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by

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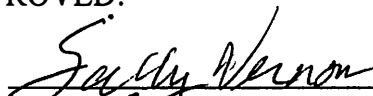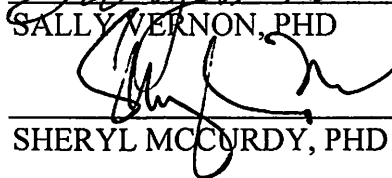
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ASSESSING THE READINESS OF RELATIVES TO UNDERGO CASCADE GENETIC

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National guidelines recommend cascade genetic testing (CGT) for blood relatives after a cancer predisposition gene mutation is identified in an individual. Despite recommendations for CGT, only 30-60% of first-degree relatives (FDRs) complete CGT. The proportion of untested relatives who are planning to have CGT is unknown. We used the Transtheoretical Model to assess the readiness (stage of change) for CGT among living, untested FDRs at-risk for a hereditary predisposition to cancer.

An anonymous, online survey was open to U.S. adults with an autosomal dominant, adult-onset, hereditary predisposition to cancer. Participants reported demographic information, their genetic testing information, and information on FDRs (the number of each relative, vital status, uptake of CGT, and readiness for CGT among those alive and untested). Data were analyzed using descriptive statistics, non-parametric McNemar, Friedman, Wilcoxon Signed Rank, Kruskal-Wallis, and Mann-Whitney tests. A two-sided p-value of 0.05 was considered statistically significant.

Responses were analyzed from 150 predominantly female (88.0%), white (93.3%) and non-Hispanic (92.7%) adults. Commonly reported gene were *CHEK2* (28.7%), BRCA1/2 (23.3%), the Lynch syndrome genes (16.0%), and the *SDHB* and *SDHC* genes (13.3%), all associated with cancer and tumor risks for men and women. Participants reported 825 FDRs, of which, 70.3% were aware of the mutation, and 30.5% had completed CGT. Rates of CGT were higher in siblings than parents or children (p<0.001). Rates of CGT varied by sex, whereby mothers and sisters had higher rates of CGT than fathers and brothers (p<0.001 and p=0.002, respectively). Of living, untested FDRs, 79.4% were in the precontemplation stage and there was no significant difference in readiness by relative's relationship to the participant (p=0.646) or by relative's sex (p=0.892).

The rates of awareness and CGT among FDRs in this study are consistent with prior studies of CGT. Most untested relatives were in the precontemplation stage and not planning to have CGT in the next six months. Future programs to support CGT may consider interventions grounded in stage-matched processes of change and should evaluate the decision-making processes of relatives to better understand and support the information and counseling needs of untested relatives.

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BACKGROUND

Inherited Predisposition to Cancer

Approximately five to ten percent of all cancers are due to a germline mutation (pathogenic or likely pathogenic variant) in a cancer predisposition syndrome gene, often referred to as hereditary cancer (National Cancer Institute, 2017). Hereditary cancer syndromes are characterized by significantly increased risks over one's lifetime to develop cancers or tumors, increased risk to develop multiple primary cancers, a family history of early-onset cancers, patterns of specific cancer types occurring within the family, and cancer occurring in multiple generations of a family (American Cancer Society medical and editorial content team, 2017). When an individual has a personal or family history with the features of a hereditary cancer syndrome, evaluation may be performed with a genetics professional (genetic counselor, genetics nurse, or geneticist) and through germline genetic testing.

Hereditary cancer syndromes can be categorized by their penetrance, prevalence in the general population, adult or childhood onset, and inheritance pattern. Penetrance refers to the proportion of individuals with a genetic mutation who develop the features, or phenotype, of the genetic syndrome or condition (Griffiths, 2000). There are three categories of hereditary cancer gene penetrance: high, moderate, and low penetrance (Economopoulou, Dimitriadis, & Psyrri, 2015). Hereditary cancer syndromes caused by high penetrance gene mutations are the most clinically relevant, and are associated with a greater than 5 times increased relative risk to develop cancer, as compared to moderate penetrant (1.5 to 5 times increased relative risk) and low penetrant (1.5 times increased relative risk) hereditary cancer gene mutations (Economopoulou et al., 2015). Typically, high penetrant hereditary cancer

gene mutations occur at low frequencies in the general population, while moderate and low penetrant mutations are more prevalent (Foulkes, 2008).

There are two well-studied conditions in the field of clinical cancer genetics characterized by their high-penetrance, relatively high population prevalence, adult-onset cancer risks and autosomal-dominant inheritance: Hereditary Breast and Ovarian Cancer syndrome (HBOC) and Lynch syndrome (also known as Hereditary Nonpolyposis Colorectal Cancer or HNPCC). These two conditions are included in the CDC's Tier 1 Genomics Applications due to their significant potential for positive impact on public health if identified and if prevention and early detection interventions are initiated (O. o. P. H. G. Centers for Disease Control and Prevention, 2014).

HBOC is caused by inherited mutations in the *BRCA1* and *BRCA2* genes, which is estimated to occur in 1:400 – 1:500 individuals in the general population, and 1:40 individuals in the Ashkenazi Jewish population (Petrucelli N, 1998). Individuals with a mutation in *BRCA1* or *BRCA2* are estimated to have significantly increased risks of adult-onset female breast cancer (38-87% lifetime risk), ovarian cancer (17-39% lifetime risk), male breast cancer (1.2-8.9% lifetime risk), prostate cancer (8.6-20% lifetime risk), as well as increased risks for pancreatic cancer and melanoma (Petrucelli N, 1998). HBOC is inherited in an autosomal dominant pattern, indicating that men and women can inherit a *BRCA1* or *BRCA2* mutation, it does not "skip" generations, and that each child has a50% chance to inherit the mutation (Petrucelli N, 1998).

Lynch syndrome is caused by a mutation in *MLH1*, *MSH2/EPCAM*, *MSH6*, or *PMS2*, which is estimated to occur in 1:440 individuals in the general population (Kohlmann, 2004).

Individuals with a Lynch syndrome gene mutation have significantly increased risks to develop adult-onset colorectal cancer (52-82% lifetime risk), endometrial/uterine cancer (25-60% lifetime risk), ovarian cancer (4-12% lifetime risk), gastric/stomach cancer (6-13% lifetime risk), and other cancers; however cancer risks vary depending on which gene is involved (Kohlmann, 2004). Lynch syndrome is also inherited in an autosomal dominant fashion (Kohlmann, 2004).

Criteria for identifying individuals who may have a higher likelihood of having HBOC or Lynch syndrome, and who are recommended to have genetic testing are outlined by the National Comprehensive Cancer Network (NCCN) guidelines (National Comprehensive Cancer Network, 2018a, 2018b). Genetic testing for hereditary cancer predisposition genes in the United States has changed over the past several years due to the impact of a variety of legal and cultural factors. Influences include the increased use of next-generation sequencing technology to decrease the time and cost of genetic testing, the Supreme Court ruling in the Association for Molecular Pathology vs. Myriad prohibiting gene patents, the public announcement by Angelina Jolie of her HBOC diagnosis and subsequent risk-reducing bilateral mastectomy, and the increasing calls for precision medicine in health care (Borzekowski, Guan, Smith, Erby, & Roter, 2014; Hooker et al., 2017). In response to several of these factors, genetic testing for hereditary cancer syndromes increasingly relies upon the use of multi-gene panels, which evaluate both high and moderate penetrant genes associated with a variety of cancer predisposition syndromes in a single genetic test. As the use of multi-gene panel genetic testing increased, a greater number of individuals have been identified to have moderate-penetrant cancer gene mutations.

Examples of moderate penetrant cancer genes frequently detected on multi-gene panel genetic testing include mutations in *ATM* and *CHEK2*.

In the past, genetic testing for *ATM* was primarily performed to evaluate for the rare, child-onset, autosomal recessive (homozygous *ATM* gene mutations) condition: ataxia-telangiectasia (Gatti, 1999). Individuals with a single, heterozygous *ATM* mutation are estimated to have a 4-fold increased risk to develop breast cancer, consistent with a moderate penetrant cancer predisposition gene (Gatti, 1999). An estimated 1-2% of the general population have a heterozygous *ATM* mutation (Jerzak, Mancuso, & Eisen, 2018). Germline variants in *CHEK2* are also classified as moderate-penetrant cancer genes with associated breast cancer risks estimated to be 2-3 times increased over general population risks, with a prevalence of the common 1100delC *CHEK2* mutation of approximately 1% of the general population (Apostolou & Papasotiriou, 2017; Foulkes, 2008). Although mutations in these moderate-penetrant cancer genes are both inherited in an autosomal dominant fashion, and are more common than mutations in the high-penetrant HBOC and Lynch syndrome genes, the optimal breast cancer screening and risk-reducing strategy for these genes has not been identified. While management recommendations for these genes are available from the NCCN, these recommendations have been based on general consensus and extending prior breast cancer risk-based screening approaches, and may evolve over time as more studies are performed (National Comprehensive Cancer Network, 2018a).

Implications of Identifying a Hereditary Predisposition to Cancer

When an individual undergoes evaluation for a hereditary predisposition to cancer, genetic testing is offered if NCCN genetic testing criteria are met and if the individual is an informative candidate for testing within their family. Informed consent for genetic testing for hereditary predisposition to cancer include discussion of the purpose and indication for the genetic testing, potential outcomes, benefits and limitations of the information obtained from the test, and considerations regarding patient privacy and genetic discrimination protections (Riley et al., 2012). Concerns for discrimination based on the results of genetic testing is a relevant concern for many individuals, however the Genetic Nondiscrimination Act of 2008 prohibited genetic discrimination in employment and health insurance and the Affordable Care Act of 2010 protection for individuals with "pre-existing conditions" have increased protections against discrimination (Allain, Friedman, & Senter, 2012; Brooks, Hoverman, & Colla, 2017). While protections have increased over time, there are limitations to existing laws and not all health insurance policies and employers fall under the protections of GINA, and discrimination continues to be permitted among life insurance, long-term care, and disability insurance policies (Allain et al., 2012).

Cost is also a relevant consideration during the informed consent process prior to performing genetic testing. In the United States, most private health insurance payers recognize the NCCN guidelines as the criteria for hereditary cancer genetic testing approval. Medicare has similar guidelines for coverage of genetic testing, however requires that the individual undergoing genetic testing have a personal history or diagnosis of a relevant cancer. Patients who are uninsured, underinsured, or covered by a policy with a genetic

testing exclusion may qualify for no-cost or reduced cost genetic testing through financial

assistance programs of the genetic testing laboratories (Hinchcliff, Bednar, Lu, & Rauh-Hain,

2019). The out-of-pocket costs for hereditary cancer genetic testing have decreased from the

$4000 list price of testing of five to ten years ago, now to self-pay prices of $250 or less in

2019.

There are significant implications for an individual when genetic testing identifies a

hereditary cancer gene mutation. A hereditary cancer gene mutation indicates that the tested

individual has inherited increased risks to develop specific cancers, as informed by the gene

and the mutation identified. Guided by the increased cancer risks, the individual qualifies for

high-risk cancer screenings, and consider risk-reduction and cancer prevention procedures.

For example, the identification of a *BRCA1* or *BRCA2* mutation in a woman would indicate

significantly increased lifetime risks to develop breast and ovarian cancer. The NCCN

management recommendations for a woman with HBOC include: high-risk breast cancer

screening including annual mammogram with breast MRI beginning as early as age 25,

ovarian cancer risk-reduction through bilateral salpingo-oophorectomy (removal of the

ovaries and fallopian tubes) upon completion of childbearing or by age 35-45, and options

for chemoprevention including oral contraceptive pills and/or selective estrogen receptor

modulators (National Comprehensive Cancer Network, 2018a). Likewise, if an individual is

found to have a Lynch syndrome mutation, NCCN management recommendations include

frequent colonoscopy screening every 1-2 years beginning as early as age 25, and screening

for endometrial and ovarian cancer with consideration of risk-reducing hysterectomy

(National Comprehensive Cancer Network, 2018b). Even moderate penetrant genes, such as

ATM or *CHEK2* have NCCN recommended high-risk breast cancer screening (National Comprehensive Cancer Network, 2018a).

If the individual undergoing genetic testing has a diagnosis of cancer for which they are undergoing treatment, the results may have direct implications on cancer treatment. For women with ovarian cancer associated with an inherited *BRCA1* or *BRCA2* mutation, treatment with a PARP inhibitor may be recommended (Buchtel et al., 2018). Other cancer types are also testing the use of PARP inhibitor therapy, primarily in breast, pancreatic, and prostate cancers (Dalia, Christopher, Jagdeep Singh, & Vikaash, 2018). For individuals with colorectal cancer or advanced-stage endometrial cancer with a Lynch syndrome gene mutation, immunotherapy may be indicated (Longoria & Eskander, 2015). Targeted therapy is a growing field of research and drug development, which may provide new treatment and prevention options to patients and families with hereditary cancer predisposition syndromes in the coming years.

Additionally, the identification of a hereditary cancer gene mutation indicates that the mutation was, in most cases, inherited and that the individual may pass the mutation on to offspring. Results have direct implications for first-degree blood-relatives and other, more distant relatives of the tested individual.

Cascade Genetic Testing

Cascade genetic testing is the process of performing genetic testing for blood relatives of individuals with a hereditary cancer gene mutation, whereby relatives are tested for the specific gene mutation identified in their family member (American College of Obstetricians

and Gynecologists, 2018; Caswell-Jin et al., 2018). Cascade genetic testing is a systematic approach of initiating mutation-specific genetic testing starting with first-degree relatives, so that their genetic testing status can then inform second- and third-degree relatives of their the risk to inherit the mutation. Cascade genetic testing can identify relatives who have inherited the mutation and the associated cancer risks, and identify relatives who have not inherited the mutation (also known as "true negative") who then have cancer risks most comparable to individuals in the general population.

Since mutation status can have a significant impact on the initiation and frequency of cancer screening for at-risk relatives, cascade genetic testing is recommended by the NCCN guidelines, the American College of Obstetricians and Gynecologists, the Evaluation of Genomic Applications in Practice and Prevention group, and the Society of Gynecologic Oncology (American College of Obstetricians and Gynecologists, 2018; EGAPP Working Group, 2009; National Comprehensive Cancer Network, 2018a, 2018b). Although cascade genetic testing is recommended by a variety of national organizations and can provide important information for relatives, the uptake of testing among at-risk relatives is not robust.

A systematic review of 30 published studies evaluated the communication of genetic testing results and the uptake of cascade genetic testing in families with HBOC and Lynch syndrome (Menko et al., 2018). Generally, families share and communicate the genetic testing results with relatives at high rates, with most studies reporting that 75% to 90% of relatives were aware of the genetic testing results in the family (Menko et al., 2018). However, the uptake of cascade genetic testing among at-risk relatives is lower, with most studies reporting cascade genetic testing rates of 20% to 50% (Menko et al., 2018). Cascade

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genetic testing rates in families with moderate-penetrant hereditary cancer predispositions have not been reported.

Researchers and clinicians have been evaluating the clinical processes for offering and coordinating genetic testing, and implementing various interventions in an attempt to increase the uptake of cascade genetic testing. There are three general processes that are considered in the study of cascade genetic testing, including family communication, access to genetic testing services, and the role of barriers, facilitators, and determinants of individual behavior.

The first cascade genetic testing consideration is the process of communicating risk information and cascade testing recommendations within the family. An at-risk relative may not know that they are at risk for an inherited cancer predisposition syndrome without receiving this information from either a relative found to have a mutation or from a health care provider able to identify family histories with characteristics of hereditary cancer syndromes. In the setting whereby a hereditary cancer mutation is identified in a relative, the typical clinical practice after a mutation is found is for a healthcare provider to discuss the inheritance pattern of the mutation and the implications for relatives during a post-test genetic counseling consultation. Genetic counselors and other health care providers encourage the patient or "proband" with the gene mutation to inform their relatives of the risk to have the mutation, and the recommendation for relatives to pursue cascade genetic testing. Often, a "family letter" is shared with the patient to facilitate transmission of the information to relatives, however this approach does not guarantee success of information sharing within families and may impose a burden upon the patient (Dheensa, Lucassen, &

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Fenwick, 2017). Given the concern that family letters may not reach at-risk relatives, direct contact of relatives by health care providers has been evaluated.

Studies have assessed the awareness and cascade genetic testing-related effects of direct contact of blood relatives by a health care provider with the consent of the patient. The results of direct-contact approaches on family communication and uptake of cascade genetic testing are mixed, and may not be acceptable in all patient populations (Aktan-Collan et al., 2007; Forrest, Burke, Bacic, & Amor, 2008; Hodgson et al., 2016; Suthers, Armstrong, McCormack, & Trott, 2006). Ethical considerations regarding communication of genetic testing results, especially from the perspective of health care providers have been well documented, and include debates over the balance of individual patient autonomy and privacy with the physician's duty to warn relatives of a hereditary disease risk (Offit, Groeger, Turner, Wadsworth, & Weiser, 2004).

Other approaches to increase communication of genetic testing results within families have included a randomized study of a six-step communication skills-building program (Daly et al., 2001). The outcomes of this intervention found that the communication training did not significantly improve the sharing of information within families with hereditary cancer syndromes compared to individuals not receiving the intervention, and it did not significantly improve the ability of relatives to accurately report the genetic testing result of the relative (Daly, Montgomery, Bingler, & Ruth, 2016; Montgomery et al., 2013). A second study to improve communication within families assessed the acceptability of a motivational interviewing intervention to aid patients in sharing the genetic testing results with relatives. While the intervention was acceptable, the communication and cascade genetic testing rates

were not reported (de Geus et al., 2016). A pilot educational intervention to promote risk

information sharing within families with HBOC found no statistically significant difference

in communication or cascade genetic testing when comparing the control and intervention

groups (Kardashian, Fehniger, Creasman, Cheung, & Beattie, 2012). Approaches to

improving communication within families have had limited impact on outcomes of relatives'

awareness of their risk status or uptake of cascade genetic testing.

The second consideration regarding cascade genetic testing is the process by which

relatives access genetics services including genetic testing. Studies have sought to decrease

the frequently reported financial and geographic barriers to accessing genetic counseling and

genetic testing for relatives. A genetic testing laboratory studied the uptake of reduced cost

($50) cascade genetic testing coordinated through an online platform by first-degree relatives

invited to participate by their mutation-positive family member (Caswell-Jin et al., 2018).

The study identified that 48% of invited relatives underwent cascade genetic testing through

the online platform, similar to cascade genetic testing rates reported in clinical genetic testing

settings (Caswell-Jin et al., 2018). Other ongoing research studies, like the MAGENTA and

GENERATE studies, also allow relatives to access no-cost or reduced-cost cascade genetic

testing through an online platform, however the impact of this cascade genetic testing

delivery model on the uptake of cascade testing among relatives is yet to be demonstrated

(U.S. National Library of Medicine, 2016, 2018).

Prior intervention studies have focused primarily on barriers to cascade genetic

testing that are external to the individual relative, including the interpersonal communication

between patients and at-risk relatives, and the interaction between at-risk relatives and the

health care system. The mixed or null outcomes of interventions acting upon these external barriers to improve cascade genetic suggests that the cascade genetic testing process may be more complex, and that additional factors and determinants have not been fully evaluated or incorporated into prior intervention studies. The third consideration for cascade genetic testing is the role of personal barriers, facilitators, and determinants of testing. A logic model of cascade genetic testing, in **Figure 1** includes factors that may impede cascade genetic testing in at-risk relatives, based on existing literature. External factors that serve as barriers to cascade genetic testing, in addition to cost or geographic access, include incomplete anti-discrimination policies, incomplete health insurance coverage of recommended high-risk screening and risk-reducing procedures in the U.S.; lack of recommendation for genetic testing from healthcare providers, and competing demands on individual's time (such as employment and childcare) (Allain et al., 2012; Anderson et al., 2012; Hamilton et al., 2017; Jbilou et al., 2014; Nair et al., 2017; Prince, 2015; Roberts et al., 2018). Also included in **Figure 1** are various personal psychosocial determinants identified to influence an individual's decision to pursue genetic testing, such as attitudes about genetic testing, perceived risks of testing, and self-efficacy to pursue testing (Sweeny, Ghane, Legg, Huynh, & Andrews, 2014).

Figure I. Logic Model of the Problem: Lack of Cascade Genetic Testing

Personal Determinants	**Behavior(s) of At-Risk Group**	**Health Problem(s)**
• High perceived risk of CGT • Low perceived benefit of CGT • High perceived barriers to CGT • Low perceived control over cancer risks, development of cancer • Lack of knowledge of CGT or implications of CGT • Negative attitude about CGT, healthcare • Beliefs and norms about CGT, risk-reduction, cancer, and healthcare • Low motivation to have CGT • Low self-efficacy to have CGT	**Behavior**: Lack of cascade genetic testing (CGT) **At-risk group**: first-degree relatives of individuals found to have a hereditary predisposition to cancer	• Unrecognized, increased risk to develop cancer • Lack of appropriate cancer screening • Missed opportunities for risk-reduction and prevention • Delayed determiniation of eligibility for targeted therapy

Environmental Conditions & Behavior of Environmental Agents

Interpersonal
- Lack of communication within family
- Lack of recommendation from health care provider

Community Conditions
- Poor access to healthcare services
- Limited access to genetics services

Societal Conditions
- Lack of health insurance
- Lack of coverage (high-deductible) for genetic testing, high-risk screening/risk-reduction procedures
- Lack of comprehensive discrimination protections

There are opportunities to apply behavioral science theories to evaluate the interaction and impact of these various psychosocial determinants on cascade genetic testing processes, and to develop appropriate clinical interventions for this population. One framework that could combine behavioral science theory with cascade genetic testing programs and interventions is intervention mapping. Intervention mapping provides a multi-step framework for program development, production, implementation and evaluation that is grounded in behavioral science theories (Bartholomew Eldredge et al., 2016). Intervention mapping has been used sparingly in cancer prevention and control program design, and rarely in clinical cancer genetics research, as a 2018 systematic review of cancer-related interventions using intervention mapping identified only one published study of intervention mapping used in hereditary cancer research (Lamort-Bouché et al., 2018).

The Transtheoretical Model

One behavioral science theory, the Transtheoretical model (TTM), was developed by comparative analysis of numerous theories of psychotherapy, health behavior, and psychopathology (J.O. Prochaska, Redding, & Evers, 2015). The TTM has two primary components: the Stages of Change, which are the steps of changing a behavior over time, and the Processes of Change, which are the ways in which a behavior is changed (J.O. Prochaska et al., 2015). The TTM was first applied in populations of adult smokers to evaluate their use of processes of change, and progress through the stages of change as they attempted to quit smoking. The TTM has since been applied to a variety of other health behaviors, such as cancer screening, medication compliance, and alcohol abuse; however, the TTM has not been applied to evaluate cascade genetic testing within families (J.O. Prochaska et al., 2015; James O. Prochaska & Velicer, 1997). Cascade genetic testing is a behavior that an individual must contemplate, make a decision about, then prepare to take action over a period of time, which is similar to other behaviors studied using the TTM. One relevant difference is that most health behaviors evaluated using the TTM occur repeatedly over time, while cascade genetic testing occurs only once for an individual; therefore, the stages of change after a behavior has occurred (maintenance, termination, and relapse) are likely not relevant in cascade genetic testing processes.

The TTM outlines six stages of change, based on the readiness to change or perform a health behavior, including: precontemplation, contemplation, preparation, action, maintenance, and termination (J.O. Prochaska et al., 2015). Individuals may move through

the stages one by one, but may also relapse to a prior stage. The precontemplation stage is the "least ready" to make a behavior change, and is defined as having no intention to take action within the next six months (J.O. Prochaska et al., 2015). Contemplation stage is when an individual intends or plans to take action and change behavior within the next six months, and preparation stage is when an individual intends take action within the next thirty days. The action stage represents that the behavior change has occurred, but is a recent change, having occurred within the past six months. The later stages, maintenance and termination, represent prolonged behavior change for more than 6 months, and when there is no temptation to relapse, respectively. When evaluating the distribution of individuals across the stages of change for a variety of health behaviors, generally 40% of individuals are in precontemplation stage, 40% are in contemplation stage, and 20% are in preparation stage (James O. Prochaska & Velicer, 1997). It is unknown if at-risk relatives will be similarly distributed across these stages for the behavior of cascade genetic testing.

Specific processes of change are associated with each stage of change, and application of appropriate processes can help individuals progress toward the action stage of change. For individuals in the precontemplation stage, the associated processes of change include consciousness raising, dramatic relief, and environmental re-evaluation (J.O. Prochaska et al., 2015). Consciousness raising is the process of obtaining information to increase awareness and understanding of the health problem(s) associated with the behavior (J.O. Prochaska et al., 2015; Romain, Horwath, & Bernard, 2018). Dramatic relief is the use of emotions (positive or negative) to motivate behavior change (J.O. Prochaska et al., 2015). Environmental re-evaluation is the process of considering the rational and emotional impacts

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of one's behavior upon their social and physical environments (J.O. Prochaska et al., 2015; Romain et al., 2018).

Individuals moving between the contemplation and preparation stage may employ the self-reevaluation process of change (J.O. Prochaska et al., 2015). Self-reevaluation is the process of evaluating the rational and emotional impact of the behavior on one's self and self-image (J.O. Prochaska et al., 2015; Romain et al., 2018). Finally, individuals in preparation moving toward action may employ self-liberation processes (J.O. Prochaska et al., 2015). The self-liberation process of change includes recognition of social norms, belief in ability to make a change in behavior, and the ability to commit to take action (J.O. Prochaska et al., 2015; Romain et al., 2018). Throughout the stages of change, the constructs of decisional balance and self-efficacy can impact behavior change (J.O. Prochaska et al., 2015). Decisional balance can be described as the balance of perceived pros (benefits) and cons (risks or limitations) to making a behavior change, whereas self-efficacy describes the confidence and perceived ability to make a change (J.O. Prochaska et al., 2015).

The TTM constructs have been applied sparingly in the field of clinical cancer genetics. One study published in 1997 applied the TTM constructs of stage of change and decisional balance to evaluate whether women undergoing mammography screening were interested in having a hypothetical genetic test for hereditary breast cancer (Jacobsen, Valdimarsdottir, Brown, & Offit, 1997). The study found that approximately 46% of surveyed women were in preparation stage for this hypothetical genetic test, 30% were in contemplation stage, and 24% were in precontemplation stage, whereby the decisional balance score was a predictor of readiness to pursue genetic testing (Jacobsen et al., 1997).

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A second study applied only the decisional balance construct of TTM to a population of high-risk women with breast cancer to understand why some did not complete a recommended genetic counseling appointment (O'Neill, Peters, Vogel, Feingold, & Rubinstein, 2006). Recently, a randomized controlled trial evaluated the impact of a psychoeducational intervention on the TTM stage of change (intent) to pursue cancer genetic counseling among patients with breast cancer (Kasting et al.). This study reported that 55% of patients were in precontemplation and 39% were in contemplation at baseline, and after the intervention, 28% of participants moved toward action stage compared to 7.7% in the control group (p=0.01) (Kasting et al.). To date, no studies have applied the TTM to cascade genetic testing among relatives at-risk for a hereditary predisposition to cancer.

Public Health Significance

Diagnosing and investigating health problems; informing, educating, and empowering individuals about health issues; and linking people to personal health services are essential public health services that apply to the promotion and delivery of cascade genetic testing within families at increased risk for hereditary cancer (Centers for Disease Control and Prevention, 2018). Caring for populations with higher than average risk for disease is an activity included within the essential public health service of monitoring health status (University of Kansas, 2018).

Additionally, Healthy People 2020 includes two objectives specific to hereditary cancer genetic counseling and genetic testing: (G-1) to increase the proportion of women with a family history of breast and ovarian cancer who receive genetic counseling, and (G-2)

to increase the proportion of individuals with colorectal cancer who receive genetic counseling and genetic testing for Lynch syndrome (Office of Disease Prevention and Health Promotion, 2017). The inclusion of cancer genetic counseling and genetic testing objectives in this population health program signifies the relevance, importance, and potential impact of identifying and appropriately managing individuals with hereditary cancer predispositions.

Cascade genetic testing is an efficient and cost-effective approach to identifying individuals with the highest probability of having a hereditary cancer predisposition, in an era of increasing health care costs and over-treatment (Ansari et al., 2012; Lyu et al., 2017; Tuffaha et al., 2018). While families with hereditary predispositions to cancer are "rare" in the general population, they represent an important high-risk population of individuals where specific, effective risk reduction and cancer prevention options are available, warranting the attention and efforts of public health agencies. Cascade genetic testing may be one of the strongest examples of the how our health care and public health systems could increase efforts around "precision prevention," whereby individual genetic information is used to tailor medical care and prevention activities to optimize health outcomes (Yurgelun, Chenevix-Trench, & Lippman, 2017).

Hypothesis, Research Question, Specific Aims or Objectives

The research study aims to address the question: what is the distribution of stage of change (readiness) for cascade genetic testing among living, untested, at-risk first-degree relatives? The primary objective of the study is to evaluate what proportion of living, at-risk, first-degree relatives who have not undergone cascade testing for a hereditary predisposition

to cancer are in the TTM's precontemplation, contemplation, preparation, and action stages of change.

Secondary study objectives are to evaluate what proportion of first-degree relatives are aware of the mutation in the family, and have undergone cascade testing. Additionally, we aim to evaluate associations between first-degree relatives' awareness and cascade testing status with their sex, relationship to the participant (parent, sibling, child), gene mutated in the family, involvement of a genetics professional in participant's genetic testing, and participant's demographic factors.

METHODS

Study Design

We developed and implemented an anonymous survey of U.S. adults with a hereditary predisposition to tumors and cancer to evaluate the cascade genetic testing status and readiness for cascade genetic testing among their at-risk first-degree relatives. The survey is a cross-sectional study, measuring the participants' demographic characteristics, and their relatives' genetic testing status (including vital status, awareness of the mutation in the family, and completion of cascade genetic testing), and the readiness to undergo cascade genetic testing among living untested relatives at a single point in time.

Clinical practice and practical considerations informed the design of the study. Standard clinical practice following the identification of a hereditary cancer predisposition in an adult individual is for the health care provider to encourage the individual to inform their relatives of the test results and the recommendation to seek cascade genetic testing. The

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individual found to have the hereditary cancer gene mutation serves as a "gatekeeper" of the cancer risk information for their family. Relatives in supportive families with open communication behaviors often share health information openly, including updates on their genetic counseling and genetic testing status. An individual found to have a hereditary cancer gene mutation might be able to reliably report on the known or suspected genetic testing status of relatives with whom they share communication, however this may not always occur and depends largely on the communication preferences and interpersonal dynamics within a family.

An alternative approach to the study would be to request responses directly from at-risk family members, which would need to include those who may not be aware of the mutation in their family, and those who are resistant to, or have declined genetic testing. Direct contact of these relatives for research purposes has significant ethical implications, and from a recruitment perspective, these relatives may be less likely to interact with a voluntary research survey about a topic in which they are disinterested, have negative feelings, or may perceived as intrusive. Therefore, to respect family communication preferences and to improve the recruitment for the study, we initiated contact with individuals with a hereditary cancer gene mutation and asked that individual to report on behalf of other family members.

To respect participant time and effort, the survey was designed to be simple, quick to complete, and collect only the minimum information necessary to complete study objectives. This study introduced minimal risk to patient safety since it was anonymous and collected no personally identifiable health information. The UTHSC Committee for Protection of Human

Subjects considered the study exempt, and a waiver of informed consent was obtained

(protocol number HSC-SPH-180397, See Appendix A for the exempt status approval letter).

Study Population

Since this was an exploratory and descriptive study, no minimum number of

participants were required, and no specific outcomes were required or anticipated.

Participant eligibility/inclusion criteria included:

- Men and women who are ≥18 years of age, residing in the United States, who are able
  to complete a questionnaire in English, and

- Have at least one known blood relative, and

- Have received a "positive" genetic test result, indicating a "deleterious/pathogenic" or
  "suspected deleterious/pathogenic" mutation in one autosomal dominant, adult-onset
  cancer/tumor predisposition genes currently available for clinical genetic testing

Participant exclusion criteria included:

- Individuals under the age of 18 at the time of the study, and/or

- Individuals who are unable to read and complete a questionnaire in English, and/or

- Individuals who have not undergone genetic testing for a cancer/tumor predisposition
  syndrome, and/or

- Individuals who have received a "negative" genetic test result, or a "variant of
  uncertain significance" genetic test, without a "positive" result, and/or

- Individuals who have no knowledge of their blood relative(s)

Study Recruitment

The survey was open to participants for six months (August 1, 2018 through March 1, 2019). Study recruitment occurred online, and the study was promoted by a Twitter account (@CascadeStudy) and by various hereditary cancer patient support and advocacy groups such as FORCE (Facing Our Risk of Cancer Empowered), Young Previvors, the Pheo Para Project, and others. Each group or organization who agreed to share the study information distributed the survey link and a brief description of the study via the online platform of their choice, including but not limited to: e-newsletter, discussion forum, or social media (Facebook, Twitter, etc.). Recruitment materials used for social media distribution are available in Appendix B.

At the completion of the survey, participants could provide their email address to enter into a raffle for a $25 gift card. The personal email address was not tied to the survey responses and was not included in data analysis. The raffle occurred two weeks following the close of the survey. An email was sent to notify the winner to confirm that their email address was functional and to send an electronic Amazon gift card. If the raffle winner's email address was invalid or no response was received after 2 weeks, a new winner was selected and notified.

Study Procedures

The online survey was created and implemented using UTHealth's Qualtrics software. A participant was expected to be able to complete the survey in less than 60

minutes; however, time to complete the survey could vary by the size of the participant's family and the extent that the participant preferred to collect information from relatives. Collection of information from relatives by the participant was not a requirement of the study; however, some participants may have elected to do so. The median time to complete the survey was 7.8 minutes.

Qualtrics validation tools were implemented for relevant questions (ex: age numbers must range from 18-120), and eligibility questions were required to be answered before proceeding to family member questions. Participants who were ineligible for the study based on the response to a question were redirected to a thank-you statement, and exited the survey. Questions not directly tied to eligibility determination could be skipped or unanswered.

The following data was collected by the survey: demographic factors of the participant including: age, sex, U.S. state of residence, race/ethnicity, and personal history of cancer (yes/no question), genetic testing questions (to assess prior testing result, gene involved, year testing was completed, and if testing was coordinated by a genetics professional or non-genetics professional). Participants were asked about first-degree relatives, including: number, vital status, their awareness of the genetic testing results, their uptake of cascade testing, and if no cascade testing and the relative is alive: their stage of change. The survey also collected information on second and third degree relatives' including: suspected or confirmed inheritance (maternal or paternal), number of each relationship type (aunt, uncle, etc.), number aware of the results, and number who have had cascade testing. A question was included to attempt to evaluate what percent of living, untested second- and third-degree relatives were in each stage of change, however the

question was difficult to interpret without additional information about family structure. Ultimately, the results of second and third degree relatives' awareness and cascade testing status were not included in analysis due to the complexity of interpreting the data without collection of a more complete family history. A copy of the survey instrument is included in Appendix C.

Statistical Analysis

This study is exploratory and descriptive in nature; therefore, a specific sample size was not needed in order for outcomes to be informative, and a minimum number of participants was not required. Descriptive statistics such as frequencies, means, and medians were used to characterize the clinical and demographic variables in the study sample. Proportions and percentages were calculated for first-degree relatives' vital status, awareness of the variant (aware, unaware), cascade genetic testing status (tested, untested), and readiness for cascade genetic testing among living, untested first-degree relatives.

To assess for potential differences between the relationship to the participant (parent, sibling, or child) and first-degree relatives' awareness, cascade testing status, and readiness by the relative's sex (male or female), McNemar and Friedman tests (for comparisons between paired or n-group-related samples of categorical variables) and Wilcoxon Signed Rank tests (for comparisons involving paired samples of non-parametric continuous data) were employed. Potential associations between participant factors (including age, involvement of a genetics professional during the genetic testing process, year of genetic testing, and gene with variant) and first-degree relatives' awareness and uptake of cascade

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genetic testing were assessed using the Kruskal-Wallis (n-group comparison of nonparametric data) and Mann-Whitney tests (2-group comparison of nonparametric data). Differences in awareness among living, untested first-degree relatives was analyzed using a Friedman test. A 2-sided p-value of 0.05 was considered to be statistically significant. Statistical analysis was performed using IBM SPSS version 24.

Assessing Relatives' Readiness for Hereditary Cancer Cascade Genetic Testing

Genetics in Medicine

Abstract

Purpose: To explore the readiness of living, untested first-degree relatives (FDRs) to have cascade genetic testing (CGT) for a hereditary predisposition to cancer.

Methods: Adults with a hereditary predisposition to cancer completed an anonymous, online survey about their genetic testing and the vital status, awareness of the variant, and uptake of CGT among FDRs, and readiness for CGT among living, untested FDRs using Transtheoretical Model Stages of Change.

Results: One hundred-fifty participants completed the survey and reported 825 FDRs. Overall, 70.3% of FDRs were aware of the variant and 30.5% had completed CGT. Siblings had higher rates of awareness and CGT than parents or children (p<0.001). Relatives' sex was associated with awareness and CGT; mothers were aware and had CGT at higher rates than fathers (p=0.049 and p<0.001), sisters were aware and had CGT at higher rates than brothers (p=0.041 and p=0.002), and daughters had higher rates of awareness than sons (p=0.038). Of 340 living, untested FDRs, 79.4% were in the precontemplation stage of change, with no difference by relatives' sex or relationship to the participant.

Conclusion: Most living, untested FDRs were in precontemplation stage, indicating they are not ready or planning to have CGT within the next six months.

Key words (5):

Hereditary cancer, cascade testing, genetic testing, Transtheoretical model, Stage of Change

INTRODUCTION

Cascade genetic testing is the systematic process of providing genetic counseling and genetic testing to at-risk blood relatives after a germline pathogenic variant is identified in a family member[1,2]. In the setting of hereditary cancer and tumor predisposition syndromes, cascade genetic testing can provide relatives with information about their variant status, the probability for their children to inherit a predisposition to cancer, estimates of risks to develop cancer or tumors, and which cancer screening and risk-reduction strategies are recommended. The National Comprehensive Cancer Network, the American College of Obstetricians and Gynecologists, the Society of Gynecologic Oncology, the Evaluation of Genomic Applications in Practice and Prevention, and the National Cancer Moonshots Blue Ribbon Panel recommend cascade genetic testing for relatives after the identification of a pathogenic or likely pathogenic cancer predisposition variant in a family member[1,3-7].

Although cascade genetic testing provides important information to relatives, and several organizations recommend testing, the uptake of cascade genetic testing within families with hereditary predispositions to cancer is not robust. Most studies of cascade genetic testing for hereditary cancer predispositions have focused on families with Hereditary Breast and Ovarian Cancer (HBOC) and Lynch syndrome, which are due to inherited germline variants in *BRCA1*, *BRCA2*, and *MLH1*, *MSH2*, *EPCAM*, *MSH6*, and *PMS2*, respectively. In families with HBOC or Lynch syndrome, relatives' awareness of the familial variant is high (60 to 90% are aware), but rates of cascade genetic testing completion among at-risk relatives are lower, with rates of testing uptake ranging from 8% to 97%, with most studies reporting rates between 30 and 60%[8,9]. Cascade genetic testing patterns in

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families with moderate-penetrant gene variants, increasingly identified on multi-gene panel genetic testing, have not been characterized.

Behavioral science theory can aid in understanding the role of determinants, barriers, and facilitators of cascade genetic testing within families. The Transtheoretical Model is a behavioral science theory that provides a framework for understanding how people change health behaviors over time, and includes six stages of change through which an individual progresses when changing a health behavior[10]. The stages of change include precontemplation (no intention to take action in the next six months), contemplation (intention to act within the next six months), preparation (intention to act within the next 30 days), action (behavior changed for less than six months), maintenance (behavior changed for more than six months), and termination (no temptation to relapse to prior behavior)[10,11]. Several studies have used the Transtheoretical Model to evaluate intention to have genetic counseling and genetic testing among individuals with breast cancer[12-14]. No published studies have applied the stages of change to assess at-risk relatives' readiness to undergo cascade genetic testing for hereditary cancer predisposition. In this study, we applied the Transtheoretical Model's stages of change to explore the readiness of living, untested first-degree relatives to undergo cascade genetic testing for a hereditary cancer predisposition variant identified in a family member.

MATERIALS AND METHODS

Approval for the conduct of the research study with a waiver of informed consent was obtained from the University of Texas Health Science Center at Houston Institutional Review

Board. Data were collected using an anonymous, online Qualtrics survey. Individuals were eligible to participate if they were at least 18 years of age, resided in the United States (U.S.), were able to complete a survey in English, reported having a pathogenic or suspected pathogenic variant detected in one of 73 autosomal dominantly inherited, adult-onset cancer predisposition genes, and could provide information about at least one blood relative. Genes were selected for inclusion in the study by review of several U.S. laboratories' clinical genetic testing offerings in early 2018, and autosomal dominant inheritance and adult-onset cancer and tumor risks were assessed by reviewing GeneReview and OMIM entries[15,16]. Participant recruitment occurred between August 1, 2018 and March 1, 2019. The survey opportunity was shared by a study Twitter account and through the social media, newsletters, and patient forums of various hereditary cancer patient support and advocacy organizations who agreed to distribute the research opportunity. Participants could enter a raffle for one of four $25 gift cards upon completion of the survey.

The survey collected participant's demographic information (age, biologic sex, race, ethnicity, state of residence, and if they had a cancer diagnosis), and genetic testing information (relevant gene, year of testing, healthcare providers who ordered the genetic testing and who helped to explain the results, and if the variant was confirmed or suspected to be maternally or paternally inherited). Participants provided information about their first-degree relatives including: the total count of each relative (parents, siblings, and children), each relative's vital status, awareness of the variant in the family, and if the relative has had cascade genetic testing. Individuals who completed cascade testing were in the "action" stage of the Transtheoretical Model. Living, untested first-degree relatives' stage of change

(cascade genetic testing readiness) was evaluated by, "Which of the following best describes your [mother/father/sister/brother/son/daughter]'s readiness for genetic testing?" The available choices included: [He/She] does not plan to ever have genetic testing, [He/She] plans to have genetic testing but not in the next 6 months, [He/She] plans to have testing in the next 6 months, [He/She] plans to have genetic testing in the next month. If the relative planned to never have genetic testing, or planned to have testing but not in the next six months, they were considered to be in precontemplation stage. Relatives who planned to have testing in the next six months were in contemplation stage, and relatives who planned to have testing in the next month were in preparation stage. The time frames were selected based on the Transtheoretical Model's defined stages of change[10]. Participants could skip any survey question not directly tied to eligibility determination.

Descriptive statistics such as frequencies, means, and medians were used to characterize the clinical and demographic variables in the study sample. Proportions and percentages were calculated for first-degree relatives' vital status, awareness of the variant (aware, unaware), cascade genetic testing status (tested, untested), and readiness for cascade genetic testing among living, untested first-degree relatives. To assess for potential differences between the relationship to the participant (parent, sibling, or child) and first-degree relatives' awareness, cascade testing status, and readiness by the relative's sex (male or female), McNemar and Friedman tests (for comparisons between paired or n-group-related samples of categorical variables) and Wilcoxon Signed Rank tests (for comparisons involving paired samples of non-parametric continuous data) were employed. Potential associations between participant factors (including age, involvement of a genetics

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professional during the genetic testing process, year of genetic testing, and gene with variant) and first-degree relatives' awareness and uptake of cascade genetic testing were assessed using the Kruskal-Wallis (n-group comparison of nonparametric data) and Mann-Whitney tests (2-group comparison of nonparametric data). Differences in awareness among living, untested first-degree relatives by their relationship type (parent, sibling, or child) were analyzed using a Friedman test. A 2-sided p-value of 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS version 24.

RESULTS

At the conclusion of study recruitment, 204 individuals initiated a survey, 153 were eligible to participate, and 150 completed the survey and were included in analysis as outlined in **Figure 1**. Participant demographics are reported in **Table 1**, whereby participants were predominantly female (88.0%), white (93.3%), non-Hispanic (92.7%), and more than half (51.3%) reported a personal history of cancer. Nearly half of participants (48.7%) completed genetic testing recently, between 2017 and 2019. Genes reported to have a pathogenic variant by participants were varied, with the most commonly reported genes including *CHEK2* (28.7%), *BRCA1* and *BRCA2* (23.3%), Lynch syndrome genes (16%), and *SDHB* and *SDHC* (13.3%). Of note, only six participants reported variants in genes that have been associated with only female-specific cancer risks to date (four *BARD1*, two *BRIP1*), with all other reported genes having cancer and tumor risk implications for men and women. Most participants (82.0%) reported the involvement of a genetics professional (genetic counselor or geneticist) during their genetic testing process (pre-test, post-test, or both).

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Relatives' Awareness of the Familial Variant

Participants reported 825 first-degree relatives including 296 parents, 283 siblings, and 246 children. Overall, 580 (70.3%) first-degree relatives were aware of the participant's genetic testing results and 252 (30.5%) had completed cascade genetic testing. The proportion of mothers, fathers, brothers, sisters, sons, and daughters who are aware, have had cascade genetic testing, and who are living and untested are provided in **Table 2**. Awareness of the familial variant varied by relatives' sex, with a higher proportion of mothers aware compared to fathers (p=0.049), sisters aware compared to brothers (p=0.041), and daughters aware compared to sons (p=0.038). Awareness also varied by the relative's relationship to the participant, with significantly higher awareness reported for siblings than for parents or children (p<0.001). Relatives' awareness of the variant was not statistically significantly different based on whether the associated variant in the family was in a high penetrant, well-characterized cancer predisposition syndrome (HBOC or Lynch syndrome) or a lesser-studied, rare, or moderate-penetrant gene (p=0.870). The involvement of a genetics professional during the participant's genetic testing process was not significantly associated with awareness in relatives (p=0.258). The time since the participant's genetic testing (recently in 2017-2019, or prior to 2017) was not associated with a significant difference in relatives' awareness of the variant (p=0.345).

Relatives' Uptake of Cascade Genetic Testing

Completion of cascade genetic testing varied by relatives' sex for parents and siblings, whereby a higher proportion of mothers had testing compared to fathers (p<0.001) and sisters had testing compared to brothers (p=0.002). However, there was no significant difference in cascade genetic testing in daughters compared to sons (p=0.178). Cascade genetic testing also varied by relationship to the participant, whereby siblings had significantly higher rates of cascade genetic testing than parents or children (p<0.001). Cascade genetic testing among first-degree relatives was higher when participants completed genetic testing prior to 2017 (mean testing rate of 42.5%) as compared to those with more recent testing (mean testing rate of 24.3%) (p=0.003). First-degree relatives' cascade genetic testing rates were not significantly different based on the cancer predisposition syndrome (HBOC and Lynch syndrome, versus all other genes) (p=0.376), or based on the involvement of a genetics professional in the participant's genetic testing process (p=0.751).

Relatives' Readiness for Cascade Genetic Testing

Of the total 340 first-degree relatives who were living and untested, the majority (270, 79.4%), were in the precontemplation stage of change, and were either planning to never have cascade genetic testing or were not planning to have cascade genetic testing in the next six months. Only 23 (6.8%) first-degree relatives were in the contemplation stage and planning to have cascade genetic testing in the next six months, and 15 (4.4%) were in the preparation stage and planning to have cascade genetic testing in the next month. The remaining 32 living, untested first-degree relatives had no status reported by the participant.

Unlike awareness and cascade genetic testing status, there were no statistically significant differences in readiness for cascade genetic testing by sex among living, untested relatives when comparing male first-degree relatives to female first-degree relatives (p=0.892), or when comparing mothers and fathers (p=0.317), brothers and sisters (p=0.655), or sons and daughters (p=0.180). There was also no statistically significant difference in readiness by the relatives' relationship to the participant, as living, untested parents, siblings, and children were all primarily in the precontemplation stage (p=0.646).

Of note, living, untested children in the precontemplation stage were often categorized as planning to pursue cascade genetic testing but not within the next six months (61.2%), whereas most parents and siblings in the precontemplation stage were planning to never have cascade genetic testing (78.7% and 50.0%, respectively). One potential reason for this difference could be relative's age, since the age of a child is a relevant consideration in the recommendation of cascade genetic testing for adult-onset cancer predisposition. We evaluated this consideration from the perspective of participant age, and found that participants who were under age 50 had more untested children compared to participants age 50 or older (p=0.007), which suggests that younger participants' children may be under 18 and not yet recommended or ready to pursue cascade genetic testing.

Another relevant consideration for the readiness of parents to undergo cascade genetic testing is whether the variant was inherited from the participant's mother or father. In some families, the inheritance of a variant is confirmed by the results of cascade genetic testing in a parent or a more distant (second or third degree) relative, the inheritance may be suspected based on family history of cancer, or the inheritance may be unknown due to lack

of family history of cancer and lack of cascade genetic testing. Evaluating the relationship

between inheritance and the readiness of parents to have cascade genetic testing was

complicated by the significantly higher rates of cascade genetic testing among mothers, and

the high proportion of living, untested parents in the precontemplation stage, in all

inheritance scenarios. Among participants who reported that the gene variant was confirmed

or likely maternally inherited, three of three (100%) living and untested mothers, and 26 of

29 (90.0%) living and untested fathers were in the precontemplation stage. Participants who

reported that the variant was confirmed or likely paternally inherited had 19 of 20 (95%)

living, untested mothers and 10 of 11 (91.0%) living, untested fathers in the

precontemplation stage.

Awareness of the variant is another relevant consideration in the readiness for cascade

genetic testing. Most (79.7%) living, untested first-degree relatives were aware of the variant

in the family, which did not vary by relationship (parent, sibling, or child) to the participant

(p=0.368). This finding suggests that awareness was not a major factor contributing to the

lack of readiness to pursue cascade genetic testing among living, untested relatives.

DISCUSSION

Consistent with prior studies, 70.3% of first-degree relatives were aware of the

hereditary risk for cancer in their family, but only 30.5% had completed cascade genetic

testing. Also consistent with prior studies, these rates varied by relatives' sex, with female

relatives having higher rates of awareness and cascade genetic testing as compared to male

relatives. There was no difference in first-degree relative's awareness of the variant based on

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how recently the participant completed genetic testing, which aligns with studies reporting that individuals communicate their results to close relatives within 48 hours to one month after receipt of a positive test result[17,18].

Our study found that only 11.2% of first-degree relatives who had not completed cascade genetic testing were ready and planning to have testing in the near future (within the next one to six months). Most first-degree relatives were in the precontemplation stage of change for cascade genetic testing, which is the Transtheoretical Model stage of change with the least readiness for action or behavior change. The majority of living, untested first-degree relatives were aware of the variant, suggesting that this was not a likely cause for the lack of cascade testing readiness. Notably, readiness of relatives to undergo cascade genetic testing did not vary by the relatives' sex or relationship to the participant (parent, sibling, or child).

Lack of cascade genetic testing for hereditary predispositions to cancer among at-risk relatives is a concern among scientists, clinicians, and patient advocates, primarily due to the missed opportunity to reduce cancer incidence and mortality through recommended cancer screening, risk-reduction, and use of targeted cancer therapies. Interventions to increase communication of risk-information within families and to improve access to genetic testing have had limited or null effects on cascade genetic testing outcomes, have focused predominantly on well-characterized hereditary cancer syndromes (HBOC and Lynch syndrome), and may not translate across settings due to differences in country and state laws, health care policies, and care-delivery infrastructure[2,19-28]. Although environmental barriers to cascade genetic testing in the U.S. have changed, leading to increased access to genetic counseling and testing, decreased genetic testing costs, improved protections against genetic

discrimination through the Genetic Information Nondiscrimination Act, and increased rates of health insurance coverage secondary to the Affordable Care Act, cascade genetic testing rates have not noticeably increased.

The results of this study may guide future efforts to increase rates of cascade genetic testing by encouraging greater consideration of the stages and processes of behavior change and the family members who may benefit from cascade genetic testing interventions. For example, sharing of genetic test results and rates of awareness of a variant in a family are relatively high, and represent an important precursor to cascade genetic testing. However, rates of awareness are lower among male relatives, prior efforts to improve communication within families may not be reaching male relatives effectively, and communication-focused interventions alone have not significantly influenced the cascade genetic testing decision-making and behavior change processes of relatives. Similarly, interventions that provide more accessible genetic counseling and genetic testing to at-risk relatives may benefit the relatives actively seeking cascade genetic testing in the contemplation and preparation stages, which represent only 11% of living, untested relatives in our study. Focusing on increasing accessibility of genetic testing is unlikely to address the needs of at-risk relatives in the precontemplation stage. Comprehensive, theoretically grounded, and tailored approaches in cascade genetic testing intervention and research program design are needed.

A benefit of using the Transtheoretical Model to study behavior change include the stage-matched processes of change, and relevance of self-efficacy, or the confidence to make a behavior change; and decisional balance, the perceived pros and cons of behavior change, throughout an individual's behavior change process[10]. Prior studies of psychosocial factors

involved in genetic testing decision-making have consistently identified decisional balance (perceived benefits and perceived barriers and risks) as an important determinant of genetic testing[29]. The Transtheoretical Model processes of change associated with moving individuals from the precontemplation stage toward the contemplation stage include: consciousness raising, environmental reevaluation, and dramatic relief[10]. Consciousness raising includes activities that increase an individual's awareness of the health problem (hereditary cancer predisposition) and the health behavior (cascade genetic testing), the causes of the health problem, the consequences performing the health behavior, and the treatments and risk-reduction options for those with a hereditary cancer predisposition[10]. Our study found that first-degree relatives have high rates of awareness of the variant in the family, however, it is unknown whether relatives are equally aware of the consequences of cascade genetic testing, treatment and management options for hereditary predisposition to cancer, and other implications of cascade genetic testing for themselves and their family. A second process, environmental reevaluation, includes both cognitive and affective self-assessments about how an individual's behavior impacts others, and how the individual may serve as a role model for others through their behavior and actions[10]. For cascade genetic testing, environmental reevaluation-based interventions may include guided discussion and reflection on family dynamics and support systems, assessing the impact of not having cascade genetic testing on their current or future children, or considering how relatives who have tested positive for the variant or who are undergoing cancer treatment may perceive disinterest in cascade testing by the individual. Sharing stories of other families facing similar hereditary cancer predispositions and cascade genetic testing decisions, and how

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cascade genetic testing has affected relationships between relatives, spouses, and other members of their social network could support the environmental reevaluation process. Finally, dramatic relief is a process to increase emotional experiences associated with the behavior change[10]. Interventions using dramatic relief to promote readiness for cascade genetic testing could include personal testimonies or family stories about the emotional benefits (relief of knowing, empowerment to manage one's health, decreased uncertainty) of learning one's variant status and taking action to prevent cancer in themselves and their family. These Transtheoretical Model constructs and processes of change can be used to design and measure the effect of interventions to promote cascade genetic testing behavior within families, especially among relatives in precontemplation stage.

Study Limitations

Since the study was anonymous and designed to be simple and quick to complete for participants, we were unable to verify the genetic testing results of participants, collect ages and cancer histories for each relative, or evaluate if multiple participants were from the same family. The participants in our study may not be representative of families with hereditary cancer predisposition, in part due to the study recruitment strategy that relied upon social media platforms, and hereditary cancer awareness and advocacy organizations, which may serve specific populations of individuals with hereditary predisposition to cancer. Participants may have erroneously or accidentally misreported information about their relatives' awareness, testing, or readiness status. To minimize the data entry burden on participants, we did not collect the ages, cancer history, or other determinants of cascade

genetic testing for relatives. Future studies may consider collecting additional data points about relatives, and may investigate pathways for relatives to self-report their own information, to ensure the accuracy of cascade genetic testing status and readiness.

Future studies of cascade genetic testing should incorporate behavioral science theories and frameworks in order to evaluate the interaction of relevant psychosocial constructs, such as decisional balance, self-efficacy, and stage of change over time. Validated instruments exist for the measurement of these variables; however, these instruments have not been adapted and validated in populations with hereditary cancer syndromes, representing an opportunity for collaboration between behavioral scientists and genetics professionals. Future programs seeking to impact cascade genetic testing behaviors should incorporate behavioral science theories, and apply frameworks such as intervention mapping, in the development of programs[30]. Intervention mapping can help link hypothesized determinants and psychosocial factors to the development of evidence-based interventions and measurement of outcomes.

Given the large proportion of living, untested relatives found to be in precontemplation stage in our study, future studies should further evaluate the factors involved in the decision to forgo or postpone cascade genetic testing, relatives' perceived importance of each factor in the decision-making process, and the potential for misinformation to influence an individual's decision about cascade genetic testing. Assessment of the information and counseling needs of relatives in precontemplation stage may aid in the development of appropriate interventions and genetic counseling tools for families to support informed decision-making processes.

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Acknowledgements

Figure 1. Participant Survey Responses and Reasons for Ineligibility

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│                      │
│ 204 Survey responses │
│                      │
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           │              ┌──────────────────────────────────────┐
           │              │            51 Ineligible             │
           │              │   •  8   No age provided             │
           ├──────────────┤   •  9   No state selected           │
           │              │   •  16 No genetic testing performed │
           │              │   •  9   No variant found on testing │
           │              │   •  9   No gene selected            │
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│                      │
│ 153 Eligible         │
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           │              │   information                                │
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│                      │
│ 150 Included in      │
│ analysis             │
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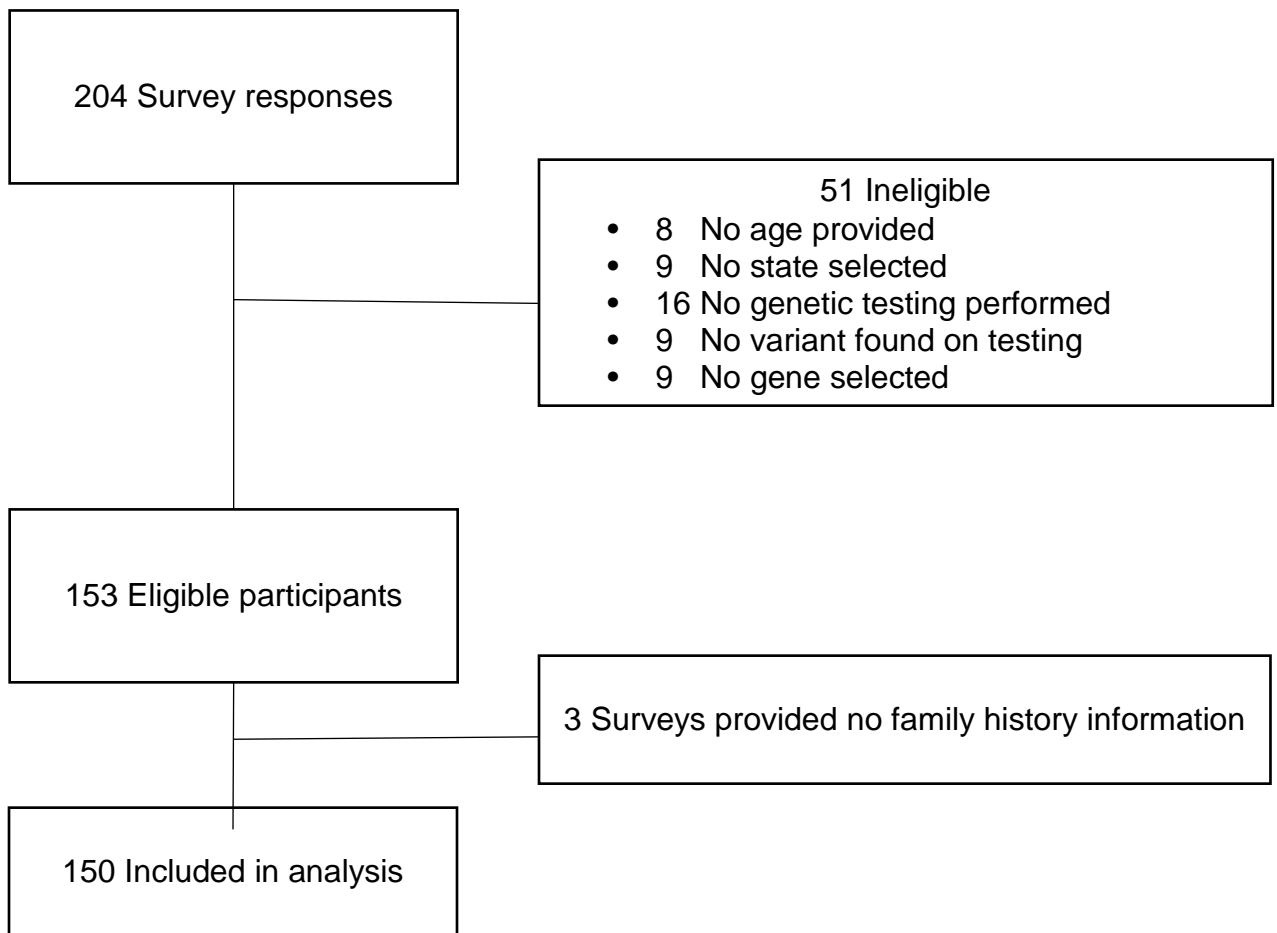
Table 1. Participant Demographics and Genetic Testing Characteristics

Characteristic		N	%
Age (years)		Mean: 46.2	Range: 19-78
Sex	Male	18	12.0
	Female	132	88.0
Race	White	140	93.3
	Other race(s)[a]	10	6.7
Ethnicity [b]	Non-Hispanic	139	92.7
	Hispanic	10	6.7
History of Cancer Diagnosis			
	Yes	77	51.3
U.S. State of Residence (U.S. Census Region)			
	South	43	28.7
	Northeast	42	28.0
	Midwest	33	22.0
	West	32	21.3
Gene with Variant			
	CHEK2	43	28.7
	BRCA1	20	13.3
	SDHB	16	10.7
	BRCA2	15	10.0
	PMS2	10	6.7
	MSH6	6	4.0
	PALB2	5	3.3
	ATM	5	3.3
	MLH1	4	2.7
	MSH2	4	2.7
	BARD1	4	2.7
	SDHC	4	2.7
	BAP1	3	2.0
	PTEN	3	2.0
	Other[c]	8	5.3
Year of Genetic Testing			
	2007 and prior	5	3.3
	2008-2010	10	6.7
	2011-2013	14	9.3
	2014-2016	48	32.0
	2017-2019	73	48.7

a. Other races included: 2 Black/African American, 2 American Indian/Alaska Native, 1 Asian Indian, 1 Chinese, 4 Other
b. 1 selected "prefer not to answer" and was not included into either Hispanic or Non-Hispanic
c. Other genes included: 2 BRIP1, 2 AXIN2, 1 APC, 1 NF1, 1 TP53, and 1 VHL

Table 2. Relatives' Awareness and Uptake of Cascade Genetic Testing

Relation to participant	Total Number	Aware of Familial Variant		Completed Cascade Genetic Testing		Alive, Untested	
		n	%	n	%	n	%
Father	146	77	52.7	17	11.6	55	37.7
Mother	150	93	62.0	48	32.0	39	26.0
Brother	167	120	71.9	46	27.5	67	40.1
Sister	116	107	92.2	76	65.5	27	23.3
Son	132	93	70.5	32	24.2	78	59.1
Daughter	114	90	78.9	33	28.9	74	64.9
Sum:	825	580	70.3	252	30.5	340	41.2

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CONCLUSION

This study is the first to describe the readiness for hereditary cancer cascade genetic testing among living, untested first-degree relatives using the Transtheoretical Model stage of change constructs. The study found that most first-degree relatives are in precontemplation stage and not planning to pursue cascade genetic testing in the next 6 months. The proportion of eligible, at-risk first-degree relatives in precontemplation stage is informative for the design and implementation of future research, determination of which first-degree relatives are participating and benefiting from the existing cascade genetic testing initiatives, and how to tailor genetic counseling for cascade genetic testing to better serve the population of individuals in precontemplation stage. Relatives who are in the precontemplation stage of change may benefit from more targeted cascade genetic testing interventions that apply the Transtheoretical Model processes of change.

An important strength of this study was the acceptability of an anonymous, online survey by study participants. Over 150 individuals sought to participate in our study, and participants included in the study analysis were diverse in terms of age, location, and hereditary cancer predisposition syndrome. Most participants completed their survey in under 10 minutes. An online and social-media directed recruitment and survey-delivery approach may provide greater opportunities for patients and families to participate in hereditary cancer research.

Another strength of the study is the application of behavioral science theory and psychosocial constructs in the setting of hereditary cancer and cascade genetic testing. Prior studies of cascade genetic testing have not consistently applied theories to their study design,

nor measured psychosocial variables that are relevant to participant's behavior and decision-making. Applying the Transtheoretical Model stages of change to cascade genetic testing behavior has provided an opportunity to learn new and clinically relevant information about hereditary cancer families, and to identify opportunities for future research.

The major limitations of the study are primarily due to study design. First, participant anonymity restricted the collection of genetic testing results to confirm mutation status. Further, we were unable to determine if multiple relatives from a single family participated in the study. The survey was brief and simple, which resulted in limiting or excluding the collection of other relevant variables such as relatives' ages, the outcomes of cascade genetic testing, and sociodemographic factors such as income, education, and health insurance status. Additionally, participants reported the status of relatives, rather than collecting this information directly from relatives, which may introduce the possibility for erroneous information.

Further research is needed to understand the decision-making process, the information used to form decisions about cascade genetic testing, and to identify what resources would help support informed decision-making within the population of at-risk individuals in the precontemplation stage. Future studies may wish to explore opportunities to interact with living, untested first-degree relatives to study the interaction of environmental and personal psychosocial determinants of cascade genetic testing. The field of genetic counseling and hereditary cancer genetics should incorporate behavioral science theory, frameworks, and methods into the design of future interventions to improve cascade genetic testing.

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APPENDICES

Appendix A: HSC-SPH-18-0397 Exempt Status and Waiver of Informed Consent

UTHealth
The University of Texas
Health Science Center at Houston

Committee for the Protection of Human Subjects

6410 Fannin Street, Suite 1100
Houston, Texas 77030

Erica Bednar
UT-H - SPH - Student

June 10, 2018

HSC-SPH-18-0397 - *Assessing the readiness of relatives to undergo cascade testing for inherited predispositions to cancer using the Transtheoretical Model Stages of Change*

The above named project is determined to qualify for exempt status according to 45 CFR 46.101(b)

CATEGORY #2 : *Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:*

a. information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; AND ,

b. any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

(NOTE: The exemption under Category 2 DOES NOT APPLY to research involving survey or interview procedures or observation of public behavior when individuals under the age of 18 are subjects of the activity except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.)

CHANGES: Should you choose to make any changes to the protocol that would involve the inclusion of human subjects or identified data from humans, please submit the change via iRIS to the Committee for the Protection of Human Subjects for review.

INFORMED CONSENT DETERMINATION:
Waiver of Documentation of Informed Consent

INFORMED CONSENT: When Informed consent is required, it must be obtained by the PI or designee(s), using the format and procedures approved by the CPHS. The PI is responsible to instruct the designee in the methods approved by the CPHS for the consent process. The individual obtaining informed consent must also sign the consent document. Please note that only copies of the stamped approved informed consent form can be used when obtaining consent.

HEALTH INSURANCE PORTABILITY and ACCOUNTABILITY ACT (HIPAA):
Exempt from HIPAA

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Appendix B: Study Recruitment Materials

Study introduction email message to organizations:

My name is Erica Bednar, and I am a cancer genetic counselor at the University of Texas MD Anderson Cancer Center and a student at the UTHealth School of Public Health. As part of my Public Health degree, I have created a research study to better understand and assess the "readiness" of relatives to undergo genetic testing (cascade testing) for a known mutation in the family associated with a hereditary cancer or tumor syndrome. I am contacting you to ask for your assistance in sharing this survey with members of your group or organization.

Cascade testing is often recommended for family members so that they can determine their cancer risks. If relatives have inherited increased risks to develop cancer, they can work with their doctors to prevent cancer or reduce their risks. Prior studies have found that the current strategies in the United States to encourage family members to have cascade testing do not work well and can be a burden on patients and families.

This research study will include men and women who have a mutation in one of several inherited cancer/tumor genes. The research study uses a theory called the Transtheoretical model to explore what "stage of readiness" relatives are in regarding having cascade testing. When someone is in a "stage of readiness," there are communication strategies that may be helpful. Our hope is that the findings of this research study will be used to develop tools for the hereditary cancer community, doctors, and genetic counselors to make cascade testing communication more effective. Additionally, participants who participate in the study and complete the survey will have the opportunity to enter a raffle for a gift card.

This research study is being performed to fulfill a thesis requirement for a Master's of Public Health degree and has been approved by the UTHealth Institutional Review Board (IRB). This survey is anonymous and does not collect any identifying information. Only my advisors at UTHealth and I will have access to the data. The study is funded by myself, with no assistance or funds from genetic testing laboratories, genetic counseling companies, or my employer. When the study is completed, we intend to publish the results so that participants can read about the findings and be acknowledged for their contributions.

If you are able to distribute the survey for the research study, please let me know, as I would greatly appreciate your support! The link to the survey is here: (include Qualtrics link) and will be active between (Start date – End date). If you have any questions or concerns about the survey or sharing it with your community, please feel free to contact me.

Thank you very much,

Erica Bednar, MS, CGC, MPH Student at UTHealth School of Public Health
Email: Erica.m.bednar@uth.tmc.edu

Social media advertising materials

No character limit (email, website, Facebook, other):

Have you had genetic testing to determine if a risk for cancer runs in your family? Did you receive a positive result? Was a mutation found in a cancer predisposition gene on your genetic testing? Do you have family members who are recommended to have genetic testing for this mutation?

Researchers at UTHealth are working with people like to you to learn more about whether family members are ready to have genetic testing for a mutation found in one of their relatives (called cascade testing). This research study is an anonymous survey and has been approved by the UTHealth Institutional Review Board. At the end of the survey you can enter for a chance to win a gift card! Learn more here: /link/

280 characters (Twitter):

Your inherited cancer genetic testing results are positive. You were told that your family members should have genetic testing too. Help us learn how ready your family members are to have genetic testing by completing this anonymous research survey: /link/

Do you have an inherited gene mutation that increases your chance to develop cancer? Are family members considering genetic testing to learn their risks? Take this anonymous research survey to help us learn about family member readiness to have cascade testing: /link/

Have you tested positive for a hereditary cancer gene mutation? We want to learn if family members are ready to have genetic testing too. You can help by participating in our research study by taking this anonymous survey, with a chance to win a gift card. Learn more here: /link/

Was an inherited mutation in *gene from list* found on your genetic testing? We are studying if family members are ready to have genetic testing for the *gene* mutation. You can help our research study by taking this anonymous survey + enter to win a gift card: /link/

Cascade testing can provide important information for at-risk relatives when an inherited risk for cancer has been found in the family. Have you tested positive for an inherited risk for cancer? Help us learn more about your family's readiness to have cascade testing by taking our research survey here:

If you have tested positive for a gene mutation that increases your risk to develop cancer, your relatives may have the mutation too. We are seeking your help to better understand if relatives are ready to have genetic testing for mutations that run their family. Find out more about our research study here:

Do you have an inherited risk for cancer found on genetic testing, and want to contribute to research? Check out our study! We are using a survey to learn if relatives are ready to have genetic testing for an inherited risk for cancer that is in their family. Find out more, here:

Have you tested positive for hereditary cancer risks? We are studying how family members

have genetic testing using an anonymous research survey. Learn more here: /link/

Social media hashtags that may be added to social media ads to increase study dissemination:

#gencsm (genetic cancer social media)	#cowdensyndrome	#lynchsyndrome
#/gene list/	#hereditarycancer	#GeneticCancers
#hereditarycancersyndrome	#GCChat (Genetic counselor chat)	#PancChat (Pancreatic cancer chat)
#bcsm (breast cancer social media)	#breastcancer	#pancreaticcancer
#gyncsm (gynecologic cancer social media)	#ovariancancer	#endometrialcancer
#uterinecancer	#crcsm (colorectal cancer social media)	#coloncancer

Raffle Winner email

Good morning/afternoon,

Thank you very much for completing the survey about family members' readiness to have genetic testing.

You have been selected as a winner of the gift card raffle for this study – Congratulations!

Please reply by (Date) with your gift card receipt preference (electronic via email, or by mail if you would like to provide your mailing address). If we do not receive a response from you by this time, a new winner will be selected for the raffle.

Sincerely,
The study team at UTHealth School of Public Health

Appendix C. Survey Instrument

Survey Page 1: Study description and agreement to participate

It is estimated that 5-10% of all cancers are inherited or hereditary: due to an underlying genetic change (mutation) that is passed down from generation to generation in a family. After a mutation is found, blood relatives of the person with the mutation may decide to have genetic testing for the specific gene mutation identified in their family. This is called "cascade testing."

Cascade testing can provide important information. Relatives who test positive for the mutation may have higher risks to develop cancer or tumors. Relatives who test negative for the mutation typically have lower cancer risks. The results of cascade testing can help people and their doctors determine the best options for cancer screening or surgery to reduce their chance to develop cancer.

Not all relatives have cascade testing, even if it is recommended by a doctor. This survey will count the number of relatives that you have, and will ask if they have had cascade testing. For relatives who have not had cascade testing, the survey will ask how ready the family member is to have testing. The results from this survey will help us to better understand cascade testing in families and may help us develop resources and tools to help family members decide if cascade testing is something they would like to do and how testing could help them.

To participate in this study, you must:
+ Be 18 years of age or older
+ Live in the United States
+ Be able to complete a survey in English
+ Have at least one blood-relative (such as a parent, sibling or child)
+ Have a positive genetic testing result for an inherited cancer or tumor condition
A positive result is sometimes written as a "deleterious", "pathogenic", or "suspected deleterious/pathogenic" mutation on a laboratory report. Testing for inherited cancer is typically done on blood, saliva, or a skin biopsy.

The time needed to complete the survey will depend on how many relatives you have (larger families may require more time than smaller families). If you are unable to complete the survey in one sitting you may close the survey and return to it by re-clicking the survey link while using the same phone or computer that you used to start the survey.

This study has been approved by the University of Texas Health Science Center at Houston Institutional Review Board. Your participation in this study is entirely optional. This survey will not collect any information that will identify who you or who your family members are. The survey is anonymous and confidential. Only the study team will have access to

survey responses. After the study is completed, all data collected by this survey will be destroyed.

This survey may include questions that make you feel uncomfortable, and you can skip any questions that you do not want to answer, unless they are required to determine study eligibility. Completing this survey may not have any direct benefits to you. At the conclusion of the survey, you will have the opportunity to enter into a raffle to win a $25 gift card. Entering the raffle is not required. The chance of winning the raffle will depend on the number of people who complete the survey and enter the raffle.

If you have any concerns or problems completing the survey, please contact the study team at (include study twitter account, study facebook account).

By clicking "I agree" below, you agree to participate in this study
- **I agree**
- **I do not agree**

Qualtrics:
Response is required
Question type: Multiple choice > Single answer
Responses: "I agree" will take participant to page 2 of survey.
              "I do not agree" = ineligible and will direct participant to last page of survey,
              thanking them for their interest in the study.

Survey Page 2: Demographic characteristics

        1. How old are you?

<u>Qualtrics:</u>

    Response is required

    Question type: Text Entry > Single line

    If number entered is <18 = ineligible and will direct participant to last page of survey, thanking them for their interest in the study

    Invalid responses are numbers under 18 and numbers over 120

        2. Please select the state where you currently live

<u>Qualtrics:</u>

    Responses: 50 U.S. states

    Response is required

    Question type: Multiple choice > Dropdown list

        3. What is your biologic sex (assigned at birth)?

<u>Qualtrics:</u>

    Responses: Male, Female, Other, Prefer not to answer

    Question type: Multiple choice > Single answer

        4. How do you describe your race? Check all that apply

<u>Qualtrics:</u>

    Responses (include current/proposed U.S. Census categories): White, Black or African American, American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Asian Indian, Japanese, Chinese, Korean, Filipino, Vietnamese, Samoan, Middle Eastern, African, Other/Prefer not to answer

    Question type: Multiple choice > Multiple answer

        5. Are you of Hispanic or Latino origin?

<u>Qualtrics:</u>

    Responses include: Yes, No, Prefer not to answer

    Question type: Multiple choice > Single answer

        6. Have you ever been diagnosed with cancer?

<u>Qualtrics:</u>

    Responses include: Yes, No

    Question type: Multiple choice > Single answer

Survey Page 3: Genetic Testing

> **7. Have you had genetic testing for a hereditary cancer or tumor condition?**
> Genetic testing for inherited or hereditary cancers is typically performed on blood, saliva, or a skin biopsy.

Qualtrics:

Responses include: Yes, No
Response is required
Question type: Multiple choice > Single answer
If response = no = ineligible and will take participant to last page of survey, thanking them for their interest in the study.

> **8. Did you receive a "positive" genetic test result?**
> A "positive" result means that a mutation has been found. Laboratory results may include wording such as a "deleterious" or "pathogenic" mutation, or a "suspected deleterious" or "suspected pathogenic" mutation. Results that identify a "variant of uncertain significance" are <u>not</u> considered positive results.

Qualtrics:

Responses include: Yes, No
Response is required
Question type: Multiple choice > Single answer
If response = no = ineligible and will take participant to last page of survey, thanking them for their interest in the study.

> **9. Which of the following genes were "positive" for a mutation on your genetic testing?**
> Please select only one. If you had a "positive" result for more than one gene mutation, please select only of the genes from the list.

Qualtrics:

Responses include: *AIP, APC, ATM, AXIN2, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73 (HRPT2), CDH1, CDK4,CDKN1B, CDKN2A, CEBPA, CHEK2, DDX41, DICER1, EGFR, EPCAM, ETV6,FH, FLCN, GALNT12, GATA2, GREM1, HOXB13, KIT, LZTR1, MEN1, MET, MITF, MLH1, MSH2, MSH6, NBN, NF1, NF2, NTHL1, PALB2, PDGFRA,PMS2, POLE, POLD1, POT1, PRKAR1A, PTCH1, PTEN, RAD51C, RAD51D, RB1, RECQL, RET, RUNX1, SDHA, SDHB, SDHC, SDHAF2, SMAD4, SRP72, STK11, SUFU, TERC, TERT, TMEM127, TP53, TSC1, TSC2, VHL, WRN, XRCC2* (Gene categories will be included in analysis but not survey)
Response is required
Question type: Multiple choice > Dropdown list

> **10. What year did you have genetic testing for a hereditary cancer or tumor condition?**

Qualtrics:

Responses include: "before 2000", 2001, 2002…2018, 2019"
Question type: Multiple choice > Dropdown list

11. Who helped to order your genetic testing?

<u>Qualtrics:</u>

Responses include: Genetic counselor, Genetics doctor (geneticist), Cancer doctor (oncologist), Family doctor or primary care provider, Gynecologist, Research study, Self (ordered testing online, such as 23&Me or Color), Other
Question type: Multiple choice > Multiple answer

12. Who helped to explain the results of your genetic testing?

<u>Qualtrics:</u>

Responses include: Genetic counselor, Genetics doctor (geneticist), Cancer doctor (oncologist), Family doctor or primary care provider, Gynecologist, Doctor's office staff (such as a nurse or physician assistant), Research study, Self (received results online, like through 23&Me or Color), Other
Question type: Multiple choice > Multiple answer

Survey Page 4: Family Members (First-Degree Relatives)

"Please complete the following questions about your family to the best of your knowledge. Some people may find it helpful to talk with their relatives as they complete this portion of the survey. You are not required to communicate with relatives in order to complete these questions.

Please include only family members who are related to you by blood (biological relatives). Do not include relatives who are related to you through marriage (spouses, step-children), or adopted into your family."

First-Degree Relatives

13. Do you know who your birth parents are?
   a) Yes, I know my birth mother and birth father
   b) I know my birth mother, but not my birth father
   c) I know my birth father, but not my birth mother
   d) I do not know my birth parents

Qualtrics:
Question type: Multiple choice > Single answer
Logic: If D selected: move to Sibling questions
      If A, B, or C selected: Parent Questions

Parent Questions:
14. Check all of the boxes that apply to your (Mother/Father)
   a) She/He knows about my genetic testing result
   b) She/He has had genetic testing
   c) She/He is alive

Qualitrics:
Question type: Multiple choice > Multiple answer
Logic: if B is not selected and C is selected: Stages Question

Stages Question
15. Which of the following best describes your Mother/Father's readiness for genetic testing?
   a) She/He do not plan to ever have genetic testing
   b) She/He plans to have genetic testing, but not in the next 6 months
   c) She/He plans to have genetic testing in the next 6 months
   d) She/He plans to have genetic testing in the next month

Qualtrics:
Question type: Multiple choice > Dropdown list

Siblings Questions

Full-siblings are brothers and sisters who share both the same mother and the same father as you. For the next set of questions, please count the number of full-siblings that you have, including those who are living and those who have died.

16. How many full-brothers do you have?
      a) 0 – 10 (options)

17. How many full-sisters do you have?
      a) 0 – 10 (options)

Qualtrics
Question type: Multiple choice > Dropdown list
Logic:
    (Per sibling type) answers 1 through 10 will display as up to 10 columns:

18. Please provide the following information about your brother(s)

	Brother 1	Brother 2	Brother 3	Brother 4	Brother 5
They know about my genetic test results	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
They have had genetic testing	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
They are alive	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No

19. Please provide the following information about your sister(s)

	Sister 1	Sister 2	Sister 3	Sister 4	Sister 5
They know about my genetic test results	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
They have had genetic testing	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
They are alive	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No

Qualtrics
Question type: Side by side
Logic: (Per sibling) No Genetic Testing + Alive: that sibling will display as a row

You noted that the sister(s) below have not yet had genetic testing. If no sisters appear below this question, please proceed to the next question.

20. Which of the following categories best describes their readiness for genetic testing?

Sister 1	a) They do not plan to ever have genetic testing b) They plan to have genetic testing, but not in the next 6 months c) They plan to have genetic testing in the next 6 months d) They plan to have genetic testing in the next month
Sister 2	a-d as above
Sister 3	a-d as above

Sister 4	a-d as above
Sister 5	a-d as above
Sister 6	a-d as above
Sister 7	a-d as above
Sister 8	a-d as above
Sister 9	a-d as above
Sister 10	a-d as above

You noted that the brother(s) below have not yet had genetic testing. If no brothers appear below this question, please proceed to the next question.

21. Which of the following categories best describes their readiness for genetic testing?

Brother 1	a) They do not plan to ever have genetic testing b) They plan to have genetic testing, but not in the next 6 months c) They plan to have genetic testing in the next 6 months d) They plan to have genetic testing in the next month
Brother 2	a-d as above
Brother 3	a-d as above
Brother 4	a-d as above
Brother 5	a-d as above
Brother 6	a-d as above
Brother 7	a-d as above
Brother 8	a-d as above
Brother 9	a-d as above
Brother 10	a-d as above

Qualtrics
Question type: Matrix Table > Likert > Dropdown list

Children Questions

22. How many sons do you have?
a) 0 -10 (options)

23. How many daughters do you have?
a) 0 – 10 (options)

Qualtrics
Question type: Multiple choice > Dropdown list
Logic:
(Per child type) answers 1 through 10 will display as up to 10 columns:

24. Please provide the following information about your son(s)

	Son 1	Son 2	Son 3	Son 4	Son 5
They know about my genetic test results	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
They have had genetic testing	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No

They are alive	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No

25. Please provide the following information about your daughter(s)

	Daughter 1	Daughter 2	Daughter 3	Daughter 4	Daughter 5
They know about my genetic test results	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
They have had genetic testing	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
They are alive	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No

Qualtrics
Question type: Side by side
Logic: (Per child) No Genetic Testing + Alive: that child will display as a row

You noted that the son(s) below have not yet had genetic testing. If no sons appear below this question, please proceed to the next question.

26. Which of the following categories best describes their readiness for genetic testing?

Son 1	e) They do not plan to ever have genetic testing
	f) They plan to have genetic testing, but not in the next 6 months
	g) They plan to have genetic testing in the next 6 months
	h) They plan to have genetic testing in the next month
Son 2	e-h as above
Son 3	e-h as above
Son 4	e-h as above
Son 5	e-h as above
Son 6	e-h as above
Son 7	e-h as above
Son 8	e-h as above
Son 9	e-h as above
Son 10	e-h as above

You noted that the daughter(s) below have not yet had genetic testing. If no daughters appear below this question, please proceed to the next question.

27. Which of the following categories best describes their readiness for genetic testing?

Daughter 1	e) They do not plan to ever have genetic testing
	f) They plan to have genetic testing, but not in the next 6 months
	g) They plan to have genetic testing in the next 6 months
	h) They plan to have genetic testing in the next month
Daughter 2	e-h as above
Daughter 3	e-h as above

Daughter 4	e-h as above
Daughter 5	e-h as above
Daughter 6	e-h as above
Daughter 7	e-h as above
Daughter 8	e-h as above
Daughter 9	e-h as above
Daughter 10	e-h as above

Qualtrics
Question type: Matrix Table > Likert > Dropdown list

Survey Page 5: Family members (Second and Third-degree relatives)
Please complete the following questions about your family to the best of your knowledge. Some people may find it helpful to talk with their relatives as they complete this portion of the survey. You are not required to communicate with relatives in order to complete these questions.

Please include only family members who are related to you by blood (biological relatives). Do not include relatives who are related to you through marriage (spouses, step-children), or adopted into your family.

Second and Third-Degree Relatives

28. Do you know from which side of your family that you inherited the gene mutation?
a) The mutation is from my mother's family (mother or other maternal relative has tested positive)
b) The mutation is from my father's family (father or other paternal relative has tested positive)
c) The mutation is probably from my mother's family, but this is not confirmed
d) The mutation is probably from my father's family, but this is not confirmed
e) The mutation was not inherited, and is new in me (mother and father were tested and they do not have the mutation)
f) I do not know

Qualtrics
Question type: Multiple choice > single answer
If A, C, or F selected: show maternal questions
If B, D, or F selected: show paternal questions

Second and Third-Degree Relatives

29. Please provide the number of relatives from your maternal (Mother's) side of the family for each of the categories

	Total (living and deceased)	Know about the mutation in the family	Have had genetic testing
Aunts			
Uncles			
Grandmother			
Grandfather			
Male cousins			
Female cousins			
Half-sisters			

Half-brothers			

Qualtrics
Question type: Matrix Table > Constant Sum > Scale Point
Validation: Max number = 100

Second and Third-Degree Relatives

30. Please provide the number of relatives from your paternal (Father's) side of the family for each of the categories

	Total (living and deceased)	Know about the mutation in the family	Have had genetic testing
Aunts			
Uncles			
Grandmother			
Grandfather			
Male cousins			
Female cousins			
Half-sisters			
Half-brothers			

Qualtrics
Question type: Matrix Table > Constant Sum > Scale Point
Validation: Max number = 100

31. Please provide the number of relatives from your family for each of the categories

	Total (living and deceased)	Know about the mutation in the family	Have had genetic testing
Nieces			
Nephews			

Qualtrics:
Question type: Matrix Table>Constant Sum>Scale Point
Question will display if number of brothers is >0 or if number of sisters is >0.
Validation: Max number = 100

32. Please provide the number of relatives from your family for each of the categories

	Total (living and deceased)	Know about the mutation in the family	Have had genetic testing
Granddaughters			
Grandsons			

Qualtrics
Question type: Matrix Table > Constant Sum > Scale Point
Question will display if the number of sons is >0 or if the number of daughters is >0.
Validation: Max number = 100

Think about all of the second and third-degree relatives from the previous questions (aunts, uncles, grandparents, cousins, etc.).

33. For female relatives who are <u>alive</u> and who have <u>not</u> had genetic testing, about what percentage are in the following categories?
For reference: 0%= none, 50%=half, 100%=all

<u>Text box (number):</u>	
	% - Do not plan to ever have genetic testing
	% - Plan to have genetic testing, but not in the next 6 months
	% - Plan to have genetic testing in the next 6 months
	% - Plan to have genetic testing in the next month

Qualtrics
Question type: Constant Sum > Choices > Must Total 100%

Think about all of the second and third-degree relatives from the previous questions (aunts, uncles, grandparents, cousins, etc.).

34. For male relatives who are <u>alive</u> and who have <u>not</u> had genetic testing, about what percentage are in the following categories?
For reference: 0%= none, 50%=half, 100%=all

<u>Text box (number):</u>	
	% - Do not plan to ever have genetic testing
	% - Plan to have genetic testing, but not in the next 6 months
	% - Plan to have genetic testing in the next 6 months
	% - Plan to have genetic testing in the next month

Question type: Constant Sum > Choices > Must Total 100%

Survey Page 7: Raffle entry
If you would like to enter into the raffle for a chance to win a gift card, please provide your email address below.
If you provide your email address, it will not be linked to your study responses, and only the study coordinator will have access to this email address. The raffle is planned to occur during March 2019 – please check your email and spam filters around that time to see if you were selected. After the raffle is complete, all emails will be deleted.
Qualtrics
Question type: Text Entry > Single line
Have two entries with second to confirm address, and both must be valid email addresses.

Survey Page 8: Final Page
Thank you for your interest and participation in this survey. The survey is now complete, and you may close the page.

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