 3 study arms and explore potential underlying theoretical mediating and moderating mechanisms that will further specify and elucidate significant 6-month and 12-month intervention effects, if such effects are observed. The study arms will be compared with regard to beliefs (threat and efficacy), informed decision-making indicators (knowledge, decisional conflict, and decision regret and satisfaction) and emotional factors (psychological distress, perceived stress, cancer worry and fear) and provider communication and recommendation about CGRA. Structural equation modeling (SEM) for the hypothesized mediational pathways will be conducted[158]

The interventions may not be beneficial for all study participants. Thus, a sensitivity analysis will be done to identify subgroups for which the interventions have or do not have an effect (e.g., sociodemographics such as age at enrollment and diagnosis, time since diagnosis, family history of breast and/or ovarian cancer, rural/urban status, race/ethnicity, recruitment site, education level, having at least one living close at-risk relative, household income; health literacy; cultural factors such as acculturation, language preference, familism, stress, family support of CGRA, provider recommendation, and logistical barriers such as concerns about out-of-pocket expenses, travel and competing demands). This will provide important information about subgroups who are particularly receptive or resistant to each intervention.

The economic evaluation alongside this trial will consider the following outcomes based on a *priori* trial specifications: 1) average cost per patient for ascertainment, scheduling, health coach-participant interaction time; 2) average cost per CGRA and genetic testing; and 3) average time spent with health coach. We will also examine overall health care use (including, visits to genetic professionals and other providers, and genetic testing) by study arm (and covariates as needed) at 6 months and 12 months. The incremental cost-effectiveness ratio (ICER) for the pairwise comparisons of each arm of the trial is derived from the following formula: $ICER = (C_A - C_B)/(E_A - E_B)$ where C_A and C_B refer to average total costs of each alternative and E_A and E_B refer to average total effectiveness for each alternative. The resulting ICER calculated for each combination of comparators, TCN, TP, and UC, can be used to assess the value provided by alternative A when compared to alternative B, as it represents the investment required for each additional unit of effect gained. All analyses will be completed on an intent-to-treat basis. Uncertainty in estimates will be tested using probabilistic sensitivity analysis to assess key drivers of results such as rural/urban residence, cancer type, ethnicity, language preference, age, education, household income and family composition (have at least one living at risk first-degree relative).[159] Uncertainty in the ICER will be evaluated using cost-effectiveness acceptability curve plots. [160]

We will apply the Reach, Adoption, Implementation and Maintenance (RE-AIM) framework to assess reach and effectiveness, implementation and adoption issues overall and by ethnic and geographic subgroup, as well as socioeconomic status and cultural variables (e.g., language, medical mistrust).[161–163] We will describe adherence to the theoretical aspects of the intervention and MI using MITI global scores.[114]

4.8. Sample Size and Power Calculations.

The statistical power evaluation of the study was based on the primary outcome of CGRA uptake. The key assumptions for the power calculations stem from the literature and preliminary data that were available in 2015. Given the study's hypothesis that the TCN intervention will have greater effects over both the UC and TP arm.[164] We expect no greater than 7% CGRA uptake by 6 months in UC, with at least 12% increments for TP and TCN, respectively. With the adjusted significance level (alpha) of 0.017 for the multiple comparisons using Holm's correction, 163 participants per study arm will provide 80% power to detect a 12% difference in the CGRA uptake 6 months between the UC and TP arms. For the comparison between TP and TCN, 247 participants per arm is required to

detect a 12% difference (19% vs. 31%) at the adjusted 0.025 alpha level. The test statistic used was the two-sided Likelihood Ratio test. For the secondary and exploratory analyses we expect at least 80% power to assess the intervention effect about 10-12% differences in genetic testing uptake and small to medium effect sizes of psychosocial targets between the arms given the measures' standard deviations. Randomizing 741 participants based on 1:1:1 relative sizes ensures > 80% power for all contrasts. Assuming up to 20% attrition after baseline assessment, we will recruit 309 individuals for each arm. The sample size and power were evaluated using PASS13 software.[165]

5. Discussion

Identification of and care delivery for individuals with inherited cancer predisposition is a key national priority in the United States. Although genetic counseling has been recommended by multiple organizations to enhance understanding, informed consent, preventive behaviors, and individualized care,[18, 166–168] less than half of women with breast or ovarian cancer who meet national criteria for referral to a CGRA receive genetic counseling and/or testing.[169–171] The GRACE trial addresses the critical need to identify effective strategies for increasing CGRA utilization and adherence to national guidelines among cancer survivors at increased risk for inherited cancer predisposition. The optimal testing strategy starts with a relative who has cancer. If a mutation is identified, testing for the known gene mutation can be offered to relatives to determine if they have the cancer predisposition.[13, 172] The trial is guided by evidenced-based behavior change counseling strategies to promote risk-based care delivery and reduce disparities around individual, cultural, social and system-level factors. For our diverse target population, both print and telephone have been found to be acceptable ways to communicate CGRA information but personalized counseling and navigation vs. targeted print has not been effectively tested in this social and clinical context.[37, 108, 115, 173] Identifying high-risk cancer survivors through statewide cancer registries enables access to populations that are geographically diverse and underserved by traditional healthcare settings. Cancer registries are in an ideal position to identify and reach large numbers of underserved high-risk cancer survivors who may benefit from risk information that can help them make informed decisions about their or their biological relatives' health.[174, 175] This approach will help to reach the larger population of family members who are at increased risk for HBOC. Further underscoring our study's significance is the availability of the interventions in both English and Spanish and the portable nature of the interventions, that if successful, can be delivered by other states and their cancer registries alone or in collaboration with cancer centers. [176]

Several important issues were considered when designing this study. First, based on our preliminary work and others' research, it appears that high-risk women use printed materials as their primary information source (other than talking with a health professional). Second, we designed this study to ensure representation of underserved populations, especially Hispanics, rural dwellers and people at lower socioeconomic strata. Third, our approach appears to be highly feasible, given our prior success in recruiting from central cancer registries, English and Spanish-speaking Hispanics and rural dwellers. Although we are not able to provide free genetic testing through this grant mechanism, the cancer genetic counseling clinics at UNM, UCO and the Cancer Institute of New Jersey have success in

obtaining free or low cost testing for uninsured indigent patients. Patients will be provided with resources in their respective states to help them get the recommended care. Further underscoring the significance of our study, we will be able to identify key barriers and facilitators and determine if there are common patterns related to CGRA and testing, and whether these differ by ethnicity and rurality, and other key factors (e.g., other sociocultural factors/demographics, type and time of cancer diagnosis). Fourth, we will also be able to estimate the proportion of women in CO, NM, and NJ who received CGRA and genetic testing prior to our study as we will screen participants regarding this during our study recruitment process. Fifth, the TCN intervention will be implemented as a multi-level intervention (sending a letter and participant's tailored letter to their health care provider, with their permission). Our[115] and others' research[105, 177] shows that the provider involvement is a powerful predictor of whether someone obtains recommended health services, including CGRA. Furthermore, more intensive, multi-component interventions directed at clinicians and/or participants are generally more effective than less intense single-component or generic interventions.[178, 179] Finally, we considered recruiting women who had been diagnosed in the previous 10 years; however our[37] and others' work indicate that most survivors treated in earlier years have never had CGRA or genetic testing. This highlights the need to include woman who were diagnosed in the distant past to maximize the study's impact. Future plans include integrating male survivors, cascade counseling and testing of relatives of patients in whom a mutation is found, and analysis of family communication of genetic test results.

In summary, this study has numerous key strengths including strong internal and external validity. The trial is innovative in its programmatic approach to testing a low intensity targeted intervention with a high intensity personalized intervention with regard to their impact on increasing CGRA uptake. The intervention approach is designed with dissemination and sustainability in mind, underscoring the study's high impact. It addresses both patient, cultural, societal and system level factors, activates patients and providers (TCN arm), and is aligned with the precision medicine/prevention paradigm and national priorities to reduce health disparities. Furthermore, our study will help determine whether the expected effect of TCN is great enough to outweigh the costs. If successful, our intervention approach has the potential to reach large numbers of high-risk families through broad dissemination and ultimately to reduce the public health burden of HBOC. Data from this trial will be useful to policy makers, cancer registries, cancer centers and other clinical practices when making decisions about intervention delivery and sustainability to ensure adherence to national guidelines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
GRACE Study: A Conceptual Model

Figure 2.

Extended Parallel Process Model (EPPM) and Motivational Interviewing (MI) Strategies to Increase CGRA Utilization

Figure 3.
Proposed Study Design and CONSORT Diagram

Table 1.

Eligibility and Sampling Criteria

Inclusion Criteria	Exclusion Criteria
At least one of the following: <ul style="list-style-type: none"> Breast cancer diagnosis ≥ 50 years Bilateral breast cancer Invasive epithelial ovarian cancer Diagnosis of triple negative breast cancer 	Unable to give informed consent (incoherent, dementia)
Age 21 and older	No access to a telephone
Female	In hospice care
Fluent in English or Spanish	Permanent residence outside of Colorado, New Jersey or New Mexico
	Incarcerated Prior cancer genetic counseling or HBOC genetic testing
	Planning on relocating out of CO, NJ, or NM within the next year

Table 2.**Overview of Tailored Counseling and Navigation Arm**

<i>Step 1: Introduction and Rapport Building.</i>
<i>Step 2: Address HBOC Threat Perceptions.</i> To enhance HBOC risk perception, the health coach elicits the women's awareness and thoughts about the CGRA referral guidelines. The coach provides information about the participant's personal risk for a HBOC-related second cancer, and acknowledges that male and female blood relatives maybe at increased cancer risk. Participant responses are used to enhance cognitive processing of information.
<i>Step 3: Address Barriers and Efficacy.</i> The coach elicits the participant's response efficacy beliefs, including risk management options for HBOC. If desired by the participant, the health coach describes the CGRA/genetic counseling process; its effectiveness in helping women like them and their blood relatives; and addresses questions, concerns or misconceptions about CGRA. The coach uses the "Importance" Ruler (1 - 10 scale) to elicit participant talk around desire and reasons for CGRA. The coach uses the "Readiness" Ruler (1 - 10 scale) to elicit participant talk around ability, confidence, and commitment to obtain CGRA within the next six months. Throughout the interaction, the health coach utilizes open-ended questions to elicit and reinforce the participant's reasons for undergoing CGRA. The coach explores factors that the participant believes would increase priority and/or efficacy to get a CGRA. The coach also elicits and attempts to resolve the participant's two most important barriers to getting CGRA.
<i>Step 4: Construct an Action Plan.</i> Using the readiness ruler and action planning visual aids, the coach prompts the participant to create a personalized action plan. The health coach applies implementation intention principles by encouraging the participant to formulate a plan (or a hypothetical plan if she is not ready or willing to make an actual plan) to obtain a CGRA.
<i>Step 5: Provide Navigation as Needed.</i> The coach offers assistance (navigation) to help the patient overcome barriers and asks permission to follow-up with them to provide further help as needed. For example, coaches may help participants find a genetic provider, access health insurance, help participants determine if their insurance covers genetic counseling/testing, assist with making the appointment, and assist with arranging transportation. The dose and follow-up navigation activities (patient interaction time and additional coach time) are tracked and analyzed as process variables.
<i>Step 6: Summary, Closing and Follow-up.</i> The coach provides a summary of the participant's primary reasons for getting CGRA, how they will address the top two barriers (if any barriers are identified) as well as the action plan. The coach asks permission to send a letter to the patient's primary provider letting them know that the participant meets the referral criteria for CGRA according to national guidelines and a copy of the participant's tailored letter. For participants who identify barriers, the coach delineates the next steps (navigation strategy as needed), and schedules a time for a follow-up call with the patient. A tailored letter is mailed immediately after the phone session that includes the women's personalized action plan. Women receive a follow-up call from the health coach 7 weeks after the telephone call to assess need for additional navigation and provide assistance. The number, dose (i.e., time) and nature of the navigation assistance are tracked and evaluated in the cost analysis.

Table 3.

Secondary Outcomes and Mediating Variables

Domain	Measure	Timepoint ^a
Threat Beliefs	Risk Behavior Diagnosis Scale[133, 134] perceived susceptibility and severity of HBOC subscales	T1, T2, T3, T4
Efficacy Beliefs	Risk Behavior Diagnosis Scale[133, 134] self-efficacy and response efficacy regarding genetic counseling subscales	T1, T2, T3, T4
Fear	Fear of HBOC risk (self, family): Affect in Risk Scale[135–137]	T1, T2, T3
Defensive Avoidance	Defensive Avoidance[35, 138]	T1, T2, T3
Distress, Stress and Worry	Cancer Worry Scale; [139, 140] Psychological distress: anxiety and depression subscales of the Brief Symptom Inventory:[141–143] Short Perceived Stress Scale[144, 145]	T1, T2, T3, T4
Decisional Regret and Satisfaction about genetic counseling and testing decisions	SURE Scale[146, 147]; Decision Satisfaction Scale[148, 149] and original contributions	T1, T2, T3, T4
Genomics and HBOC Knowledge	Items from the National Center for Human Genome Research Knowledge Scale and additional items specific to breast and ovarian cancer survivors[150, 151]; Original contributions assess whether participants heard about or were referred for CGRA and HBOC genetic testing (e.g., BRCA1/2) prior to being contacted for this study	T1, T2
Genetic Self Efficacy	Items assess confidence in their ability to understand genetic information and how it applies to personal health[152–154]	T1, T2
Belief that the GINA law would adequately protect against genetic based discrimination	Genetic Information Non-Discrimination Act (GINA) Law Confidence Scale[155]	T1, T2
Facilitators and Barriers Regarding CGRA	Facilitators and Barriers to genetic counseling and testing at the individual, interpersonal, structural and system-level are assessed[23, 101, 105, 108]	T1, T2, T3, T4

^aT1 = baseline; T2 = 1 month after baseline for UC or 1 month following TP or TCN; T3 = 6 months after baseline for UC or 6 months following TP or TCN; T4 = 12 months after baseline for UC or 12 months from TP or TCN