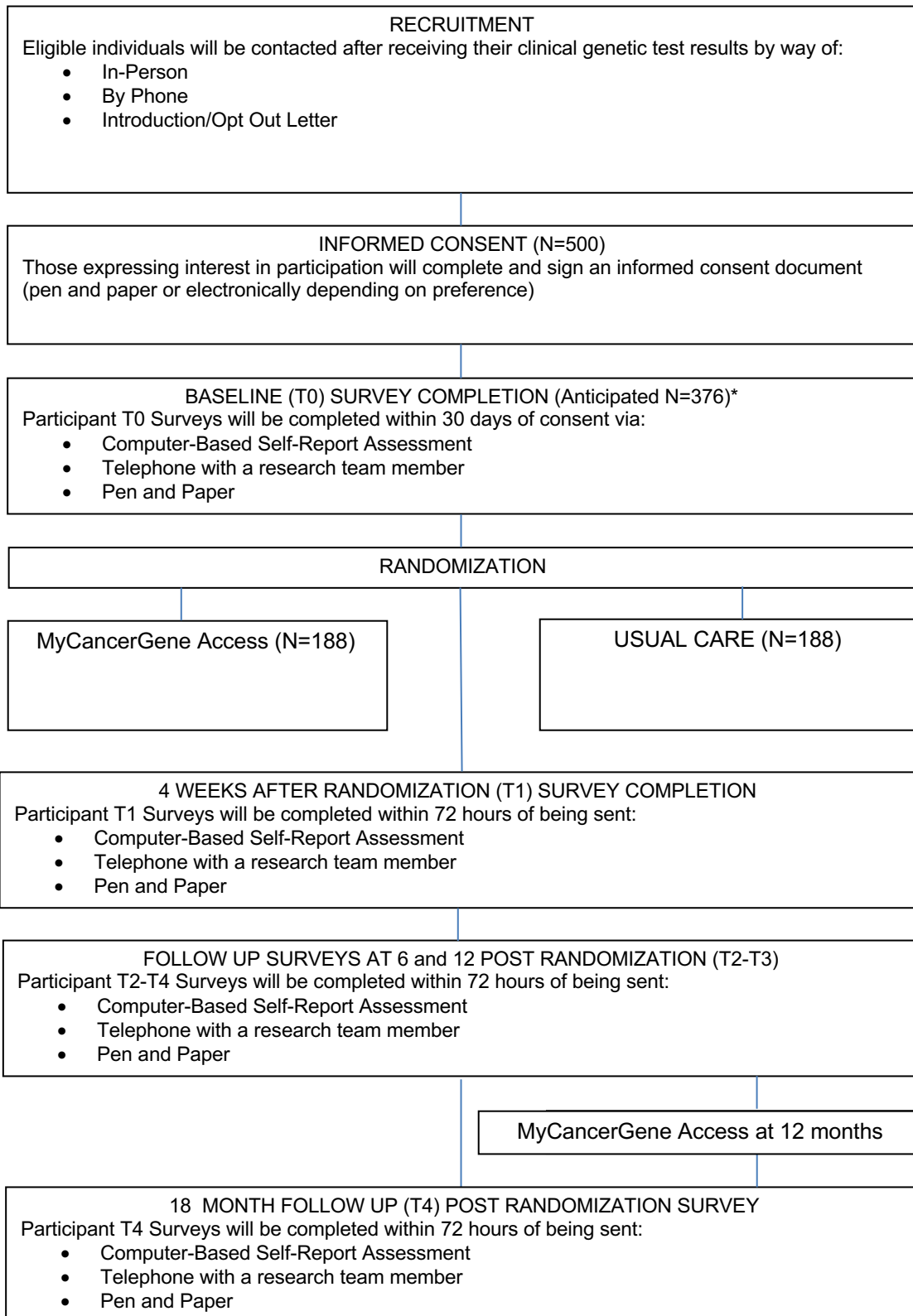


TITLE: *Effectiveness of MyCancerGene to optimize genetic testing outcomes*

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SCHEMA



*75% response rate

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1.0 Background

Basic science advances in genetics have provided great promise for improving human health and reducing the burden of cancer.^{1,2} The promise of precision medicine is the ability to tailor treatment or screening of individual patients based on their genotype.²⁻⁵ With these advances, there is an increasing need for multidisciplinary translational research that focuses on how to advance precision medicine discoveries into clinical practice and to capitalize on connectivity (e.g. eHealth) applications in ways that benefit the health of entire populations.^{1,3,5-8} Thus, even after gene discovery effectiveness and implementation studies, evaluating how genetic medicine is implemented in “real-world” clinical practices is necessary to realize the health benefits of precision medicine.^{1,3,9-11}

Advances in clinical sequencing leave many patients with uncertainties regarding interpretation, implications and recommendations, which will change over time. *BRCA1/2* and Lynch Syndrome testing for predisposition to breast, colon and gynecologic cancers are examples of evidence-based standard-of-care applications of precision medicine.^{12,13} Recently, mutations in many other genes (e.g. *PALB2* and *CHEK2*) have been associated with elevated risks of cancer.¹⁴⁻¹⁸ Thus, multi-gene panel testing (MGPT) has entered clinical practice to screen many cancer susceptibility genes simultaneously.^{17,19-21} Many of the genes included in MGPT are moderate-penetrance genes, increasing the risk of cancer by only 2-4 fold and in many cases risks estimates are based on limited data and continue to evolve over time.^{18,20} There is also uncertainty regarding optimal screening given constantly evolving medical management recommendations (e.g. NCCN and other guidelines for many of the newly included genes are evolving as new data emerges). Thus, even positive results leave many unknowns regarding cancer risks, optimal management and the value of testing unaffected relatives.^{18,20} Additionally, MGPT has been associated with higher rates of variants of uncertain significance (VUS), which are difficult for patients to understand and will be reclassified over time. This clinical transition from discrete (i.e. single gene) to broad (i.e. MGPT, whole-genome) sequencing in clinical genetic testing presents challenges that will only increase as precision medicine applications expand.²⁰ With “broader” sequencing, an increasing number of patients will be left at risk for misunderstanding, uncertainty and evolving interpretations and recommendations.^{17,22} These uncertainties will be clarified over time, but we lack models to maintain longitudinal communication with patients in order to provide updated information regarding their test result or medical recommendations and to obtain updates in their personal and medical history remains unclear.^{22,23} In the current standard-of-care, the commercial lab contacts the ordering provider, who in turn contacts the patient. This model is not sustainable and unsuccessful due to outdated contact information.²³ Alternatively, patients can “call-in” annually,²⁴ but this places a burden on patients and has not been proven to be successful.²⁵⁻²⁷ Thus, effective, evidence-based alternative strategies for longitudinal communication and care for genetic patients are critical to realizing the promise of precision medicine.

Other studies have been evaluating the cognitive, affective and behavioral outcomes of clinical genetic testing in the era of MGPT in the METEOR (MultiplEx Testing for Evaluation Of breast cancer Risk, IRB# 820274) and multi-center COGENT study (A Study of the Communication of Genetic Test Results by Telephone: A Multi-Center Study, R01 CA160847/IRB# 816768). With the advent of MGPT, there was a need to develop a new approach to genetic counseling and informed consent. In collaboration with six clinical cancer genetics programs, our team developed and piloted the tiered-binned model for genetic counseling and informed consent.^{28,29} This model was used in

the multi-center COGENT study, recruiting 1178 sociodemographically diverse patients undergoing cancer genetic testing. We found that telephone disclosure is non-inferior to in-person disclosure (e.g. usual care for knowledge and short-term distress outcomes, even in the setting of MGPT^{21,30}). Preliminary longitudinal analyses are consistent with other published studies showing that genetic knowledge declines after cancer genetic testing.³¹⁻³³ Importantly, knowledge gain at 6 months was lower for those who did not return for follow-up (-0.77) compared to those who returned (-0.17, $p=0.08$). These data highlight the need for longitudinal follow-up with patients after genetic testing.^{34,35} Additionally, the COGENT longitudinal data reveal subgroups who could benefit from longitudinal follow-up after genetic testing. Declines in knowledge were greater among participants with a VUS or negative result, which represents over 70% of patients undergoing cancer genetic testing. These groups are critically important given concerns that those with a VUS will misinterpret their risk and perform risk reducing interventions inappropriately or that uninformative negative patients with a familial risk will misinterpret their result to mean they are not at risk. Further, anxiety and cancer worry decline less among patients with positive results, identifying a group where ongoing support could optimize psychosocial adjustment to testing.

The Institute of Medicine has highlighted the importance of patient-centered care and improved transparency to enhance the delivery and outcomes of medical care.³⁶⁻³⁸ Data from the Pew Research Center reports that 84% of Americans use the internet³⁹, and patients have high interest in communicating electronically with providers.⁴⁰⁻⁴² Thus, Interactive Health Communication Applications (IHCAs) have been implemented to facilitate this goal of enhanced transparency and communication.^{38,43} IHCAs may be particularly effective in chronic disease, where longitudinal care is crucial, informational needs change over time or vary among patients, when coping and adjustment are part of the “journey” and improved medical outcomes requires changing health behaviors.⁴³ Studies from a variety of chronic disease settings, but not including genetics, have shown that IHCAs can improve knowledge,⁴³ self-efficacy,⁴³⁻⁴⁶ satisfaction,^{41,47-49} clinical outcomes,^{43,47,49,50} and unmet communication needs.^{46,49,51} Recent randomized studies have shown reductions in distress with IHCAs.^{41,44,52-54} Further, IHCAs may provide education in a way that is more simple, accessible and salient resulting in better knowledge retention.⁴³

Yet, many have identified limitations to the currently published data of the risks and benefits of IHCAs.^{38,46,55,56} Various forms of IHCAs have been used and limited function electronic patient portals (i.e. providing access to records only) may have less impact on outcomes.³⁸ Until recently, the majority of randomized studies have been relatively small (<100 per arm) and there still remain few high quality studies.^{41,46,47,49,52-54} Further, in some studies, participants rarely or never log on, which may impact outcomes and diminish power.⁵⁷⁻⁶¹ Additionally, studies including socioeconomically diverse patient populations are needed, as minority patients are significantly less likely to use electronic patient portals, which could exacerbate health care disparities.^{41,46,53,54,57,61-63} Importantly, there are no published studies evaluating IHCAs in clinical cancer genetics, which shares many of the characteristics of chronic illness (evolving information over time, adjustment and need for behavior change and communication with relatives and other health care providers). Thus, cancer genetic testing is an ideal clinical context to study the benefits and limitations of a theoretically and stakeholder informed patient-centered Cancer Genetic IHCA to optimize patients’ outcomes after cancer genetic testing and clinical implementation of Precision Medicine.

- **PRELIMINARY STUDIES and THEORETICAL MODEL**

To consider the advantages and disadvantages of a cancer genetic IHCA to maintain longitudinal communication with patients, stakeholder feedback from patients and providers has been obtained. Provider stakeholders included genetic counselors and physicians (N=17) at the 5 COGENT sites. Patient stakeholder interviews were conducted with 15 randomly selected COGENT participants across sites to represent the view of sociodemographically diverse patients who had undergone genetic testing. Patients were 29-69 years old, and included 2 men, 3 patients without college education, 2 non-white patients and a range of test results. Provider and patient advantages were utilized to inform the development of the proposed intervention and IHCA content (Appendix J) as well as provided feedback and suggestions for improvements which were ultimately incorporated.

To better understand willingness to utilize a cancer genetic IHCA among patients who had undergone clinical cancer genetic testing, COGENT participants were also asked

Patient Interest in a genetic IHCA				
	All (n=307)	Positive (n=52)	Negative (n=187)	VUS (n=34)
Would an IHCA be helpful?	81%	92%	82%	83%
Any barriers to using an IHCA?	25%	19%	24%	21%
Would use an IHCA	74%	92%	72%	71%
Would participate in RCT	76%	85%	74%	88%

Indicates somewhat or very willing/likely.

feasibility questions as part of their surveys at all five participating sites. The majority of patients reported a genetic IHCA would be useful. Few reported potential barriers and challenges, including the risk of a privacy breach (9%), unfamiliarity/discomfort with

using websites (6%), remembering the password (4%), and an increase in the chance for information to be misunderstood (3%). Few patients (2%) reported lack of access as a barrier.

Consistent with our related research (COGENT, Returning Genetic Research Panel Results for Breast Cancer Susceptibility (RESPECT), IRB#822601, etc.) the proposed study will be informed by our theoretical model to evaluate innovations to delivery of genetic information. This model, also informed by the Consolidated Framework for Implementation Research (CFIR), provides an innovative framework for studying the effectiveness of an eHealth intervention (Aims 1 & 2) and barriers and facilitators to future dissemination and implementation (Aims 3a & 3b).

As improved patient outcomes are contingent upon high-risk individuals adopting preventive health behaviors and communicating their results to at-risk relatives, the effectiveness of genetic testing for disease susceptibility is contingent upon successful communication and behavior modification.^{6,64,65} The Self-Regulation Theory of Health Behavior (SRTHB) has been utilized in intervention-based research involving the study of health threats and health behavior.⁶⁶⁻⁷⁰ Simplistically, our conceptual model, grounded in SRTHB proposes that the reaction to and use of health (genetic) information is the product of an individual's understanding, (i.e. knowledge and perceptions of the disease threat) and the biopsychosocial impact of the risk and the health behavior.^{66,68,70-73} The SRTHB, emphasizes "common-sense" representations rather than medical or scientific definitions, and incorporates individual experiences, and the impact of knowledge and perceptions on risk modification for individuals and their families. As the

model is iterative and dynamic, it is responsive to changes in understanding, reactions to and use of genetic information that might occur as a result of engagement with an eHealth intervention to provide longitudinal updates to genetic information, communication and support. The literature and our preliminary data support the hypothesis that outcomes will be moderated by biological (test result,⁷⁴⁻⁷⁷ cancer history^{76,78-80}) and sociodemographic (race/ethnicity,^{76,80-82} access burden^{74,75}) factors. Equally important, data suggests that outcomes of IHCAs are moderated by access and use^{41,46,53,54,57,61}. Thus, it will be critical to understand factors that moderate outcomes and to incorporate this knowledge into future dissemination and implementation of MyCancerGene.

Even after health related interventions have proven effectiveness, many fail to translate into clinical settings.^{36,83} Thus, there is increasing recognition of the importance of evaluating and addressing barriers to implementation across diverse health care settings. CFIR provides an overarching theoretical framework to evaluate barriers, enhancements and adaptations to increase successful implementation of evidence-based interventions.⁸⁴ We have included constructs from each of the 5 major CFIR domains (intervention characteristics, outer setting, inner setting, characteristics of individuals and process) as they relate to our intervention, which will be evaluated in our multi-stakeholder mixed-methods process evaluation (Aim 3b). As in other studies⁸⁵⁻⁸⁷, evaluation of CFIR components is expected to identify patient, provider and system barriers and enablers of MyCancerGene to future dissemination to increase access and adoption of genetic services.

2.0 Purpose of Study

Genetic testing has become more complicated with the transition from single gene testing (e.g. *BRCA1/2*) to multi-gene panels and whole-exome sequencing. Genetic test results are now more complex to understand and are frequently associated with residual uncertainty (e.g. what risk is associated with this gene mutation? What is the best screening? Is this variant associated with a risk for cancer or simply a benign change of no clinical significance?). Over time, these uncertainties will resolve as new data emerge. But, the adoption of more complex genetic testing and the promise of Precision Medicine has created a critical and urgent need for longitudinal clinical follow-up with patients who undergo cancer genetic testing.

The promise of precision medicine is the ability to tailor treatment or screening of patients based on their genotype, and to translate those recommendations into modified patient behaviors or treatment. With these advances, there is an increasing need for multidisciplinary translational research that focuses on how to advance precision medicine discoveries into clinical practice and to capitalize on connectivity (e.g. eHealth) interventions in ways that optimize cancer risk reducing behaviors in real-world clinical populations.^{1,3,5-8}

BRCA1/2 and Lynch Syndrome testing for predisposition to breast, colon and gynecologic cancers are examples of evidence-based standard-of-care applications of precision medicine.^{12,13} Recently, mutations in other genes (e.g. *PALB2* and *CHEK2*) have been associated with elevated risks of cancer,¹⁴⁻¹⁸ and multi-gene panel testing (MGPT) has been increasingly utilized in clinical practice.^{20,29,88} For example, in the COGENT study, a multi-center randomized study of phone versus in-person disclosure of cancer genetic test results over 60% of patients had MGPT, and MGPT increased

over time.²¹ Many of the risk estimates for genes included in MGPT are based on limited data and will continue to evolve over time.^{17,18} There is also uncertainty regarding optimal screening given constantly evolving medical management recommendations (e.g. clinical guidelines are evolving as new data emerges). These uncertainties will be clarified over time, but we lack “real-world” delivery care models to maintain longitudinal communication with patients in order to provide updated information regarding their genetic test result or medical recommendations.^{22,23} Thus, effective and evidence-based strategies for longitudinal communication for patients who have had clinical genetic testing are critical to the clinical translation of Precision Medicine.

To address this clinically significant gap in the delivery of genetic medicine, we have obtained patient and provider stakeholder input to develop a patient and provider informed electronic Interactive Health Communication Application (IHCA) called “MyCancerGene” to enhance longitudinal patient understanding of, and affective and behavioral responses to genetic testing, particularly in the era of evolving evidence and risk information. Studies from a variety of chronic disease settings, but not including genetics, have shown that IHCA can improve knowledge,⁴³ social support,⁴³ self-efficacy,^{43-45,49} satisfaction,^{41,47-49} and clinical outcomes.^{43,47,49,50} Given the increasing complexity of genetic testing applications (e.g. multi-gene testing, whole exome sequencing) and the need for longitudinal follow-up, we expect this research to inform evidence-based practice guidelines and potentially change the paradigm of delivery of Precision Medicine. We propose a Hybrid Type 1 effectiveness-implementation study. In this randomized study of access to MyCancerGene compared to usual care after receipt of genetic testing in 375 clinical patients, we will include a concurrent implementation process evaluation to inform future adaptation and dissemination of our intervention. The aims of the proposed research are to:

Aim 1: (Short-term Effectiveness): Evaluate the effectiveness of the MyCancerGene to improve short-term understanding (e.g. knowledge) and reactions to (e.g. anxiety) clinical genetic testing compared to usual care. Primary outcomes include knowledge and general anxiety from baseline to 1 month.

Aim 2: (Longitudinal Effectiveness): Evaluate the effectiveness of MyCancerGene to: a) improve longitudinal understanding of (e.g. knowledge), reactions to (e.g. anxiety and uncertainty) and use of (e.g. communication to relatives and health care providers and performance of risk reducing health behaviors) genetic test results; and b) to reduce genetic provider time as compared to usual care.

Aim 3 (Implementation): To conduct a multi-stakeholder mixed-methods process evaluation, to understand a) potential moderators (e.g. intervention usage, adherence and attrition, sociodemographic factors, genetic test result) of short-term and longitudinal changes in understanding of, reactions to and use of genetic test results to understand who benefits more or less from access to the intervention; and b) facilitators and barriers to implementation and recommendations for future adaptation and sustainability of MyCancerGene for widespread clinical use.

It is hypothesized that access to MyCancerGene will be associated with short-term and longitudinal increases in knowledge, decreases in distress, increases in communication with relatives and health care providers and performance of risk reducing health behaviors (Aims 1 & 2). Equally important, we hypothesize that our CFIR (Consolidated Framework for Implementation Research) informed process evaluation (Aim 3) will

inform recommendations for future adaption and sustainability for other Precision Medicine applications.

Intervention Development and Testing

In Year 1, we will use our theoretically and stakeholder informed prototype to build upon feedback collected during the COGENT study (See “Preliminary Studies”) and complete development and testing of the intervention (MyCancerGene).

User and Usability testing will be conducted with a multi-phase approach to include Concept Assessment, Prototype Format and Content Assessment and Usability Testing of an electronic Prototype (Appendix G).

Utilizing a Verbal Consent (Appendix H), patient and provider stakeholders will be assessed to inform the development and finalization of the MyCancerGene application. To ensure sufficient diversity, cancer patients will be identified by and purposefully sampled from both the University of Pennsylvania’s Cancer Risk Evaluation Program and the University of Pennsylvania’s Telegenetics Program, focusing on gender, age, education and race/ethnicity selection.

To facilitate patient stakeholder assessments, individuals will be asked by their physician and/or genetic counselor if a member of the research study team can contact them regarding the user/usability assessment. A member of the research team will approach individuals and conduct assessments, sharing supporting documentation such as prototype screen shots (Appendix J) or application testing web-link, either in-person or by telephone depending on patient preference.

In all phases, stakeholders will be asked for both specific and general feedback using interview guides (Appendix I) and interviews will be audio recorded.

(1) Patient User Testing – Prototype format and content assessment (Phase 2): As above, we will obtain feedback from 12-20 cancer genetic patients and up to 15 Penn genetic providers utilizing best practice approaches.⁸⁹⁻⁹¹ Informed by DOI constructs and International Patient Decision Aid Standards⁹², patients and providers will be asked to both provide feedback regarding the hypothetical benefit and potential limitations of the MyCancerGene prototype screenshots in addition to assessing the extent to which the MyCancerGene mock-ups are advantageous (i.e. useful), compatible (i.e. personally relevant), easily interpreted, comprehended and accessible (i.e. complexity), fit into clinical care and patient/provider interactions and communication, (i.e. impact on social relations) and accessible and timely. Participants will be probed for additional suggestions to enhance the content, salience, and appearance of the graphics.

(2) Provider User Testing – Prototype format and content assessment (Phase 2): We will also obtain provider stakeholder feedback from up to 30 genetic counselors. This will include genetic counseling professionals at the University of Pennsylvania as well as external genetic counseling staff from the COGENT study participating institutions (Fox Chase Cancer Center, University of Chicago, John H. Stroger Jr. Hospital of Cook County and the MD Anderson Cancer Center at Cooper). Additionally, we conduct provider stakeholder assessments with genetic counseling professionals by way of the National Society of Genetic Counselors Cancer Special Interest Group (NSGC SIG) listserv to ensure well-rounded feedback. Providers completing user testing from

external institutions, including those collected from the NSGC SIG, will be offered a \$25 incentive for their time. Interview guides will similarly evaluate DOI constructs assessing the extent to which the MyCancerGene mock-ups are advantageous (i.e. useful, compatible (i.e. personally relevant), easily interpreted, comprehended and accessible and timely. Participants will be probed for additional suggestions to enhance the content, salience, and appearance of the graphics.

(3) Usability testing (Phase 3): Guided by the usability engineering concept, which emphasizes an iterative design approach, testing and observing users with the prototype will ensure the relevance and usefulness of the resulting products.⁹³ Studies comparing different usability evaluation methods concluded that heuristic evaluation and user-based think-aloud testing are the most common methods and both are equally efficient and effective in addressing different usability problems.^{94,95} We will identify an additional 10-12 cancer genetic patients for usability interviews evaluating user's real-time experiences interacting with MyCancerGene. As genetic providers won't utilize the MyCancerGene application directly (research team will enter and track any provider driven updates), usability testing with providers will not be conducted at this time.

Patient testing will be guided by the NCI's usability guidelines.⁹¹ During the telephone usability testing interview, participants will be requested to look for specific information or tool by navigating through the MyCancerGene prototype (Appendix J). Using the well-established think-aloud method, participants will be asked to express their reactions to different components, such as excitement, frustration, or boredom, during the navigational process.⁹⁶ The Think-aloud approach involves participants verbalizing their thoughts and feelings as they are performing a set of specific tasks. A user-centered design will also focus on providing the appropriate intensity and frequency of delivery of engagement messages to maximize use while minimizing participant burden.

(4) Intervention use (during study implementation): Early consideration of sustainability is an important and frequently overlooked aspect of eHealth interventions.⁹⁷⁻⁹⁹ Individual use of MyCancerGene will be recorded throughout the study to evaluate the impact of intervention usage (e.g. dosage) on outcomes and who benefits more and less from the intervention (Aim 3a). Equally important, these data will also be reported in study publications (e.g. CONSORT-EHEALTH) to address the need for better reporting quality in eHealth studies to advance the field and our understanding of eHealth interventions.^{47,100} Intervention use will include actual usage, activation, adherence, attrition and engagement.^{91,100}

4a) Actual Usage: we will record the time each participant logs in and logs out. We will set timeouts at 30 minutes of inactivity to protect confidentiality and enable accurate interpretation of data.¹⁰⁰ Actual usage will be evaluated for the intervention in general and secondarily for specific intervention content (e.g. My Updates, My Family History or My Screening, Risk Reducing and Screening pages).

4b) Activation: activation will be categorized as "early" or "late". Early activation will be defined as logging into MyCancerGene for the first time within 4 weeks while late activation as any time after 4 weeks until the study ends (18-month survey).

4c) Adherence: defined as logging on in response to a 6-month update reminder if they indicate "Yes" to new information (e.g. "Has there been a change in your family history,

personal history or new testing in the Family?") OR in response to a targeted update from the research team (e.g. VUS update).

4d) Rate of attrition: defined as the number of days from activation to the day when:

- There is NO login activity AND no survey completion AND no response to 6-month reminder queries (YES/NO)
- OR the date of active withdrawal from the study

This intervention use data will provide opportunities to consider sustainability and how use and engagement change over time (e.g. habituation), and will be included in our concurrent process evaluation to consider adaptations and improvements for future dissemination.

The research team has experience in these usage analytics from multiple studies including RESPECT (Bradbury, CRCU), CISRC (Wen and Fleisher) and Adult Diabetes (Fleisher).

3.0 Methods

3.1 Subject Selection / Participant Characteristics

Potential subjects will include individuals who have presented to the University of Pennsylvania Cancer Risk Evaluation Program (CREP) and the Penn Telegenetics Program who are/have:

- 18 years of age or older
- English Speaking
- Male or Female
- Internet and/or mobile access
- Previously received clinical standard of care genetic disclosure counseling (defined as in-person and/or virtually with a genetic provider) and testing for hereditary cancer syndromes up to:
 - 90 days prior to recruitment for non-cancer patients
 - 6 months prior to recruitment for patients diagnosed with cancer

3.2 Enrollment Procedures

Individuals meeting the study specified eligibility criteria (see section 3.1) will be contacted by members of the research study team after the receipt of their genetic test results (see 3.1 Subject Selection / Participant Characteristics for timing).

For initial contact, eligible participants will be electronically forwarded the study introduction letter (Appendix C) by way of email and/or MyPennMedicine. Individuals who have been selected for contact will have been previously alerted by their genetics provider that they will receive information regarding the MyCancerGene Study.

Contained in the letter will be details regarding the study purpose and procedures as well as the direct REDCap web-link (a secure, web-based data platform, accessible to

and managed by research team members only) to the electronic Informed Consent and HIPAA document (Appendix A). Recruitment letter recipients will be informed they can:

1. Consent to the MyCancerGene study directly using the provided, electronic link.
2. Respond to and speak with a member to the Research Study Team for additional information
3. Decline participation and future contact regarding this study

Members of the research team will follow-up by email and telephone with individuals who do not respond using one of these three options. Individuals who wish to consent but do not want to do so electronically will be given the option of signing a paper consent document.

Those approached who actively decline participation will be asked to provide a reason, which will be captured by research staff along with de-identified characteristic data including age, race/ethnicity, marital status, and education (Appendix D). Individuals who decline will be assured that they will still receive standard-of-care follow-up attention outside of this research study.

For more detail on the informed consent process, please see Section 5.2, Informed Consent.

3.3 Study Procedures and Measures

STUDY PROCEDURES:

The overall goal of the proposed research is to evaluate the effectiveness of a theoretically and stakeholder informed cancer genetics IHCA (MyCancerGene) to enhance patient understanding of, and response to genetic information. We propose a Hybrid Type 1 effectiveness-implementation study. This will include a randomized study of access to MyCancerGene as compared to usual care follow-up among recipients of genetic testing and a concurrent multi-stakeholder mixed-methods CFIR-informed concurrent process evaluation to understand facilitators and barriers to implementation of MyCancerGene for widespread clinical use. We will recruit patients undergoing cancer genetic testing at the University of Pennsylvania Cancer Risk Evaluation Program and community patients through the Penn Telegenetics Program. Participants will be randomized to access to MyCancerGene or usual care (control condition) and complete assessments at baseline and at 3-4 weeks and 6, 12, and 18 . After 12 months (T3), participants in the usual care arm will be provided access to MyCancerGene to evaluate moderators of responses to genetic information.

• STUDY STEPS

Once participants have been successfully consented either electronically or by paper, study steps will commence as follows:

1. Completion of Baseline (T0) Survey (Appendix E)

All participants will be given the option of completing their baseline survey assessment by one of these following means:

- Computer-Based Self-Report Assessment (CBSRA)
- Telephone with a research team member

While participants will be asked to complete this survey within 14 days of consent, surveys that are completed up to 30 days after consent will still be accepted.

Once the T0 has been completed in the specified timeframe, participants will be randomized to one of the two research arms.

2. Randomization

Upon successful completion of T0, participants will be stratified by test result and site (CREP v. Telegenetics) and randomly assigned to one of the following two study arms by permuted block design.

- **MyCancerGene Access Arm (Intervention Group)**

Patients in the intervention arm will be provided a password and link to the secure intervention website. They will be asked to provide a personal, private email address to ensure the password and link are securely delivered, as well as to facilitate engagement messages regarding updating family history and messaging for other updates.

Components of the cancer genetic IHCA/MyCancerGene will include the following pages:

- i. Summary of Care – detailed individual patients’ type of testing performed, dates of services, provider names, links to primary documents with the option to print reports for relatives and other healthcare providers, mechanisms to contact their genetic team and updates if available.
- ii. Summary Note – a copy of patients’ post-disclosure summary documentation, detailing their genetic counseling sessions and findings.
- iii. My Genetic Test Result – a copy of their result document in addition to a reiteration of general information about the implications of their result.
 - This can be updated by the genetics team over time as new information emerges.
 - If after multiple reminders an update was not accessed/read by a participant, genetic counselors will contact participants through usual care methods.
- iv. My Family History Page – summary of participants’ individual family history as they originally provided to their genetic provider during their clinical pre-test counseling. On this page, a link will be provided allowing for an update to this information
- v. Provide an Update – a mechanism allowing patient driven updates to their personal, family or genetic history if personal and/or family changes develop.
- vi. Review Updates – a summary list of all updates that they have made in addition to all provider driven updates that may be provided to them during the course of the study. These updates can include patient specific details such a result

reclassification, updated result implications, etc... Additionally, general updates within the field will also be shared and accessible through this page.

- Every three months, genetic providers and clinician investigators will review and discuss any updates in the literature (e.g. new risk estimates, new testing or screening recommendations). If indicated, general updates in addition to tailored alerts will be sent to relevant participants. These will be outside of scheduled engagement reminders every 4 months.
- vii. Resources – links to reputable supportive care and informational organizations will be available via this link, periodically being monitored and updated.
 - viii. Educational Content will be included as information. Additional educational content will be considered as indicated in the field and periodically added with engagement reminders.
 - ix. Engagement Reminders will consist of the following:
 - a. General Reminders to update family history, testing in family and/or personal history – Participants with access to MyCancerGene will receive the reminders at 6, 12, and 18 months after consent.
 - b. Access to Educational Genetic Information – Participants will receive reminders pointing to educational content every 6 months to alternate with general reminders.

- **Usual Care Arm (Usual Care Group)**

Consistent with current usual care practices clinically available, patients randomized to this arm will be contacted by letter or phone with any lab updates of VUS results or other updates in the clinical program (e.g. rarely an important update is sent to all patients by mail). Patients will be, as is the standard-of-care, encouraged to contact the genetics program if there are changes in their family history. Some patients may return for annual medical follow-up based on provider recommendations and their preferences, although there are currently no systematic methods for such longitudinal follow-up. Usual care practices will be documented.

All communication and visits for each Arm will be recorded (Appendix F)

A permuted block design will be used for randomization and will be stratified by genetic test result and program (recruitment from CREP versus Telegenetics).

3. Completion of T1-T4 Surveys (Appendix E)

After randomization results have been received, participants will be asked to complete surveys at the following time-points:

- 4 Weeks Post Randomization (T1)
- 6 Months Post Randomization (T2)
- 12 Months Post Randomization (T3)
 - **ALL PARTICIPANTS IN THE USUAL CARE ARM WILL BE PROVIDED ACCESS TO MyCancerGene AFTER:**
 - **THE COMPLETION OF THE 12 MONTH/T3 SURVEY**

▪ **30 DAYS FROM THE 12 MONTH SURVEY DUE DATE
FOR THOSE WHO DON'T COMPLETE**

- 18 Months Post Randomization (T4)

All participants will be given the option of completing their baseline survey assessment by one of these following means:

- Computer-Based Self-Report Assessment (CBSRA)
- Telephone with a research team member

While participants will be asked to complete this survey within 72 hours (3 days) of when they are sent, surveys that are completed up to 3 weeks for T1 and within 45 days of the launch of T2-T4 will still be accepted.

MEASURES

1. Understanding of Genetic Information (Aims 1 & 2)

A. Knowledge of genetic disease (primary outcome) Knowledge of genetic disease will be evaluated using The KnowGene Scale, a 16-item scale administered to patients after genetic testing and/or genetic counseling to measure their understanding of the health implications of genetic testing results. it includes health implications to oneself as well as relatives. This measure covers penetrance, actionability, limitations of current technology, and monogenic inheritance patterns^{101,102}.

B. Test result recall (secondary outcome) will be evaluated with 3 items to evaluate recall of genetic test result.¹⁰³

C. Perceptions of genetic disease (secondary outcomes) will be evaluated with a series of quantitative scales previously used to evaluate self-regulation theory models in COGENT and related studies.^{68,71} These include perceived risk (4 items), timeline (1 item) and utility (12 items).²⁸

2. Reactions to Genetic Information (Aims 1 & 2) will be assessed using three instruments evaluating psychological distress and uncertainty

A. General anxiety and Depression will be assessed by the 4-item each short Patient Reported Outcomes Measurement Information System (PROMIS), a system of highly reliable, precise measures of patient-reported health status for physical, mental, and social well-being^{104,105}.

B. Multidimensional responses to genetic testing, including positive responses and uncertainty will be assessed using the Multi-dimensional Impact of Cancer Risk Assessment Questionnaire (MICRA) at T2 and T3. The MICRA has been utilized in many genetic studies to evaluate distress, uncertainty and positive responses to receipt of genetic test results¹⁰⁶.

C. Disease-specific distress will be measured using the 8 –item Impact of Events Scale (IES)^{76,107-112}, with strong internal consistency^{29,30,113} (alpha = 0.82-0.90) in genetic delivery studies.

3. Use of Genetic Information (Aim 2) will include:

A. Communication to relatives and health care providers (secondary outcomes): will include 4 items utilized in COGENT and related studies¹⁰².

B. Performance of risk reduction and screening behaviors (secondary outcomes) will be assessed with 13 self-report items utilized in COGENT to assess risk reducing and screening recommendations after multi-gene testing.^{114 115} These include 12 items assessing diet and exercise and other modifiable cancer lifestyle behaviors,¹¹⁶⁻¹¹⁸ selected from the Behavioral Risk Factor Surveillance System Questionnaire (BRFSS)¹¹⁹ and the Health and Diet Survey Dietary Guidelines Supplement¹²⁰, both of which provide demographic and geographic normative data.

4. Longitudinal Genetic Provider Time (Aim 2) will include a quantitative evaluation of:

- A) the number of phone or electronic messages between patients and providers;
- B) genetic provider time responding to messages and updates to family history or test interpretation;
- C) the number and type of clinic visits.

This study will also qualitatively evaluate the content of messages, provider follow-up and clinic encounters. Genetic providers will be asked to record time spent on patient related communication or care for all participants.

Moderators (Aim 3a) assessed at T0 will include:

- A) sociodemographic data (e.g. race/ethnicity, education, marital status, age);
- B) genetic test results, including the interpretation (e.g. positive, uninformative negative, true negative and VUS) and specific genotype (e.g. *BRCA1/2*, *MSH1*, *CHEK2*, etc.);
- C) personal and family history of cancer (#first and second-degree relatives with cancer),
- D) health literacy¹²¹ and comfort with technology^{44,122} at baseline, which have both been found to be associated with eHealth intervention use in related studies^{123,124}, and
- E) MyCancerGene use (e.g. general and content specific actual usage, adherence and attrition).
- F) Psychological impacts due to COVID-19 will be assessed using the 16 items adapted from items previously utilized in other studies to assess the impact of the COVID-19 pandemic. The final item was added to assess vaccination. While this protocol is independent of COVID-19, there is potential for COVID-19 events to impact the study primary and secondary outcomes. The measure is included to allow for analyses to evaluate the impact of these on study outcomes¹²⁵.

5. CFIR - Informed Concurrent Process Evaluation (Aim 3) – See Appendix K1, Implementation Assessment and Analysis

3.4 Duration of Protocol

We anticipate the total enrollment for this protocol will last 5 years.

3.5 Location where research will be conducted

- University of Pennsylvania

- To include individuals receiving clinical genetic counseling via the University of Pennsylvania Telegenetics Program

3.6 Special precautions to be taken by research staff

Not Applicable

3.7 Number of experimental subjects

An approximate 500 participants are anticipated to enroll in this research

4.0 Statistical Considerations and Analyses

Aim 1: Evaluate the effectiveness of MyCancerGene to improve short-term

outcomes. Hypothesis 1: We hypothesize that our intervention will be associated with short-term: a) increases in knowledge, and b) reductions in anxiety as compared to the usual care control group. **Approach:** Based on our patient and provider stakeholder interviews and outcomes from IHCA's in other settings, we will have two primary outcomes: changes in 1) knowledge, and 2) anxiety. All other outcomes will be considered secondary outcomes. Our primary change scores will be change between baseline (T0) and the first (T1) follow-up. We will use T-tests for the continuous variables (change in knowledge and anxiety). We will use an intention to treat approach in which we compare outcomes between randomization arms for the primary analyses. We will assess the balance of potential confounding variables between randomization arms using T-tests or Fisher's Exact tests for continuous or binary variables as appropriate. Potential confounders may include age, race, recruitment source (CREP v. Telegenetics), and time since genetic disclosure counseling or testing, for example. In secondary analyses, we will use multiple linear regressions (continuous outcomes) and a logistic regression (intention to communicate) to control for potential confounding variables that are found to be inadequately balanced by randomization. As covariates in the regressions, we will include an indicator (binary 0/1 variable) to indicate randomization arm as well as the potential confounding variables. We will repeat these analyses for the secondary outcomes and also examine the per-protocol and as-treated effects to investigate dose-response relationships. To account for missing data, we will use multiple imputation methods for the primary analyses of interest to maintain the intention to treat approach.¹²⁶ We will use complete case analyses as secondary sensitivity analyses.

Aim 2: Evaluate the effectiveness of the intervention to change longitudinal

outcomes (6-18 months) and provider time. Hypothesis 2: We hypothesize that our intervention will be associated with longitudinal a) increases in understanding; b) reductions in anxiety; and c) use of (e.g. communication or screening behaviors) genetic test results, and d) reduced provider time as compared to the usual care control group. **Approach:** For this analysis, we will examine linear (for continuous outcomes) and logistic (for binary outcomes) regressions estimated by Generalized Estimating Equations (GEE) to account for within subject correlation over time to investigate time trend trajectories. Survey time-point will be included via indicator variables (0/1 binary variables) in the longitudinal models. We will also include the intervention arm indicator and the interaction between intervention indicator and survey time-point indicators.¹²⁷ The interaction terms will enable us to examine whether the effect of the intervention varies over time-points. While Aim 2 analyses will be secondary analyses, we will examine both the intention to treat, per-protocol, and as-treated effects on time trends.

In addition to the psychosocial variables, provider time will be evaluated longitudinally at each survey time-point. We will again account for repeated measures within participants via the GEE estimated models. In secondary exploratory analyses we will additionally account for clusters of patients within provider using provider-level fixed effect terms in the models to investigate the provider-specific heterogeneity in time spent with participants across staff. **Aim 3a: Evaluate potential moderators of short-term and longitudinal outcomes to understand who benefits more or less from the intervention.** Hypothesis 3a: We hypothesize that MyCancerGene access and use, sociodemographic factors, genetic test result, time since genetic disclosure counseling or testing, and personal and family history of cancer will moderate outcomes between arms. **Approach:** For moderation (i.e. effect modifier or interaction analyses), we will include in the GEE-estimated multiple linear or logistic regressions for the outcomes of interest an indicator variable for randomization arm, the potential moderator variable, and an interaction term between the two (i.e. an interaction term will be created by multiplying the indicator variable by the moderator variable).¹²⁷ We will also examine models in which we further include the survey time-point indicators, interaction terms between survey time-point indicators and randomization arm, interaction terms between moderators and survey times-points, and the three-way interaction terms created by multiplying survey time-points indicators, randomization arm, and the moderator. To maintain power to detect moderation, we will examine non-survey time-point moderators separately. We will also examine multiple regression models in which we include potential confounding variables, as well as the main effects and interaction terms of interest. We will repeat the analyses in which we investigate 1) per protocol or 2) as-treated effects by replacing the randomization arm indicator with indicators representing 1) per protocol or 2) actual treatment, regardless of randomization assignment.

Aim 3b: To conduct a multi-stakeholder mixed-methods process evaluation to understand facilitators and barriers to implementation and recommendations for future adaptation and sustainability of MyCancerGene for widespread clinical use (Analyses described for AIM 3b in Appendix K1).

Power justification: We demonstrate the approximate sample sizes we will need to detect changes between arms in this study using T-tests for Aim 1. We set power to 85% and the Type I error rate (alpha) to 2.5% (2-sided). We chose a 2.5% Type I error by applying a Bonferroni correction to the typical Type I error rate of 5% with 2 comparisons ($5\%/2=2.5\%$). To obtain pilot data we used the change scores

Estimated sample needed for 85% power. SD=Standard deviation		
Variable	Mean RESPECT web intervention change	Sample size 2.5% α
Knowledge	2.40 (SD 5.77)	n = 125/arm
Anxiety	-0.87 (SD 2.19)	n = 137/arm

from those who used the web intervention in our RESPECT Study (R01 CA11574119: Bradbury. In the RESPECT study, we developed a web-based version of pre-disclosure education and informed consent as an alternative to pre-disclosure counseling with a genetic counselor. 85% of patients at the time of analysis chose the on-line option and outcome measures were similar to those proposed in this study. Since RESPECT is a one arm study, we assumed that the control change for this trial would be zero with the same standard deviation as reported in the power table above. The sample sizes in the above table are well below what we expect to recruit in the study (N=376). Thus, we have excellent power for the overall effect and select subgroup effects.

5.0 Informed Consent and Patient Safety

Patient participants are individuals who had been, previous to recruitment, candidates for clinically available germline genetic testing for hereditary cancer syndromes. Thus, all participants are potentially at risk for cancer/additional cancers. The potential risks of participating in the proposed research, while minimal, include loss of confidentiality and distress related to re-opening previous discussions and experiences regarding a personal history of cancer, family history of cancer and/or learning of one's changed/modified potential risk for developing cancer through updates provided during this study. Those randomized to the intervention arm will have the potential of receiving information and updates outside of the current standard-of-care, thus having the added potential risk for misunderstandings the information shared and distress related to the method this information is provided, which may have otherwise been provided by direct provider contact. Attempts will be made to minimize these risks and their possibility will be explained to all participants during the informed consent process. All participants randomized to the intervention arm will have multiple methods available to them that will allow to contact either a member of the study team and/or their genetic counselor directly. Should a participant express the need for an appointment with CREP providers or a mental health referral, they will be directed to the Social Services Program at their institution.

5.1 Payment to subjects:

Participants will be offered a gift card or cash incentive of \$20 at the completion of each study survey. Additionally, participants who complete the Implementation Aim stakeholder interview will be offered a \$40 incentive.

5.2 Informed consent:

As described in section 3.2, eligible participants will provide informed consent for participation after the completion of their clinical pre- and post-test counseling appointment. Details that are included in the electronic informed consent include:

- Only research staff will have access to patients' private health information such as their genetic test results, family history and screening plan. This information is only available to members of the University of Pennsylvania Research Team, all of which have all credentials required to view and handle patient information.
- All participant health information and survey responses will be kept in secure, password protected files located on University of Pennsylvania maintained servers only
- Those who participate can withdraw at any time, regardless of method of randomization, and will have all usual care methods of follow-up available to them as is the current standard-of-care.

5.3 Confidentiality:

To ensure confidentiality, all responses and case characteristics will be de-identified and any participant information will not be captured during any recordings made during each disclosure session. All identifying information like name, address, telephone number and email address will be securely stored in a secure, study specific web-based portal which is to be maintained at the University of Pennsylvania by the Clinical Research Computing Unit (CRCU). Clinical Research Activities at the CRCU are performed in accordance with a set of Standard Operating Procedures (SOPs) that were implemented to promote compliance with CFR 21 part 11 and other applicable human subject protection regulations and guidelines. These SOPs are reviewed and renewed every two years. The IT infrastructure consists of multiple private data networks that have appropriate security measures applied to them (separation of duties, firewalls, port and

service level restrictions, etc.), computer servers that are maintained with the appropriate network, host, and user security and access methods, and the Oracle databases, applications, and clinical research processes developed with the protection and privacy concerns addressed; as these elements relate directly to the protection of human subjects and human subject clinical research and data.

Only key study team members will have access to the portal which will require a username and password. In utilizing an online surveying tool, all entered survey data is automatically kept separate from any identifying information. This online surveying tool will also automatically compile all responses into an excel spreadsheet which will be kept with all other secure study data in a password protected computer. Data that is collected via the online survey tool will use Secure Sockets Layer encryption to ensure secure transmission of private information.

APPENDICES (TO BE SUBMITTED AS AN AMENDMENT WHEN DEVELOPED)	TITLE
A	Informed Consent Document
B	Telephone Script
C	Introduction Letter
D	Decliner Data Form
E	Surveys (T0-T4)
F	Visit Communication Log (In Draft)
G	User and Usability Testing Plan
H	User and Usability Testing Only Verbal Informed Consent Language
I	User/Usability Assessment Guide
J	MyCancerGene Prototype Screen Shots
K1	Implementation Assessment and Analysis Plan
K2	Implementation Assessment and Analysis Verbal Consent
K3	Implementation Assessment and Analysis Stakeholder Interview Guide
L	Study Flyer

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