POPULATION SCREENING FOR HEREDITARY CANCER SYNDROMES: OPINIONS FROM AMAZON MECHANICAL TURKS

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ABSTRACT

The current standard of care in genetic testing for hereditary cancer syndromes is to offer genetic testing to individuals who meet certain criteria based on personal and/or family history of cancer. With the recent advances in testing technology, it has become feasible to consider genetic testing on a wider scale. There has been a debate by experts in the field of cancer genetics of whether the family history-based approach should be supplemented or replaced with a population-screening based approach. The purpose of this study was to examine the interest level and motivations of individuals in the general population for genetic testing of genes associated with hereditary cancer as well as identify psychosocial implications. This study surveyed individuals in the dominant market of crowdsourcing used by researchers in the academic setting, Amazon Mechanical Turks.

The majority of the participants in this study (73%, n = 861) indicated that they would currently be interested in taking a genetic test for cancer. After this initial interest question, the participants were presented with six possible result scenarios. After the scenarios were presented, the participants were again asked a question regarding interest level in genetic testing for hereditary cancer. Of the 861 participants who answered this question, 40 (4.9%) of those who

initially indicated an interest on having genetic testing for hereditary cancer at some point in life, stated that they would never take such a genetic test. This data suggests that the need for informed consent and patient understanding of the test is needed. The survey responses indicated a wide variety of emotional and psychological stresses may occur as a result of genetic testing and indicates the need for additional support and resources to be in place before the implementation of a population-screening program for any genes related to hereditary cancer. A population-screening program for hereditary cancer would be a public health intervention with the goal of identifying all mutation-carriers. However, there could possibly be serious medical, psychosocial, ethical and legal ramifications should such a program like this be implemented before more research and serious thought is given into the proper infrastructure.

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1.0 INTRODUCTION

Since genetic testing for hereditary cancer syndromes such as Lynch syndrome (LS) and Hereditary Breast and Ovarian Cancer syndrome (HBOC) was first offered on a clinical basis, personal and family history guidelines and criteria have been established and continuously refined about who should be offered genetic testing. Genetic testing for hereditary cancer syndromes can currently be ordered by either physicians or licensed genetic counselors in certain states. Individuals found to carry a mutation in a gene associated with a significantly increased risk of cancer over that of the general population should take preventative measures such as increased screening, chemoprevention, and/or prophylactic surgery if these options are available for the organ or tissue at this increased risk. If an unaffected individual is found to carry a mutation in one of these genes, then the clinical goal is to either prevent cancer entirely using prophylactic measures or detect it at an early, more treatable stage.

The prevalence of *BRCA1/2* mutations in the general population is estimated to be between 1 in 300 to 1 in 500 people[1]. There have recently been a few studies in the Ashkenazi Jewish population, where the prevalence of *BRCA1/2* mutations is increased ten-fold, which suggest that the current genetic testing strategy misses approximately half of the Ashkenazi Jewish carriers of *BRCA1/2* mutations[23]. It has been suggested that this data could be extrapolated and applied to the population at large, though there are currently no published studies replicating these findings in non-Ashkenazi Jewish populations.

Some experts have used the data in these studies to propose support for population-screening programs for *BRCA1/2* mutations in order to identify individuals who would not otherwise be identified using current genetic testing strategies and then manage them appropriately[4]. In 2014, the Lasker-Koshland Special Achievement Award in Medical Science was presented to Dr. Mary-Claire King for her work specifically related to the *BRCA* genes. Using this platform, Dr. King was able to gain substantial attention and awareness of her team's research studies of population-based screening and their viewpoint of offering genetic screening of *BRCA1* and *BRCA2* to every woman in the United States over the age of 30[4]. Benefits to a population-screening based approach would include identifying mutation-carriers who previously would not have been identified and using prevention and management strategies to prevent cancer or detect it at an early stage and ultimately save lives[5]. Limitations and risks to a population-screening based approach include not obtaining proper informed consent before genetic testing, possible psychosocial effects, a sense of false-security for those who test negative, and potential ethical and practical implications[6].

There is a growing body of literature about the potential clinical utility and cost-effectiveness of using genomics to guide screening for the general population as well as some of the practical and ethical uncertainties. Several studies have also been published on the topic of current population-based genetic testing available such as newborn screening and carrier testing. However, there is little published on the interest level, knowledge, and/or attitudes of individuals in the general population in the United States for cancer susceptibility genetic testing. This research study was conducted to fill a gap in the current literature about the interest level and possible psychosocial effects from individuals in the general population in the United States on the topic of offering genetic testing for hereditary cancer genes to the general population.

1.1 SPECIFIC AIMS AND RESEARCH QUESTIONS

1.1.1 Specific Aims

Aim 1: Examine the interest level of individuals in the public (represented by the Amazon Turks Community) in taking a genetic test for hereditary cancer.

Aim 2: Use various possible scenarios in the context of population screening to evaluate the possible psychosocial impacts of genetic testing, specifically in this setting, using quantitative methods.

1.1.2 Research Questions

Question 1: Are individuals in the general population interested in a genetic test that analyzes genes associated with hereditary cancer syndromes?

Question 2: What are some possible psychosocial implications of a population-screening program for hereditary cancer syndromes?

2.0 BACKGROUND AND SIGNIFICANCE

2.1 CANCER

In the United States, approximately one in four deaths are due to cancer[7,8]. According to the National Cancer Institute, the lifetime risk of developing cancer is 43.31% for males and 37.81% for females in the United States[9]. These risks apply to the general population as a whole; however, each individual can have a different, individual risk for developing cancer depending on their own personal risk factors. These risk factors include several lifestyle and environmental factors such as tobacco use, alcohol use, obesity, lack of physical activity, ionizing radiation, environmental pollutants, infections, as well as inherited genetic factors[10].

2.1.1 Cancer Screening Approaches for the General Population

Traditionally, cancer-screening recommendations for the general population have the goal of diagnosing cancer when it is at an early, more treatable stage. There are well-established guidelines in place for the general population, or those who have an average risk for cancer, as to when cancer screenings such as mammograms and colonoscopies should take place. Cancer is typically a disease of aging, and the recommendations for the general population reflect that as many of the recommended screenings do not begin until closer to the typical age of diagnosis. For example, the American Cancer Society recommends annual mammograms starting at 45

years of age and colonoscopies every 10 years starting at 50 years of age for individuals at average risk for breast and colon cancer[11,12]. The guidelines and management recommendations for these cancer population screening programs, such as mammograms and colonoscopies, weigh the benefit of saving lives by diagnosing cancer early with the risks and costs of these screening procedures to settle on an appropriate age to start screening as well as how often these screenings should occur[13]. These screening recommendations also take into account the incidence of cancer at a given age and whether or not the screening is effective at increasing survival rates[13].

2.1.2 Categories of Cancer

All cancers develop as a result of genetic mutation, however most cancers are not the result of a single inherited mutation[14]. Typically, cancer forms as these genetic mutations are accumulated over time in certain parts of the body, either by chance or as a result of environmental or lifestyle exposures[15]. More rarely, genetic mutations in specific genes can be inherited and are then present in all of the cells of the body, causing an increased risk of cancer in the tissues in which that specific gene primarily functions. There are certain genes that, when working properly, prevent cancer from forming. These genes generally fall into one of two categories: tumor suppressor genes or proto-oncogenes.

Inherited mutations in one copy of a tumor suppressor gene, coupled with a “second hit” on the other copy, acquired somatically, leads to uncontrolled cellular division and oftentimes a tumor[16]. Mutations in these genes can facilitate cancer development because these genes are not able to perform their normal function and prevent cancer from forming[16]. An acquired mutation in specific positions of an oncogene, can lead to aberrant or overactive functioning of the resultant protein, which similarly causes uncontrolled cell growth. *BRCA1* and *BRCA2* are both

tumor-suppressor genes and function to assist in DNA repair, specifically in transcriptional regulation of genes that are involved in apoptosis, the cell cycle, and DNA repair. This transcriptional regulation is in response to damage to DNA[17]. The *RET* gene, which causes Multiple Endocrine Neoplasia type 2 (MEN2) is an example of an oncogene. Oncogenes can contribute to an increased risk of cancer by allowing some cells which normally would have gone through apoptosis to survive and proliferate instead[14].

Cases of cancer can be divided into three different categories, sporadic, familial predisposition, and hereditary predisposition[18]. Current data suggests that the majority of cancer (~60%) is sporadic and happens by chance as a result of a lifetime of exposure to a combination of lifestyle factors, environmental factors, or chance DNA replication errors[15]. Over time, these random mutations can lead to the accumulation of genetic mutations in a certain tissue, most often activating an oncogene, and causing a tumor[15].

Approximately 30% of cancers can be considered familial and are thought to have happened as a result of both genetic and environmental factors[10]. Oftentimes individuals/families that fall into the familial category have a clustering of cancers, where cancer seems to be happening more often than by chance alone, but is not characteristic of hereditary cancer[15]. Individuals in the familial category have a moderately increased risk of certain cancers and may be screened slightly earlier and/or slightly more often than those at the average risk of the general population. The last category of cancer is hereditary cancer predisposition, where a single inherited germline mutation (or very rarely, a *de novo* mutation) causes an increased risk of cancer.

Hereditary cancer makes up approximately 5 – 10% of all diagnoses of cancer[19]. Oftentimes, individuals with hereditary cancer in their family have striking personal or family

histories of cancer. There are certain characteristics that are commonly seen in cases of hereditary cancer. These characteristics are: younger ages of onset (<50 years of age), bilateral cancers, certain tumor types (e.g. triple-negative breast cancer), rare cancers (e.g. male breast cancer, ovarian cancer, chromophobe renal cell carcinoma), multiple family members on the same side of the family with the same or related types of cancer, suggestive tumor studies (e.g. colon cancer due to Lynch syndrome), and certain ethnic groups (e.g. the Ashkenazi Jewish population for *BRCA* genes)[1]. The presence or absence of these characteristics is used by genetic counselors and other healthcare providers to assess an individual's personal cancer risk and may also be used to assess an individual's chance of having a mutation and determine whether genetic testing is appropriate.

Most of the known hereditary cancer syndromes are inherited in an autosomal dominant pattern. This means that both men and women can carry these mutations and that only one of the two copies of the associated gene needs to have a mutation to cause an increased risk for cancer. If an individual has a mutation in one of these genes, there is a 50% chance of passing on the mutation and the increased risk for cancer onto his/her children[15]. In the case of a hereditary cancer mutation, this mutation was most likely inherited from one of the individual's parents. In the case of an inherited mutation, and not a *de novo* mutation, there is a 50% chance for each sibling to have inherited the mutation as well.

2.1.3 Cancer Screening Approaches for High-Risk Individuals

Individuals with a significant personal or family history of certain cancers or a known genetic mutation in a moderate to high-risk gene, are typically classified as high-risk individuals and have a significantly increased risk of cancer over the general population. There are different

guidelines in place for the management and screening of these individuals[20,21,22,1]. Those with an increased risk of cancer based on family history or a genetic mutation are typically screened starting at earlier ages and using shorter time intervals. Other options such as prophylactic surgery or chemopreventive drugs may also be available for high-risk individuals depending on the organ or tissue at risk[23]. Currently, the identification of pre-symptomatic, high-risk individuals is the result of a significant family history of cancer and/or a family member who had genetic testing where a mutation was identified.

Using the *BRCA* genes as an example, the risks for cancer are approximately a 57% lifetime risk of breast cancer, and for ovarian cancer the lifetime risk is approximately 18% for *BRCA2* mutation carriers and 40% for *BRCA1* mutation carriers[24]. Other increased cancer risks in mutation positive *BRCA* individuals include male breast cancer, prostate cancer, pancreatic cancer, and melanoma[25]. It has been found that women who are classified as being at high-risk to develop breast cancer reduce their risk by 90 – 94% by having a prophylactic mastectomy[1,26] and risk-reducing bilateral salpingo oophorectomies have been shown to decrease the risk of both breast cancer and ovarian cancer[27,28].

2.2 GENETIC TESTING OF HEREDITARY CANCER GENES

Since its advent in 1996, clinical genetic testing for *BRCA1/2* mutations has been offered to select individuals meeting certain criteria. This testing strategy has continued and is still the current strategy for identifying who should be offered genetic testing; a family history-based approach. It is common practice by physicians, genetic counselors, and some insurance companies to either follow the National Comprehensive Cancer Network (NCCN), the American

College of Medical Genetics and Genomics (ACMG) and National Society of Genetic Counselors (NSGC) joint practice guidelines, the US Preventive Services Task Force or the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group recommendations for referral and testing criteria to identify the appropriate individuals who may benefit from genetic testing[1,21,29,22]. Using the current testing strategy, goals of cancer genetic counseling include a discussion of the important elements of the benefits and risks/limitations of genetic testing with the patient prior to testing, proper informed consent, and helping the patient understand what to expect from the genetic testing and the possible effects on medical management.

2.2.1 Possible Test Results of Genetic Testing

When genetic testing for hereditary cancer syndromes is performed, there are typically three possible test results. These possible test results are: “positive,” “negative,” and “variant of uncertain significance” (VUS). The positive result means that when the lab performed the sequencing and/or deletion and duplication analysis of the requested genes, a mutation was identified, and that mutation is harming the function of the gene which causes an increased risk for certain cancers. A negative result means that no mutations were identified in the requested genes. A negative result can be a true negative, meaning that a mutation that has previously been identified in another family member has not been found in the patient. In this scenario, the individual who tested negative would have the same cancer risks as the general population. If a mutation has not been previously identified in a family and the individual’s genetic testing is negative, then that individual would be managed based on personal and/or family history of cancer. In this case, there is not currently a genetic answer for their personal and/or family

history of cancer but some of the chance that they have a hereditary cancer syndrome would be eliminated.

2.2.1.1 Variants of Uncertain Significance

A variant of uncertain significance (VUS) is not a straight-forward answer, but rather an inconclusive result. If an individual undergoes genetic testing and a VUS is found, this means that the lab analyzed the requested genes and found a change in the DNA code of the gene, but there is not enough data for the lab to be able to classify this change as either a positive or negative result. The most common type of VUS are missense substitutions which result in a single amino acid change[30]. In the case of an individual having a VUS, he/she is usually followed solely based on his/her personal and/or family history of cancer and genetic testing is not offered to other relatives outside of a research protocol[31],[15]. A VUS may be reclassified as more research on specific changes in these genes occurs in the future. Oftentimes a VUS is reclassified as a benign polymorphism (negative result), but they are occasionally reclassified as a pathogenic, disease-causing mutation as well (positive result).

The American College of Medical Genetics and Genomics (ACMG) has standards and guidelines for how to classify and interpret such variants[32]. Individuals undergoing genetic testing often have a pre-counseling session where they are informed of the three possible test results as well as the risk of getting a VUS back as a result, and what that would mean for them. As more data has been collected and classification schemes for variants have been updated, there has been a decrease in the VUS rate at many genetic testing laboratories, and this decreasing VUS rate trend is expected to continue as more individuals undergo genetic testing[33].

The chance of a patient having a VUS result depends on what specific genes were ordered as well as how many genes were analyzed. *BRCA1/2* genes have a lower rate of VUS

results due to how well-characterized they both are compared to many of the other genes known to be associated with hereditary cancer[34]. The VUS rate also depends on the laboratory performing the genetic testing. For instance, Myriad Genetics currently quotes their 2013 VUS rate as 0.6% for BRCA1 and 1.6% for BRCA2 on their website[35]. Ambry Genetics[36] currently quotes their VUS rate for *BRCA1/2* combined as 3.64% on their website and published a paper in 2014 where 2,079 patients underwent panel genetic testing for 14 – 22 cancer susceptibility genes, not including *BRCA1/2*, and found a VUS rate of 15.1 – 25.6% depending on the panel ordered[33].

There are higher rates of detecting a VUS in certain ethnic populations where relatively few individuals have undergone genetic testing[6]. As stated by Yurgelun *et al*., 2015[6] "cancer genetics is one area of modern medicine in which pervasive racial and ethnic disparities in health care access, delivery, and quality are especially prevalent." Studies into these disparities have found that when comparing women of white ethnicity to women of minority ethnicities, minority women are less likely to be aware of genetic testing and/or referred for genetic testing and are more likely to have an inconclusive, VUS result due to the lack of data on non-white and non-Ashkenazi Jewish ethnic populations[37,38,39,40]. While a population based screening program for hereditary cancer syndromes may expand access to these tests in minority populations, it is important to note that these individuals would be more likely to receive a VUS result, which may cause increased worry and anxiety, especially in the early stages of a screening program[37].

Another concern in the case of a VUS may be that an individual makes a radical medical decision based on this result. A study by Vos *et al*., 2012[41] found that variants of uncertain significance were often inaccurately perceived and usually overestimation were made in cancer

risks. Due to this misperception, some individuals had made radical medical decision (such as surgery) based on a VUS.

2.2.2 Informed Consent for Cancer Susceptibility Testing

There are proposed basic elements of informed consent for cancer susceptibility testing. The American Society of Clinical Oncology (ASCO) first released a statement on the subject of genetic testing for cancer susceptibility in 1996. The proposed basic elements have had multiple updates and revisions since that time. These basic elements currently include information on the specific genetic mutation(s), possible effects on medical care, risk to other family members, psychological implications, confidentiality problems, and implications in the case of a positive, negative, and uninformative result[31]. There are additional informed consent components in the case of pretest counseling for a multi-gene panel which include specific attention to explaining the possible limited clinical utility in the case of a mutation found in a newer, and lesser-understood gene, the high rate of variants of uncertain significance, and highlight possible implications for reproduction for genes that are associated with recessive disorders such as Fanconi Anemia[31].

2.2.3 Population-Screening Based Approach to Genetic Testing

Recently, there has been a discussion in the literature and in the medical/research community as a whole of whether the current family history-based approach should be supplemented with a population-screening approach. This discussion has primarily revolved around the *BRCA1/2*

genes. In 2014, a recommendation was made by Mary Claire-King and her research group that all women in the United States age 30 and older should be offered *BRCA1/2* testing[4].

Population screening for hereditary cancer syndromes has several implications. These implications are both clinical and psychosocial in nature. Population screening has the potential to identify those who do not meet the current testing criteria, do not have knowledge of their family histories, or do not know about/cannot access genetic testing services but in fact are carriers of a mutation in a gene associated with hereditary cancer.[6]

Many of the studies specifically related to *BRCA1/2* have focused on the Ashkenazi Jewish population, as mutations in *BRCA1/2* are much more common in this population (approximately 1 in 40) than in the general population where the prevalence is approximately 1 in 300 to 1 in 500[42,43,1]. For example, a study took place in the Ashkenazi Jewish (AJ) population of Israel where DNA samples from 8,195 male subjects were genotyped for the three founder AJ mutations in *BRCA1* and *BRCA2*. This study found that 175 of the 8,195 (2.14%) men were carriers of at least one of these mutations. Approximately half (85 out of 167) of the *BRCA* mutation carriers had little or no family history of a relevant cancer [2]. This study concluded that population-based genetic testing in the Ashkenazi Jewish population may detect up to 56% more *BRCA* carriers compared with the current gold standard of family history-based genetic testing[3]. More data in this area of genetics is needed before this data can be extended to making the same conclusions about the general population at large.

It is also important to note that the genetic testing completed in these studies was a 3-site analysis for the founder mutations found in the Ashkenazi Jewish population. The VUS rate for 3-site analysis is nearly negligible at this point in time. However, population screening in the general population would require full sequencing and deletion/duplication genetic testing to

capture mutation carriers as there are not founder mutations for the general population. With a VUS rate at best currently at 2.2% for *BRCA1/2*, population screening would identify approximately many more individuals with inconclusive results of variants (approximately 1 in 45) of uncertain significance than pathogenic mutation carriers (approximately 1 in 400)[6,44].

King *et al*[45,4]have recommended that only clear, positive results should be reported to individuals undergoing genetic testing in a population-screening context and that VUS results should not be reported, and considered to be negative. This is a controversial position because while most of the variants of uncertain significance are later reclassified as benign, there would be potential for legal, ethical, psychological, and medical ramifications in the instances where a VUS result is reclassified as pathogenic[6].

2.3 POPULATION SCREENING

2.3.1 Principles of Population Screening

The principles and goals of population screening were first developed and described in 1968 by Wilson and Jungner[46]. As stated by Khoury *et al*., 2003[47] "These principles emphasize the importance of a given condition to public health, the availability of an effective screening test, the availability of treatment to prevent disease during a latent period, and cost considerations." These initial principles and goals have been further elaborated and defined in the last five decades. The principles from Wilson and Jungner[46] have been used to guide policies regarding the use of genetic testing in a population screening program. In the United States, newborn

screening and carrier testing are examples of the use of genetic testing in population screening programs.

'Genetic Screening: Programs, Principles, and Research' is the report of the Committee for the Study of Inborn Errors of Metabolism (SIEM Committee) which was published in 1975, three years after the Committee's first meeting in August of 1972[48]. In this report, the Committee stated: "As new screening tests are devised, they should be carefully reviewed. If the experimental rate of discovery of new genetic characteristics means an accelerating rate of appearance of new screening tests, now is the time to develop the medical and social apparatus to accommodate what later on may otherwise turn out to be unmanageable growth." The general recommendations of the Committee are still used today[49] and are quoted below[48].

Recommendations of the SIEM Committee for Genetic Screening:

"Genetic screening when carried out under controlled conditions is an appropriate form of medical care when the following criteria are met:

1) There is evidence of substantial public benefit and acceptance, including acceptance by medical practitioners.
2) Its feasibility has been investigated, and it has been found that benefits outweigh costs, appropriate public education can be carried out, test methods are satisfactory, laboratory facilities are available, and resources exist to deal with counseling, follow-up and other consequences of testing.
3) An investigative pretest of the program has shown that costs are acceptable, education is effective, informed consent is feasible, aims of the program with regard to the size of the sample to be screened, the age of the screenees, and the setting in which the testing is to be done have been defined, laboratory facilities have been shown to fulfill requirements for quality control, techniques for communicating results are workable, qualified and effective counselors are available in sufficient number, and adequate provision for effective services has been made.
4) The means are available to evaluate the effectiveness and success of each step in the process."

2.3.2 Current Genetic Population Screening Programs

2.3.2.1 Newborn Screening

At birth, all infants born in hospitals in the United States use a heel-stick test to screen for a number of conditions. The disorders on a newborn screening panel are determined at the state level and vary from state to state, though there are 28 "core" conditions which all states screen for[50]. The technology used in the testing (Guthrie assay, tandem mass spectrometry, etc.) is also decided by each state and may vary from state to state[47]. According to the National Institute of Health, the intent of newborn screening is to detect conditions in newborns that can be debilitating or fatal but where outcomes can be improved if treatment is started early[51]. This is often before the newborn shows signs or symptoms of these conditions.

The Discretionary Advisory Committee on Heritable Disorders in Newborns and Children was chartered in April 2013 and has since made recommendations for a recommended uniform screening panel (RUSP) in order to combat the lack of consistencies between states. All states use this recommended panel at the minimum and some have chosen to include additional disorders not on the RUSP. Recently there has been much controversy surrounding the addition of metabolic/lysosomal storage disorders not on the RUST to state newborn screening panels because many do not have treatments. Furthermore, the screening for these conditions themselves has not been proven to be effective and thus do not meet the recommendations made by William and Jungner or by the SIEM Committee for population screening[52].

2.3.2.2 Carrier Screening for Single Gene Disorders

The first genetic condition for which community-based screening programs for autosomal recessive genetic conditions were utilized was Tay-Sachs disease[53]. Programs screening for Tay-

Sachs disease were initiated in 1971 and have since become an example for other programs due to the success in reducing the incidence of babies born with Tay-Sachs[47]. Carrier screening for many autosomal recessive genetic conditions are now made available to couples who are expecting a baby. Testing for certain conditions offered typically depends on the ethnicity of the soon-to-be parents and/or family history. For example, those of Mediterranean descent can be offered thalassemia carrier testing and pregnant women of any ethnicity should be offered cystic fibrosis carrier testing[47].

Carrier screening for certain conditions can be ordered by physicians or licensed genetic counselors and has also more recently become available through direct-to-consumer genetic testing labs. For example, the company 23andMe offers genetic testing of a few common mutations for 36 autosomal recessive conditions that consumers can order directly from 23andMe.

2.4 DIRECT TO CONSUMER GENETIC TESTING

Direct-to-consumer (DTC) genetic testing was first introduced in 2006 and allows an individual in the general population to order a genetic test directly from a lab, without the ordering medium of a physician or other healthcare professional such as a genetic counselor[54]. Those in favor of DTC genetic testing have argued that consumers should have the ability to access their own personalized risk information in order to empower the consumer to have the knowledge about diseases risks and motivation to make lifestyle and/or treatment choices that may prevent the disease[54]. However, concerns have arisen from professional organizations, governmental regulators, and other experts in the field. The professional organizations include the American

Society of Human Genetics (ASHG), the American College of Medical Genetics and Genomics (ACMG) and the governmental regulators include the Food and Drug Administration (FDA) and the Government Accountability Office (GAO). The concerns raised by these organizations include the potential for consumer misinterpretation of test results and other misunderstandings as well as a misuse of health care resources, and a possibility of psychological harms[54].

Misinterpretation of test results may result in unnecessary medical or other health-related decisions in the case of the perception of results to be higher risk than they actually may be and possible false reassurance in the case of the perception of results to be lower risk than they actually may be[54]. The possibility for misinterpretation is one of the reasons that test results are currently delivered via a trained professional (i.e. a genetic counselor or a physician).

2.5 IMPORTANCE OF GENETIC COUNSELING

It has been recommended by the American Society of Clinical Oncology (ASCO) and certain advocacy groups such as Facing Our Risk of Cancer Empowered (FORCE) that genetic testing for hereditary cancer syndromes take place in a setting with informed consent and with professional genetic counseling both pre- and post-genetic testing[31]. These recommendations have been due to the complexities that are involved in interpreting results in the context of the patient's personal and family history of cancer[6]. Many of the research studies regarding outcomes of genetic testing, such as psychosocial implications and patient's medical management decisions following testing, have taken place in the context of genetic counseling.

In 2015, Armstrong *et al*.[55], published a study on the utilization and outcomes of *BRCA* testing and counseling and found that "individuals who received genetic counseling from a GC

demonstrated higher BRCA testing knowledge scores and expressed greater self-reported understanding of the information they received prior to testing." It was also found that the patients who received genetic counseling from a genetic counselor were more satisfied in all measured categories compared to all other clinicians[55] including "explained things clearly," "listened to what I had to say," "used language I understood," "provided new information," "really understood my concerns," "cares for me," "lessened my worries," and "helped me cope better."

2.6 PSYCHOSOCIAL IMPLICATIONS AND MOTIVATIONS FOR GENETIC TESTING FOR CANCER RISK

Psychosocial implications of genetic testing have been well studied and reported on in the literature. Pasacreta[56] found motivations for genetic testing for hereditary breast and ovarian cancer (HBOC) included: (1) learning information about their children's risk; (2) to inform decisions about how often cancer screening should take place and/or surgery would be an option; (3) to relieve uncertainty; (4) to inform life decisions; and (5) to gain information about HBOC for their own purposes and their families'. Reasons found for deciding to not undergo testing included fear of insurance discrimination and a possible personal inability to emotionally deal with the information that could be gained from genetic testing[56]. Wakefield *et al.*[57] compared the attitudes towards genetic testing for cancer risk for HBOC compared to Lynch syndrome and reported the following findings: "(1) that there may be differences in the perceived benefits of genetic testing for individuals susceptible to different hereditary cancer syndromes; (2) affected individuals considering undergoing mutation search may not fully understand the implications of

receiving an inconclusive or 'mutation not found' result; (3) individuals considering genetic testing for cancer risk may be more concerned about the potential psychological impact of genetic testing than the evidence warrants, and last, (4) eliciting patients' perceived pros and cons of testing can provide valuable information to improve individual patient care and the development of patient education materials."

Specific to implications for population screening, a study was conducted using interviews and the analysis technique of grounded theory, of 14 female, asymptomatic carriers of *BRCA1/2* mutations, who belonged to families with a low prevalence of cancer. Shkedi-Rafid *et al*.[58] found that "(1) having no history of cancer in the immediate family was a source of optimism but also of confusion, (2) engaging in intensified medical surveillance and undergoing preventive procedures was preceived as health-promoting but also tended to induce a sense of physical and psychological vulnerability; and (3) there was overall support for BRCA pouplation screening, with some reservations."

2.7 AMAZON MECHANICAL TURKS

Amazon Mechanical Turks (MTurk) is the dominant method of crowdsourcing used by researchers in the academic setting[59]. MTurk has recently become a popular source of research participants and has been used in this capacity for more than five years[59]. There is a growing body of literature both using MTurk as the participant sample and on the demographics and characteristics of the workers of MTurk. While workers of MTurk have been found to not be representative of the general population as a whole, they have been found to be more diverse than the typical samples used in research such as college students or community samples[60,59].

When directly comparing studies using college student samples with MTurk samples, MTurk samples have been found to be more representative of the general population[61]. When MTurk samples are directly compared with other web-based probability samples, MTurk samples are less representative of the general population as a whole[60,62,63]. These comparisons with the general population are in terms of income, race, gender, and marital status.

2.7.1 Demographics of MTurk

The demographic characteristics of the MTurk population have been studied and reported in the literature. Amazon states that they have more than 500,000 registered workers of MTurk. The workers primarily consist of individuals from the United States and from India, although individuals from any country can register and be a worker for MTurk[59]. Many researchers limit their sample to only workers from the United States.

As a whole, workers tend to be better educated and above average in cognitive skills. They are generally younger than the population as a whole[64,65]. The workers also tend to be more liberal and less religious than the general population[66]. MTurk workers are more likely to identify as LGBTQ[59]. Asian-Americans and European-Americans are overrepresented in the MTurk workforce. African Americans and Hispanics are underrepresented in the MTurk workforce[65]. MTurk workers are more likely to be unemployed or underemployed and have lower personal incomes[67]. Workers are less likely to be married and less likely to own their own home[67,60]. However, the workers are only slightly less likely to have biological children, and may be more likely to have stepchildren[67]. There have been inconsistent findings regarding the mental health, specifically of the presence depression and anxiety in MTurk workers[67,68].

3.0 MATERIALS AND METHODS

3.1 DESIGN AND RATIONALE

The survey was designed through collaboration with several faculty members in the Graduate School of Public Health. There are four primary sections of the survey: initial interest level, six result scenarios, post-survey interest level and ordering preference, and demographics. Questions were specifically designed to elicit information relating to the interest level of the participants, their motivations for wanting testing or not, and some possible psychosocial effects.

This study was made available to participants via a survey link on the Human Intelligence Task (HIT) created for Amazon Mechanical Turk workers on March 9th, 2016. The survey was closed on March 11th, 2016. The survey was revised multiple times by members of this committee and others in the Department of Human Genetics. A pilot study was conducted with respondents from the University of Northern Iowa, the University of Pittsburgh, and Amazon Mechanical Turk workers.

Approval was obtained from the Institution Review Board at the University of Pittsburgh, IRB Approval #PRO14100612 (Appendix A).

3.1.1 Pilot Study

The pilot study for this survey was conducted using two different cohorts. The first cohort consisted of individuals from the University of Northern Iowa and the University of Pittsburgh with active recruitment and participation occurring between April 20, 2015 and May 30, 2015. A total of 320 respondents were eligible (18 or older) and answered at least one question in the survey. The second cohort consisted of workers from Amazon Mechanical Turks, with active recruitment and participation occurring between July 29, 2015 and August 21, 2015. A total of 413 respondents were eligible and answered at least one question in the survey.

This study was not originally intended to be a pilot study, but after significant analysis of parts of the study, issues with the survey design were revealed. Some of these issues included possible international responses from the Amazon Mechanical Turks, insufficient demographic questions, and unnecessary questions. In the subsequent study, these were corrected and other wording edits were made as well as the addition of a few questions.

3.1.2 Survey Design

The survey began with an eligibility question to ensure the participants were 18 years or older. Any participant who was not over the age of 18 was directed to a “thank you” page at the end of the survey. The first question of the survey assessed initial interest in a genetic test that could identify a hereditary risk of cancer. Very little background was given before this question about the test itself or possible results. The purpose of asking this question without very much information was to have the ability to compare initial gut-level interest before the participant really thought through what this test may or may not mean for them. This may be similar to a

physician or other healthcare professional simply asking someone if they would like to take this test without explaining implications of such a test. This may also be similar to a direct-to-consumer company allowing an individual to simply sign up and send in a saliva sample for a genetic test like this without going through certain steps of explanation and informed consent. After the initial question to determine interest in genetic testing for hereditary cancer risk, there was a portion of the survey that involved the participant answering several questions related to six different possible scenarios in the context of genetic testing (Appendix B).

A total of six scenarios were created and presented to participants after asking the initial level of interest question. These six scenarios were possible test results that one could receive after going through genetic testing. The first three scenarios were risk scenarios, and in each case, the individual in the scenario tested positive for a mutation in a specific gene that had a certain level of risk for cancer associated with it. The three risk levels were modeled on possible cancer risks with a mutation in a low-risk gene (<25%), a moderate-risk gene (25-49%), or a high-risk gene (50% or higher). The fourth and fifth scenario were both negative results, with the fifth scenario involving a diagnosis of cancer 15 years after receiving a negative result for this genetic test. The last scenario was a result of a variant of uncertain significance (VUS), where a change in the DNA was found, but the lab is unsure if that is a pathogenic, harmful mutation or a benign polymorphism. The purpose of having the participant go through each scenario was to have the participant more fully understand the possible results of genetic testing and to have them think through how these results may or may not affect different aspects of their lives.

The last portion of the survey before the demographics questions was the same question asked at the beginning of the survey. This was asked to demonstrate whether there was a difference in interest level after participants learned more about the testing and possible impacts.

Participants still interested in testing were then asked how they would prefer to have this testing coordinated, whether they would want to take this test directly from a testing lab (direct-to-consumer), coordinated by their primary care physician, or through a genetic counselor.

The survey concluded with questions relating to the demographics of the participants. Some of the demographic questions were based off of questions asked by census surveys. Other demographic questions were asked based on hypotheses of what personal factors may influence answers to the survey questions. These demographic questions included sex, age, significant family history of cancer, personal history of cancer, experience having had genetic testing, ranking of their knowledge/understanding of genetics, level of education, race/ethnicity, past or current employment in healthcare, income level, marital status, political views, level of religiosity, military service, and current region of residence in the United States.

3.2 AMAZON MECHANICAL TURKS PAYMENT AND SETTINGS

Amazon Mechanical Turks was selected as the source of participants because of the vast amount of research on this group that has been reported on in the literature as well as out of convenience. As a Requester, an account is set up from which the workers are paid a set amount for completing a “Human Intelligence Task” (HIT). An account was set up using the study email, pscstudy@pitt.edu, and $600 was deposited into the account via a WePay debit card. Each MTurk worker was paid $0.50 if he/she entered the correct code into the “submission” box. The fees collected by Amazon Mechanical Turks as a company were $0.20 per submission. The title of the HIT was “Survey about Opinions on Genetic Testing” and a link was provided once the worker accepted the HIT that took them to the Qualtrics survey.

Certain settings were used in our survey post on the Amazon Mechanical Turks. The first setting selected was not requiring the workers to be "Masters." MTurk Masters are those who have been identified by MTurk as high performing and have "demonstrated excellence across a wide range of HITs" as is stated on the website, and these workers must continue to pass the statistical monitoring to maintain this status. Requiring workers to be "Masters" could have created a bias in our sample, which was not desired. This HIT was limited to those workers located in the United States. Only workers who qualified for this HIT were able to view the HIT in order to eliminate the possibility of international responses.

3.3 DATA ANALYSIS

All data were recorded using respondent ID's by the Qualtrics Survey System through the University of Pittsburgh, insuring the participants' anonymity. The Qualtrics survey system was used to compile reports of the data, which were exported to Microsoft Excel. This excel spreadsheet of all of the compiled data was then imported into SPSS Statistics. SPSS was used to analyze the quantitative data. For this analysis, p-values of 0.050 or less were considered to be statistically significant.

3.3.1 Quantitative Analysis of Interest Level

Either Qualtrics Survey System or the data that had been imported into SPSS was used to analyze each demographic category of the respondents. Qualtrics Survey System automatically calculated Chi-squared tests and these tests were used for demographics where only 2 groups

were present (e.g. sex, significant family history of cancer, etc.). SPSS software was used to calculate one-way ANOVA tests were used for demographics with 3 or more groups present (e.g. race, level of education, age etc.). For the statistically significant demographics, percentages of respondents for each answer choice was calculated and stated.

3.3.2 Likert-Scale Psychosocial Questions

Each scenario of the survey had multiple statements that the participants were asked to rank agreement/disagreement with using a likert scale. The likert scale rankings used were; Strongly Disagree, Disagree, Neither Agree nor Disagree, Agree, and Strongly Agree. Each of these 5 rankings were coded 1 through 5 respectively to quantitatively assess the answers and differences between groups if present. Independent sample, 2-tailed t-tests were used to identify significant differences between demographic groups where only 2 groups exist (i.e. sex). One-way ANOVA tests were used to identify significant differences between demographic groups where 3 or more groups exist (i.e. political views). Statements were made in section 4.4 regarding significant differences between groups in each demographic. Means of each group in the demographic were used to make such statements such as “those of _____ were the most likely to agree/strongly agree with _____.”

3.3.3 Thematic Analysis

Thematic analysis was used to identify themes in the qualitative questions. Thematic analysis is used to encode qualitative data and identify themes and patterns within it. Thematic analysis is a widely-used approach to analyzing qualitative information and there are various approaches that

have been reported in the literature[69]. The approach utilized in this study was a step-by-step process developed by Braun and Clarke[70]. The step-by-step process is listed in below[70]:

1: Familiarizing yourself with your data
2: Generating Initial Codes
3: Searching for Themes
4: Reviewing Themes
5: Defining and Naming Themes
6: Producing the Report

All of the responses to the open-ended questions were read thoroughly at least twice before beginning the coding process in order to become familiar with the data (Step 1). Preliminary notes with possible coding terms were recorded (Step 2) and from there common, major themes were identified (Step 3). Usually thematic analysis is performed on more robust qualitative data such as interviews or focus groups. Since this data is not as robust, and most responses are limited to a few words to a sentence, many of the initial codes either became themes or were grouped to fit a broader theme (Step 4/5). The thematic analysis performed was inductive and data-driven as themes were not pre-set but rather emerged after the responses were read and preliminarily analyzed.

Participants' answers to these questions were divided by question into separate Microsoft Excel files. These excel tables were then imported into Microsoft Word. The highlighting tool was used in Microsoft Word to highlight the identified themes. The number of participants' whose response fit into a certain theme was quantified using percentages and used to draw conclusions.

4.0 RESULTS

4.1 SURVEY COMPLETION RATE

One thousand and forty-six Amazon Turk workers clicked on the survey link and responded to the eligibility question of the survey. One of these workers was not eligible to participate in this research study because he or she was not 18 years of age. Of those workers eligible, one thousand and forty workers responded to at least one question of the survey and eight hundred and sixty-one workers fully completed the survey. This gives a survey completion rate of 82.8% (861/1040).

4.2 DEMOGRAPHICS

Table 1 illustrates the specific breakdown of the respondent characteristics. Participants ranged in age from 18 – 83 years old with the majority being between the ages of 25-39 (52.96%). More females (55.75%) participated in the survey than males (44.25%). The majority of participants had a post-high school education, with approximately 16% having a graduate or professional degree, 38% having a bachelor degree, 10% having an associate degree, and 27% having some college, but no degree. The majority of the participants were white (80.95%).

The number of married (41.93%) and never-married (43.90%) participants were similar and made up the bulk of respondents. The majority of respondents reported that they have not ever served in the military (93.96%). The majority of participants have never been employed in healthcare (79.67%).

Respondents were from various regions of the United States. The largest portion of respondents lived in the Southeast (25.44%). The largest portion of respondents had liberal political views (45.41%).

When asked if they had a significant family history of cancer, 543 (63.07%) participants reported that they did not have a significant family history of cancer. Of the 861 respondents, 35 (4.07%) had personally had cancer. Forty-eight (5.57%) respondents had had some sort of genetic testing in the past.

The respondents were asked to rank their knowledge and understanding of genetics. Fifty-three (6.16%) respondents ranked their knowledge/understanding of genetics as ‘excellent,’ 282 (32.75%) ranked their knowledge/understanding of genetics as ‘good,’ 441 (51.22%) ranked their knowledge/understanding of genetics as ‘average,’ and 85 (9.87%) ranked their knowledge/understanding of genetics as ‘poor.’

Table 1: Demographics of Survey Respondents

Characteristic/Demographic	Categories	Number (n=861)	Percentage (%)
Sex	Male	381	44.25
	Female	480	55.75
Education	<12th grade/no diploma	3	0.35
	High School or GED	72	8.36
	Some college/no degree	236	27.41
	Associate Degree	85	9.87
	Bachelor Degree	329	38.21
	Graduate/Professional Degree	136	15.80
Age	18-24	111	12.89
	25-29	190	22.07
	30-39	266	30.89
	40-49	137	15.91
	50-59	97	11.27
	60-69	56	6.50
	70+	4	0.46
Race/Ethnicity	White	697	80.95
	Black or African American	61	7.08
	Hispanic or Latino	39	4.53
	Asian	45	5.23
	Native Hawaiian or Pacific Islander	2	0.23
	American Indian or Alaska Native	4	0.46
	Other	13	1.51
Household Income Level	Less than $10,000	46	5.34
	$10,000 – 19,999	76	8.83
	$20,000 – 29,999	109	12.66
	$30,000 – 39,999	123	14.29
	$40,000 – 49,999	110	12.78
	$50,000 – 74,999	192	22.30
	$75,000 – 99,999	99	11.50
	$100,000 – 149,999	77	8.94
	$150,000 or more	29	3.37
Marital Status	Married	361	41.93
	Never Married	378	43.90
	Widowed	14	1.63
	Divorced	82	9.52
	Separated	26	3.02
Military Service	Yes	52	6.04
	No	809	93.96

Table 1 continued:

Region of the US currently living in	Northeast (PA, MD, DE, NJ, CT, RI, MA, NH, ME, VT, NY, DC)	159	18.47
	Southeast (WV, VA, NC, SC, GA, FL, AL, MS, LA, AR, TN, KY)	219	25.44
	Midwest (OH, MI, IN, IL, WI, MN, IA, MO, ND, SD, NE, KS)	200	23.23
	Southwest (OK, TX, NM, AZ)	106	12.31
	West (WA, OR, ID, MT, WY, CO, UT, NV, CA)	173	20.09
	Alaska or Hawaii	2	0.23
	US Territory (American Samoa, Guam, Northern Mariana Islands, Puerto Rico, US Virgin Islands)	2	0.23
Political Views	Liberal	391	45.41
	Moderate	265	30.78
	Conservative	205	23.81
Work/have worked in healthcare	Yes	175	20.33
	No	686	79.67
Have had genetic testing	Yes	48	5.57
	No	813	94.43
Significant Family History of Cancer	Yes	318	36.93
	No	543	63.07
Personal History of Cancer	Yes	35	4.07
	No	826	95.93
Ranking Knowledge of Genetics	Excellent	53	6.16
	Good	282	32.75
	Average	441	51.22
	Poor	85	9.87
“Religion is an important part of my life” (likert scale)	Strongly Disagree	322	37.40
	Disagree	105	12.20
	Neither Agree nor Disagree	91	10.57
	Agree	203	23.58
	Strongly Agree	140	16.26

4.3 INTEREST LEVEL IN TAKING A GENETIC TEST FOR HEREDITARY CANCER

Study participants were asked if they would be interested in a genetic test that tests the known cancer genes both at the beginning of the survey and after the scenario portion of the survey at the end. The three possible options for this question were that the participant would take the test immediately if it were possible, they would consider taking this test in the future, or that they would never take a test like this. Table 2 and Figure 2 illustrate the participants' responses to this question, at the beginning and the end of the survey.

4.3.1 Initial Interest Level

At the beginning of the survey, the majority of respondents were interested in taking a cancer genetic test immediately (71.44%, n = 1040). Two hundred and thirty respondents (22.11%) were not currently interested, but would consider it later in life and 67 respondents (6.44%) would never take this genetic test.

Differences in initial interest in taking a genetic test for hereditary cancer risk existed between several demographic groups. Those with a significant family history of cancer were more likely (p-value = <0.001) to be interested in taking a test like this immediately (80.50%, n=318) compared to those without a significant family history of cancer (68.69%, n=543). Respondents who ranked their knowledge/understanding of genetics as "good" were significantly (p-value = 0.029) more likely (79.79%, n = 282) to be interested in taking this test immediately compared to those ranked their knowledge/understanding of genetics as "excellent" (67.92%, n = 53), "average" (70.30%, 441), and "poor" (68.24%, n = 85).

There were not statistically significant differences found in the following demographics: sex, genetic testing experience, personal history of cancer, military service, education level, race/ethnicity, income level, healthcare employment, marital status, level of religiosity, political views, or geographic region.

4.3.1.1 Themes identified for those interested immediately

Those participants who answered "Yes, I would take that test today if I could" to the initial question of interest, were asked "why would you want to take a test like this?" The major themes identified in the participants' responses to this question were: 1) knowledge or curiosity; 2) precaution/preventative measures/preparation; 3) clarifying personal cancer risks; 4) experiences with cancer (family history or personal experience); 5) children or future generations. The prevalence of each of these themes was calculated (Table 2). Specific examples of themes from participant quotes are shown in Table 3.

Table 2: **Themes identified in those Immediately Interested**

Theme	**n (%), n = 734**
Knowledge or Curiosity	439 (59.81)
Precaution/preventative measures/preparation	285 (38.83)
Clarifying Personal Cancer Risks	185 (25.20)
Experiences with Cancer	112 (15.26)
Children or future generations	57 (7.77)

Table 3: **Participant Quotes**

Theme	Quote
Knowledge or Curiosity	"I would want to take a test like this because of curiosity."
Precaution/preventative measures/preparation	"To help me watch for potential warning signs of cancer that I'm predisposed to so that I could get diagnosed early."
Cancer Risks	"In order to know if I have increased risk of cancer"
Experiences with Cancer	"Because my father died of multiple myeloma and my uncle died of colon cancer. I would like to know whether I have the gene for either of these diseases."
Children or future generations	"I would want to know to prepare for later in life and to avoid passing it to my future children."

4.3.1.2 Themes identified for those possibly interested in the future

Participants who answered "currently not interested, but would consider it later in life" to the initial question of interest in this genetic test, were asked "why would you consider taking this test in the future?" A total of 227/1025 (22.15%) respondents answered this question and themes were identified. Some of these major themes are the same as major themes identified in those wanting to immediately take this test. The themes identified were: 1) knowledge or curiosity; 2) precaution/preventative measures/preparation; 3) would like the option in the future/when older; 4) Psychological effects/anxiety; 5) Give research time to advance/"bugs" worked out; and 6) If things change/new family members get diagnosed. Prevalence of the major themes identified are depicted in Table 4.

Table 4: **Themes identified in Individuals currently not interested in testing, but may be in the future**

Theme	n (%), n = 227
Knowledge or Curiosity	49 (21.59)
Precaution/preventative measures/preparation	48 (21.15)
Would like the option in the future/when older	52 (22.91)
Psychological effects/anxiety	14 (6.17)
Give research time to advance/"bugs" worked out	9 (3.96)
If things change/new family members diagnosed	18 (7.93)

Table 5: **Participant Quotes**

Theme	Quote
Knowledge or Curiosity	"Curiosity, not that I care much."
Precaution/preventative measures/prepare	"Just so I might be prepared for what might be coming."
Would like the option in the future/when older	"I would want to know later in life to see what to possibly expect as I get older"
Psychological effects/anxiety	"I am not mentally prepared to take it now, but I would take it later since I've had family members with cancer"
Give research time to advance/"bugs" worked out	"It would give time for any 'bugs' to be worked out of it (i.e. false postives), and it may be something useful in the future as far as taking possible preventative measures that I might not otherwise take."
If things change/new family members diagnosed	"If I had a reason to believe it was a good idea, such as other family members developing cancer that could be hereditary."

4.3.1.3 Themes identified for those not interested

Participants who answered "no, I would never take a test like that" to the initial question of interest in this genetic test, were asked "why would you never take a test like this?" A total of 64/1025 (6.24%) respondents answered this question and major themes were identified. The major themes identified were: 1) conspiracy theory/distrust; 2) psychological stress/anxiety; and 3) inevitability (cannot change anything); 4) age; and 5) no interest. Prevalence of the major themes identified are depicted in Table 6 and example quotes are illustrated in Table 7.

Table 6: Themes from Individuals not Interested in Testing

Theme	n (%), n = 64
Conspiracy Theory/Distrust of the test	8 (12.50)
Psychological Stress/Anxiety	22 (34.38)
Inevitability (cannot change anything)	9 (14.06)
Age	5 (7.81)
No Interest	11 (17.19)

Table 7: Participant Quotes for those Not Interested in Testing

Theme	Quote
Conspiracy Theory/Distrust of the test	"All genetic testing has the possibility of government data collection and misuse"
Psychological Stress/Anxiety	"For me personally, it would cause a great deal of stress and worrying."
Inevitability (cannot change anything)	"I do not wish to know something like that, since I can't do anything about it anyway and it would make me feel anxious and depressed."
Age	"I'm old and I have no children. If I get a hereditary cancer then so be it."
No Interest	"There is no history of cancer in my family and I really just don't have any interest in taking a test like this."

4.3.2 Interest Level after the Result Scenarios

By the end of the survey, fewer participants were interested in taking a cancer genetic test immediately (64.92%), more participants were currently not interested but would consider taking it later in life (26.84%), and more participants decided they would never take a test like this (9.64%).

Analyzing the demographic differences for the respondents' answers to the interest level question after the scenario portion of the survey, those with a significant family history of cancer were significantly more likely (p-value = <0.001) to be interested in taking a test like this immediately (74.53%, n=318) compared to those without a significant family history of cancer (59.30%, n=543). Those who had previously undergone some sort of genetic testing were more likely (p-value = <0.001) to be interested in taking a test like this immediately (81.25%, n = 48) compared to those who have not had genetic testing (63.96%, n = 813). Respondents who ranked their knowledge/understanding of genetics as "good" were significantly (p-value = 0.004) more likely (70.92%, n = 282) to be interested in taking this test immediately and those who ranked their knowledge as "poor" were significantly less likely be interested in taking this test immediately (51.76%, n = 44) thank those who ranked their knowledge as "excellent" (60.37%, n = 53) or "average" (64.17%, n = 441). Those without current or past employment in healthcare were significantly (p-value = 0.020) more likely to be interested in taking this test immediately.

There were not statistically significant differences found in the following demographics: sex, personal history of cancer, military service, education level, race/ethnicity, income level, marital status, level of religiosity, political views, or geographic region.

4.3.3 Comparison of Interest Level Before/After Scenarios

Table 8 and Figure 2 illustrate the participants' responses to this question, at the beginning and the end of the survey.

Table 8: Participant Interest; before/after the survey

		Interest at the end of the survey			
		Yes, today	**Currently no, consider later in life**	**Never**	***Total:***
Interest at the beginning of the survey	**Yes, today**	520	86	23	*629*
	Currently no, consider later in life	39	124	17	*180*
	Never	0	9	43	*52*
	Total:	*559*	*219*	*83*	***N = 861***

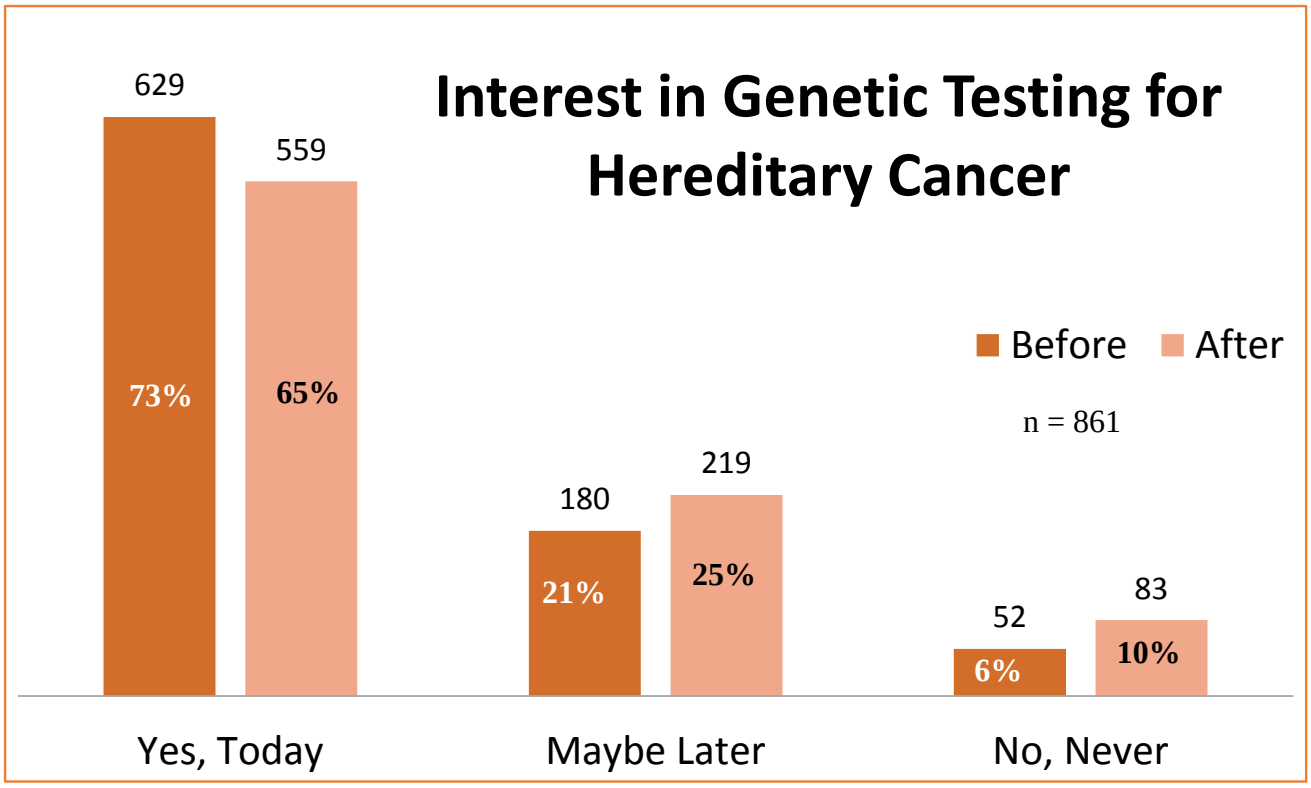

Figure 1:

Percentage of Participants Interested in Testing; Before/After

A total of 109 (17.33%) participants who had initially wanted to take this test today if they could, reconsidered after going through the scenario portion of the survey. Of the 629 participants who answered in the beginning of the survey that they would be interested in taking this test immediately, 86 (13.67%) participants decided by the end of the survey that they were actually not currently interested, but would consider it later in life and 23 (3.66%) participants decided by the end of the survey that they actually would never take a test like this. A total of 109 (17.33%) participants who had initially wanted to take this test today if they could, reconsidered after going through the scenario portion of the survey.

Of the 180 participants who answered in the beginning of the survey that they were currently not interested, but would consider taking it later in life, 39 (21.67%) decided by the end of the survey that they would actually take this test today if they could, and 17 (9.44%) decided by the end of the survey that they would never take a test like this.

For the 52 participants who originally answered that they would never take a test like this, 9 (17.31%) of them decided that they were currently not interested, but would consider it later in life. There were no participants who answered that they would never take a test like this in the beginning of the survey who had decided at the end of the survey that they would take this test today if they could.

The interest of those who answered that they had a significant family history of cancer differed from those who did not have a significant family history of cancer. The observed differences between groups occurred for the demographics of: family history of cancer, previous experience with genetic testing, knowledge/understanding of genetics, and employment in healthcare. It is also interesting to note that those who had previously had genetic testing responded exactly the same to the interest level question in both the beginning of the survey and at the end of the survey.

There was not a statistically significant difference found between individuals who have worked in healthcare and those who have not for the interest question asked at the beginning of the survey, however, there was a difference between these groups that was found to be statistically significant for the interest question at the end of the survey.

4.4 POSSIBLE RESULT SCENARIOS

Each scenario was designed to be a possible result of genetic testing in the context of population screening. For each scenario, participants were asked to indicate the degree to which they agreed or disagreed with certain statements. They were then asked 3 open-ended questions to allow the participants to elaborate more on their feelings and thought processes related to these scenarios. These questions were designed to encourage the participants to process more about how genetic testing may impact different parts of their lives given possible results. The statistically significant results are described. As some of these demographic groups are quite small, there is also a possibility that there are significant differences between other groups that were not detected by t-tests or ANOVA because there is not sufficient power.

When comparing the demographics in the scenarios, it is important to note that there may be significant demographic differences between groups that were not found to be statistically significant in our survey because there may not have been enough power to find statistically significant differences due to the small sample size of some of the variables.

4.4.1 Scenario 1

SCENARIO: You go through comprehensive genetic testing for cancer genes and are found to have a changed gene that is harmful and increases your risk of a certain type cancer (for example, colon cancer) to 50%. This would mean that over the course of your lifetime, there is a 1 in 2 chance that you would develop that certain type of cancer.

Table 9 illustrates the results from this scenario. In this first scenario, 63.36% (n = 958) of respondents agreed or strongly agreed with the statement, “this test result would affect my everyday life.” More than half of respondents (56.47%, n = 958) answered either “agree” or “strongly agree” to the statement, “this test result would affect my mental health.” The majority of participants (56.99%, n = 958) disagreed or strongly disagreed with the statement “this test result would impact my ability to find a partner (assuming you did not have a partner at the time).” The majority of participants (70.67%, n = 958) did not feel that this test result would impact their employment, disagreeing with the statement “this result would impact my ability to find and/or keep a job.” More participants agreed or strongly agreed (45.82%, n = 958) with the statement “this test result would impact my decision on whether or not to have children (each child would have a 50% chance of inheriting the harmful gene from you).” The majority of participants (66.81%, n = 958) agreed or strongly agreed with the statement “I would talk to my family about this gene and my test result.”

Table 9: Scenario 1 Likert Scale Results (n = 958)

Statement	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
This test result would affect my everyday life.	50 (5.22%)	164 (17.12%)	137 (14.30%)	449 (46.87%)	158 (16.49%)
This test result would affect my mental health	51 (5.32%)	188 (19.62%)	178 (18.58%)	382 (39.87%)	159 (16.60%)
This test result would impact my ability to find a partner (assuming you did not have a partner at the time).	231 (24.11%)	315 (32.88%)	198 (23.08%)	166 (17.33%)	48 (5.01%)
This test result would impact my ability to find and/or keep a job.	312 (32.57%)	365 (38.10%)	145 (15.14%)	102 (10.65%)	34 (3.55%)
This test result would impact my decision on whether or not to have children. (Each child would have a 50% chance of inheriting the harmful gene from you).	135 (14.09%)	192 (20.04%)	192 (20.04%)	301 (31.42%)	138 (14.41%)
I would talk to my family about this gene and my test result.	18 (1.88%)	25 (2.61%)	75 (7.83%)	427 (44.57%)	413 (43.11%)

4.4.1.1 Comparison of Demographics for Scenario 1

T-tests or one-way ANOVA statistical tests were performed where appropriate to determine if there were any groups that were statistically significantly different from each other. Table 10 illustrates the specific p-values of these differences between groups.

Table 10: Scenario 1 Statistically Significant Differences in Demographic Groups

Statement	Demographic	p-value
This test result would affect my everyday life.	Military Service	0.014
This test result would affect my mental health.	Sex	0.023
	Rank Knowledge	0.020
This test result would impact my ability to find a partner.	Sex	0.001
	Family History of Cancer	0.033
	Rank Knowledge	0.034
	Education Level	0.013
	Income Level	0.008
	Race/Ethnicity	0.013
This test result would impact my ability to find and/or keep a job.	Sex	<0.001
	Education Level	0.002
	Income Level	<0.001
	Race/Ethnicity	0.003
This test result would impact my decision on whether or not to have children.	Genetic Testing Experience	0.023
	Marital Status	0.029
	Political Views	0.015
I would talk to my family about this gene and my test result	Marital Status	0.050

Those without a family history of cancer were more likely (p-value = 0.033) to agree or strongly agree that this test result would affect the ability to find a partner. Those who had not had genetic testing were more likely (p-value = 0.023) to agree or strongly agree that this test

result would affect the decision on whether to have children or not. Those who had never served in the military were more likely (p-value = 0.014) to agree or strongly agree that this test result would impact their everyday life.

Those with an "excellent" knowledge/understanding of genetics were significantly more likely (p-value = 0.034) to disagree/strongly disagree that this test result would impact their ability to find a partner. Those with a "poor" knowledge/understanding of genetics were significantly more likely (p-value = 0.020) to agree/strongly agree that this test result would affect their mental health. Females were more likely (p-value = 0.023) to agree or strongly agree that their mental health would be affected with this test result. Men were more likely (p-value = 0.001) to agree or strongly agree that this test result would affect their ability to find a partner and were also more likely (p-value = <0.001) to agree or strongly agree that this test result would affect their ability to find and/or keep a job.

Those with some college/no degree were significantly more likely (p-value = 0.013) to disagree/strongly disagree that this test result would affect their ability to find a partner and those with less than a 12^{th} grade education were significantly more likely (p-value = 0.002) to agree/strongly agree that this test result would affect their ability to find/keep a job. Those with an income level of $150,000+ were significantly more likely (p-value = 0.008) to disagree/strongly disagree that this test result would affect their ability to find a partner and also significantly more likely (p-value = <0.001) to disagree/strongly disagree that this test result would affect their ability to find/keep a job. Those of Asian ethnicity were significantly more likely to disagree/strongly disagree (p-value = 0.013) that this test result would affect their ability to find a partner but were significantly more likely to agree/strongly agree (p-value = 0.003) that this test result would affect their ability to find/keep a job than other ethnicity groups were.

Those who were separated (marital status) were the most likely (p-value = 0.029) to agree/strongly agree that this test result would have an impact on child-bearing decisions and those who were widowed were the least likely (p-value = 0.050) to agree/strongly agree that they would discuss this gene/test result with their family. Political views had a statistically significant impact on whether this test result would impact the decision to have children or not and those who were conservative (p-value = 0.015) were the most likely to disagree/strongly disagree that this test result would have an impact on the decision to have children or not.

The t-tests performed did not show any statistically significant differences dependent on a personal history of cancer. The one-way ANOVA tests did not show any statistically significant differences between level of religiosity or for the region of the United States that the participants were located in.

4.4.2 Scenario 2

SCENARIO: You go through comprehensive genetic testing for cancer genes and are found to have a broken gene that increases your risk of a certain type of cancer (for example, colon cancer) to 80%. This would mean that over the course of your lifetime, there is a 4 in 5 chance of developing that type of cancer.

Table 11 illustrates the results from this scenario. In this scenario, the majority of participants indicated that this test result would affect their everyday life (78.17%, n = 907), and affect their mental health (74.75%, n = 907). Similar numbers of participants indicated that this test result would impact their ability to find a partner (39.47%, n = 907) as those that indicated that this would not impact their ability to find a partner (39.36%, n = 907). Most participants

indicated that this test result would not impact their ability to find and/or keep a job (53.14%, n = 907). Most participants indicated that this test result would impact the decision to have children (62.08%, n = 907). The vast majority of participants indicated that they would talk about the gene and test result with their family (90.07%, n = 907).

Table 11: Scenario 2 Likert Scale Results (n = 907)

Statement	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
This test result would affect my everyday life	35 (3.86%)	83 (9.15%)	80 (8.82%)	358 (39.47%)	351 (38.70%)
This test result would affect my mental health	34 (3.75%)	89 (9.81%)	106 (11.69%)	346 (38.15%)	332 (36.60%)
This test result would impact my ability to find a partner (assuming you did not have a partner at the time)	157 (17.31%)	200 (22.05%)	192 (21.27%)	205 (22.60%)	153 (16.87%)
This test result would impact my ability to find and/or keep a job	205 (22.60%)	277 (30.54%)	167 (18.41%)	145 (15.99%)	113 (12.46%)
This test result would impact my decision on whether or not to have children. (Each child would have a 50% chance of inheriting the harmful gene from you)	93 (10.25%)	123 (13.56%)	128 (14.11%)	259 (28.56%)	304 (33.52%)
I would talk to my family about this gene and my test result	18 (1.98%)	21 (2.32%)	51 (5.62%)	254 (28.00%)	563 (62.07%)

4.4.2.1 Comparison of Demographics for Scenario 2

Table 12 shows the statistically significant differences between demographic groups for the second scenario.

Table 12: Scenario 2 Statistically Significant Differences in Demographic Groups

Statement	Demographic	p-value
This test result would affect my everyday life.	Sex	0.004
This test result would affect my mental health.	Sex	<0.001
	Marital Status	0.018
	Political Views	0.034
This test result would impact my ability to find a partner.	(none)	
This test result would impact my ability to find and/or keep a job.	Education Level	0.039
	Income Level	0.007
This test result would impact my decision on whether or not to have children.	Marital Status	0.029
	Political Views	0.041
I would talk to my family about this gene and my test result	Family History of Cancer	<0.001
	Marital Status	<0.001

Females were more likely to agree or strongly that their everyday life (p-value = 0.004) and mental health (p-value = <0.001) would be affected with this test result. Those with a significant family history of cancer were more likely (p-value = <0.001) to indicate that they would talk about this gene/test result with their family members. Those whose highest level of education was high school/GED or lower were significantly more likely (p-value = 0.039) to agree/strongly agree that this test result would affect their ability to find/keep a job.

The participants whose household income level was less than $10,000 were significantly more likely (p-value = 0.007) to agree/strongly agree that this test result would affect their ability to find/keep a job. Those who were widowed or divorced were significantly less likely (p-value =

0.029) to agree/strongly disagree that this test result would impact their decision to have kids. Those who were never married were the most likely (p-value = 0.018) to agree/strongly agree that this test result would affect their mental health. Those who were widowed were significantly less likely (p-value = <0.001) to agree/disagree that they would discuss this test result with their family. Those who were liberal were significantly more likely (p-value = 0.041) to agree/strongly agree that this test result would impact their decision to have children compared with those who were moderate or conservative. Those who were liberal were also significantly more likely (p-value = 0.034) to agree/strongly agree that this test result would affect mental health.

Statistically significant differences for the demographics of personal history of cancer, previous genetic testing experience, military service, knowledge/understanding of genetics, level of religiosity, and what region of the United States they reside in were not found for this scenario.

4.4.3 Scenario 3

SCENARIO: You go through comprehensive genetic testing for cancer genes and are found to have a broken gene that increases your risk for a certain type of cancer to 15-25%. This would mean that over the course of your lifetime there is approximately a 1 in 5 chance of developing that type of cancer.

Table 11 illustrates the full results from the likert-scale questions in this scenario. In this first scenario, 50.67% (n = 884) of respondents disagreed or strongly disagreed with the statement, “this test result would affect my everyday life.” More than half of respondents

(69.12%, n = 884) answered either “agree” agree or strongly agree” to the statement, “this test result would affect my mental health.” The majority of participants (75.79%, n = 884) disagreed or strongly disagreed with the statement “this test result would impact my ability to find a partner (assuming you did not have a partner at the time).” The majority of participants (81.23%, n = 884) did not feel that this test result would impact their employment, disagreeing with the statement “this result would impact my ability to find and/or keep a job.” More participants disagreed or strongly disagreed (59.61%, n = 884) with the statement “this test result would impact my decision on whether or not to have children (each child would have a 50% chance of inheriting the harmful gene from you).” The majority of participants (69.12%, n = 884) agreed or strongly agreed with the statement “I would talk to my family about this gene and my test result.”

Table 13: Scenario 3 Likert Scale Results (n = 884)

Statement	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
This test result would affect my everyday life	139 (15.72%)	309 (34.95%)	182 (20.59%)	207 (23.42%)	47 (5.32%)
This test result would affect my mental health	44 (4.98%)	98 (11.09%)	131 (14.82%)	340 (38.46%)	271 (30.66%)
This test result would impact my ability to find a partner (assuming you did not have a partner at the time)	336 (38.01%)	334 (37.78%)	136 (15.38%)	57 (6.45%)	21 (2.38%)
This test result would impact my ability to find and/or keep a job	383 (43.33%)	335 (37.90%)	103 (11.65%)	42 (4.75%)	21 (2.38%)
This test result would impact my decision on whether or not to have children. (Each child would have a 50% chance of inheriting the harmful gene from you)	225 (25.45%)	302 (34.16%)	198 (22.40%)	116 (13.12%)	43 (4.86%)
I would talk to my family about this gene and my test result	44 (4.98%)	98 (11.09%)	131 (14.92%)	340 (38.46%)	271 (30.66%)

4.4.3.1 Comparison of Demographics for Scenario 3

Table 14 illustrates statistically significant findings in demographic differences for the third scenario.

Table 14: Scenario 3 Statistically Significant Differences in Demographic Groups

Statement	Demographic	p-value
This test result would affect my everyday life.	Sex	0.044
	Race/Ethnicity	0.015
This test result would affect my mental health.	Race/Ethnicity	0.030
This test result would impact my ability to find a partner.	Sex	0.027
	Education Level	0.001
	Race/Ethnicity	0.001
	Income Level	<0.001
	Region of Residence	0.003
This test result would impact my ability to find and/or keep a job.	Education Level	0.003
	Race/Ethnicity	0.005
	Income Level	<0.001
	Region of Residence	0.004
This test result would impact my decision on whether or not to have children.	Education Level	0.008
	Race/Ethnicity	0.047
I would talk to my family about this gene and my test result	Family History of Cancer	<0.001
	Marital Status	0.001
	Level of Religiosity	0.024
	Genetic Testing Experience	0.009

Those with a significant family history of cancer were more likely (p-value = <0.001) to indicate that they would talk about this gene/test result with their family members. Those who had never had genetic testing were less likely (p-value = 0.009) to indicate that they would talk about this gene/test result with their family members. Those with some college/no degree were the most likely (p-value = 0.001) to disagree/strongly disagree that this result would impact their ability to find a partner as well as the most likely (p-value = 0.003) to disagree/strongly disagree that this result would impact their ability to find/keep a job. Those with a Bachelor degree were

the most likely (p-value = 0.008) to disagree/strongly disagree that this result would impact their decision to have children or not. Those with an income of $100,000 - $149,999 were found to be the most likely (p-value = <0.001) to disagree/strongly disagree that this test result would affect their ability to find a partner as well as the most likely (p-value = <0.001) to disagree/strongly disagree that this test result would affect their ability to find/keep a job.

Those who were married were the most likely (p-value = 0.001) to agree/strongly agree that they would discuss this gene and test result with their family. Those who strongly agreed with the statement "religion is an important part of my life" were the most likely (p-value = 0.024) to agree/strongly agree that they would talk to their family about this gene and test result. The region of the United States that the participant currently resides in was found to be statistically for the ability to find a partner (p-value = 0.003) and the ability to find or keep a job (p-value = 0.004). There were only 2 participants from Alaska or Hawaii and only 2 participants from a US Territory. The participants from Alaska or Hawaii were significantly more likely to disagree/strongly disagree that this would impact their ability to find a partner where the participants from a US Territory were significantly more likely to agree/strongly agree that this would impact their ability to find a partner. The other regions, all from the continental US, were much more similar and due to the small sample size from Alaska/Hawaii or the US Territories, these differences may not be found in a more representative sample of those regions.

Those who were Hispanic or Latino were the most likely (p-value = 0.001) to disagree/strongly disagree that this result would impact their ability to find a partner, as well as the most likely (p-value = 0.005) to disagree/strongly disagree that this result would impact their ability to find/keep a job, the most likely (p-value = 0.047) to disagree/strongly disagree that this result would impact their decision to have children, and the most likely (p-value = 0.030) to

disagree/strongly disagree that this result would affect their mental health. Those of Asian ethnicity were the most likely (p-value = 0.015) to agree/strongly agree that this test result would affect their everyday life.

Statistically significant differences for the demographics of personal history of cancer, political views, military service, and levels of knowledge/understanding of genetics were not found for this scenario.

4.4.4 Scenario 4

Scenario: You go through comprehensive genetic testing for cancer genes and are found to have an uncertain result. This means that there was a change found in a gene that is associated with a certain cancer. However, it is unclear whether that change is harmless, or if that change causes an increased risk for a certain type of cancer.

Table 15 illustrates the full results from the likert-scale questions in this scenario. In this first scenario, 56.38% (n = 869) of respondents disagreed or strongly disagreed with the statement, “this test result would affect my everyday life.” More than half of respondents (51.78%, n = 869) answered either “disagree” or strongly disagree” to the statement, “this test result would affect my mental health.” The majority of participants (77.79%, n = 869) disagreed or strongly disagreed with the statement “this test result would impact my ability to find a partner (assuming you did not have a partner at the time).” The majority of participants (80.58%, n = 869) did not feel that this test result would impact their employment, disagreeing with the statement “this result would impact my ability to find and/or keep a job.” More participants disagreed or strongly disagreed (67.21%, n = 869) with the statement “this test result would

impact my decision on whether or not to have children (each child would have a 50% chance of inheriting the harmful gene from you).” The majority of participants (55.70%, n = 869) agreed or strongly agreed with the statement “I would talk to my family about this gene and my test result.”

Table 15: **Scenario 4 Likert Scale Results (n = 869)**

Statements	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
This test result would affect my everyday life	213 (24.51%)	277 (31.87%)	184 (21.17%)	162 (18.64%)	33 (3.80%)
This test result would affect my mental health	207 (23.82%)	243 (27.96%)	180 (20.71%)	185 (21.29%)	54 (6.21%)
This test result would impact my ability to find a partner (assuming you did not have a partner at the time)	376 (43.27%)	300 (34.52%)	134 (15.42%)	41 (4.72%)	18 (2.07%)
This test result would impact my ability to find and/or keep a job	425 (48.91%)	276 (31.67%)	116 (13.35%)	33 (3.80%)	19 (2.19%)
This test result would impact my decision on whether or not to have children. (Each child would have a 50% chance of inheriting the harmful gene from you)	315 (36.25%)	269 (30.96%)	187 (21.52%)	68 (7.83%)	30 (3.45%)
I would talk to my family about this gene and my test result	115 (13.23%)	114 (13.12%)	156 (17.95%)	271 (31.19%)	213 (24.51%)

4.4.4.1 Comparison of Demographics for Scenario 4

Table 16: Scenario 4 Statistically Significant Differences in Demographic Groups

Statement	Demographic	p-value
This test result would affect my everyday life.	Race/Ethnicity	0.041
	Income	0.012
	Level of Religiosity	0.036
This test result would affect my mental health.	Genetic Testing Experience	0.004
This test result would impact my ability to find a partner.	Level of Education	<0.001
	Race/Ethnicity	0.028
	Income	0.001
	Region of Residence	0.002
This test result would impact my ability to find and/or keep a job.	Level of Education	0.002
	Race/Ethnicity	0.028
	Income	0.001
	Level of Religiosity	0.021
	Region of Residence	0.003
This test result would impact my decision on whether or not to have children.	Level of Education	0.007
	Race/Ethnicity	0.006
I would talk to my family about this gene and my test result	Genetic Testing Experience	0.011
	Level of Religiosity	0.001

Table 16 shows the statistically significant demographic differences between participants for Scenario 4. Those who had previously had genetic testing were more likely (p-value = 0.004) to state that this test result would affect their mental health and more likely to state that they would talk to their family about these test results (p-value = 0.011). Those with a High School/GED education or less were the least likely to disagree or strongly disagree that this VUS test result would affect their ability to find a partner (p-value = <0.001), affect their ability to find/keep a job (p-value = 0.002), and impact their decision about having children (p-value = 0.007).

Those of Hispanic or Latino ethnicity were the most likely to disagree/strongly disagree with the statement of this test result affecting their ability to find a partner (p-value = 0.028) as well as the ability to find/keep a job (p-value = 0.004). Those of Asian ethnicity were the most

likely (p-value = 0.006) to disagree/strongly disagree that this test result would impact their decision about having children. Those of Native Hawaiian or Pacific Islander ethnicity were the most likely (p-value = 0.041) to disagree/strongly disagree that this test result would affect everyday life and those of American Indian or Alaskan Native ethnicity were the most likely to agree/strongly agree that this test result would affect everyday life. However, there were only 2 participants of Native Hawaiian or Pacific Islander ethnicity and only 4 participants of American Indian or Alaskan Native ethnicity and these statements and result for these groups may not apply to that ethnic group as a whole.

Those who reported a household income of less than $10,000 were the least likely (p-value = 0.001) to disagree/strongly disagree that this test result would affect their ability to find a partner as well as the least likely (p-value = 0.001) to disagree/strongly disagree that this test result would affect their ability to find/keep a job and the most likely (p-value = 0.012) to agree/strongly agree that this test result would affect their everyday life.

Those who strongly disagreed with the statement “religion is an important part of my life” were the most likely (p-value = 0.021) to disagree/strongly disagree that this test result would affect their ability to find/keep a job as well as the most likely (p-value = 0.036) to disagree/strongly disagree that this test result would affect their everyday life and the least likely (p-value = 0.001) to agree/strongly agree that they would talk about this gene/test result with their family.

Region of residence in the United States was shown to have statistically significant differences between regions for the statements of ability to find a partner (p = 0.002) and ability to find/keep a job (p = 0.003) for this scenario. The extremes were again found in the groups of those residing in Alaska/Hawaii or a US Territory, with the 2 participants in Alaska or Hawaii

being the most likely to disagree/strongly disagree that this test result would affect their ability to find a partner or find/keep a job and the 2 participants in a US Territory being the most likely to agree/strongly agree that this test result would affect their ability to find a partner or find/keep a job. Because of the almost negligible amount of participants in these two groups, it is not likely that these differences would be applicable to the population at large in these two regions.

The sex of the participants, significant family history of cancer, personal history of cancer, military service, knowledge/understanding of genetics, marital status, and political views were not proven to have significant differences between groups.

4.4.5 Scenario 5

SCENARIO: You go through comprehensive genetic testing for cancer genes and are found to be negative for any changes in the genes that we can test for at this time. Although the test indicates that you are likely not at an increased risk for cancer, it is important to remember that most cancers are not hereditary, meaning that they are not caused by a change in a gene that can be passed down through families. As a result, you still could develop cancer in the future, but your risk is likely similar to other people in the general population.

Table 9 illustrates the full results from the Likert-scale questions in this scenario. In this scenario, 64.08% (n = 863) of respondents agreed or strongly agreed with the statement, “I would continue regular, early-detection screenings for cancer (mammograms, prostate exams, pap smears, etc.). More than half of respondents (73.24%, n = 863) answered either “disagree” or “strongly disagree” to the statement, “this test result would affect my everyday life.” The

majority of participants (74.39%, n = 863) disagreed or strongly disagreed with the statement "this test result would affect my mental health." The majority of participants (59.10%, n = 863) agreed or strongly agreed with the statement "I would talk to my family about this test result."

Table 17: Scenario 5 Likert Scale Results (n = 863)

N = 863	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
I would continue regular, early-detection screenings for cancer (mammograms, prostate exams, pap smears, etc.)	114 (13.21%)	69 (8.00%)	127 (14.72%)	327 (37.89%)	226 (26.19%)
This test result would affect my everyday life	340 (39.40%)	292 (33.84%)	126 (14.60%)	81 (9.39%)	24 (2.78%)
This test result would affect my mental health	362 (41.95%)	280 (32.44%)	110 (12.75%)	87 (10.08%)	24 (2.78%)
I would talk to my family about my test result	104 (12.05%)	106 (12.29%)	143 (16.57%)	289 (33.49%)	221 (25.61%)

4.4.5.1 Comparison of Demographics for Scenario 5

Table 18: Scenario 5 Statistically Significant Differences in Demographic Groups

Statement	Demographic	p-value
I would continue regular, early-detection screenings for cancer	Sex	0.005
	Knowledge of Genetics	0.042
	Political Views	0.043
This test result would affect my everyday life	Family History of Cancer	0.039
	Genetic Testing Experience	0.039
This test result would affect my mental health.	Level of Education	0.003
	Region of Residence	0.016
I would talk to my family about this gene and my test result	Sex	0.038
	Family History of Cancer	0.028
	Marital Status	0.040
	Level of Religiosity	0.001
	Political Views	0.009

There was a statistically significant difference between sexes for the statement “I would continue regular, early-detection screenings for cancer (mammograms, prostate exams, pap smears, etc.)” ($p = 0.005$). There was also a statistically significant difference between sexes for the statement “I would talk to my family about my test result” ($p = 0.038$). Females were more likely to agree or strongly agree with both of these statements.

The presence or absence of a significant family history of cancer showed some statistically differences in their answers for whether this test result would affect everyday life ($p = 0.039$) and whether they would talk to their family or not about these results ($p = 0.028$). Having had or not had genetic testing before had a statistically significant difference between groups for whether this test result would affect everyday life ($p = 0.039$).

The level of knowledge and/or understanding of genetics showed a statistically significant difference between groups for whether they would get the regular screenings for cancer currently available ($p = 0.042$). Those who ranked their knowledge/understanding as “excellent” were the most likely to agree/strongly agree that they would continue regular cancer screenings given a negative result.

Both the level of education and the region of residence in the United States showed a statistically significant difference between groups using a one-way ANOVA test for whether this test would affect mental health. The group of participants with some college/no degree were the most likely ($p = 0.003$) to disagree/strongly disagree that this result would affect their mental health. Those in the Southwest region of the United States were the most likely ($p = 0.016$) to disagree/strongly disagree that this result would affect their mental health.

Marital status showed a statistically significant difference between groups for whether they would talk to their family about the test result ($p = 0.040$). Those who were married were

the most likely to agree/strongly agree that they would talk about this test result with their family.

Level of religiosity also showed a significant difference between groups for whether they would talk to their family ($p = 0.001$) as well as showing a difference between groups for if this result would affect their everyday life ($p = 0.048$). Those who strongly disagreed with the statement "religion is an important part of my life" were the least likely to agree/strongly agree that they would talk with their family about this test result. Those who were widowed were the most likely to disagree/strongly disagree that this test result would affect their everyday life.

Political views showed a statistically significant difference between groups for whether they would continue to get the regular screenings for cancer and whether they would talk to their families about the test result. Those who were liberal were the most likely ($p = 0.043$) to agree/strongly agree that they would continue to get regular screenings for cancer. Those who were moderate were the least likely ($p = 0.009$) to agree/strongly agree that they would talk to their family about these results.

Military service, personal history of cancer, race/ethnicity, and income level were all demographics that did not show a statistically significant difference between groups in this particular scenario.

4.4.6 Scenario 6

SCENARIO: You go through comprehensive genetic testing for cancer genes and are found to be negative for any changes in the genes that we can test for at this time. (0% increased risk for hereditary cancer, your risk is likely similar to the general population). However, 15 years later, you are diagnosed with cancer.

Table 14 illustrates the full results from the likert-scale questions in this scenario. In this scenario, 54.01% (n = 861) of respondents disagreed or strongly disagreed with the statement, "I would have negative feelings about the genetic testing I had done." A somewhat similar number of participants agreed/strongly agreed (39.37%, n = 861) as did disagree/strongly disagree (45.41%, n = 861) with the statement "I would question the accuracy of the genetic testing I had done." The majority of participants disagreed/strongly disagreed (52.49%, n = 861) with the statement "I would have negative feelings about genetic testing in general." More than half of the participants agreed/strongly agreed (50.75%, n = 861) with the statement "I would want to be retested."

Table 19: **Scenario 6 Likert Scale Results (n = 861)**

Statements	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
I would have negative feelings about the genetic testing I had done	164 (19.05%)	301 (34.96%)	117 (13.59%)	204 (23.69%)	75 (8.71%)
I would question the accuracy of the genetic testing I had done	143 (16.61%)	248 (28.80%)	132 (15.33%)	222 (25.78%)	117 (13.59%)
I would have negative feelings about genetic testing in general	178 (20.67%)	274 (31.82%)	141 (16.38%)	172 (19.98%)	96 (11.15%)
I would want to be retested	124 (14.40%)	182 (21.14%)	118 (13.70%)	284 (32.98%)	153 (17.77%)

4.4.6.1 Comparison of Demographics for Scenario 6

Table 20: Scenario 6 Statistically Significant Differences in Demographic Groups

Statement	Demographic	p-value
I would have negative feelings about the genetic testing I had done	Rank Knowledge	0.021
	Race/Ethnicity	<0.001
	Income	0.004
	Political Views	0.007
I would question the accuracy of the genetic testing I had done	Education Level	0.039
	Race/Ethnicity	0.002
	Political Views	0.036
I would have negative feelings about genetic testing in general	Rank Knowledge	0.005
	Education Level	0.008
	Race/Ethnicity	<0.001
	Level of Religiosity	0.018
	Political Views	<0.001
I would want to be retested	Sex	0.045
	Education Level	0.017

Males were more likely (p-value = 0.045) to agree/strongly agree that they would want to be retested. Those who ranked their knowledge/understanding of genetics as "poor" were the most likely to agree/strongly agree that they would have negative feelings towards this particular testing (p-value = 0.021) as well as for genetic testing in general (p-value = 0.005). Those with a high school/GED education or less were the most likely to agree/strongly agree that they would question the accuracy of the genetic testing they had undergone (p-value = 0.039) as well as have negative feelings about genetic testing in general (p-value = 0.008) and were also the most likely to agree or strongly agree that they would want to be retested (p-value = 0.017).

Those who answered the race/ethnicity demographic question as "other" were the most likely (p-value = <0.001) to agree/strongly agree that they would have negative feelings about the cancer genetic testing they had undergone and were the most likely (p = 0.002) along with those of black/African American ethnicity to question the accuracy of the genetic testing. Those

of black/African American ethnicity were the most likely ($p = <0.001$) to have negative feelings about genetic testing in general. Those who were conservative were the most likely ($p = 0.007$) to agree/strongly agree that they would have negative feelings about the cancer genetic testing, to question the accuracy of the testing ($p = 0.036$), and to have negative feelings about genetic testing in general ($p = 0.002$).

Those with a household income of $50,000 - $74,999 were the most likely ($p = 0.004$) to agree/strongly agree that they would have negative feelings towards the cancer genetic testing. Participants who answered "neither agree nor disagree" with the statement of "religion is an important part of my life" were the most likely to agree/strongly agree ($p = 0.018$) that they would have negative feelings about the cancer genetic testing.

Significant family history of cancer, personal history of cancer, experience of having genetic testing, military service, marital status, and region of residence in the United States were all demographics that were not shown to have statistically significant differences between groups for this specific scenario.

4.5 DESIRED METHOD OF ORDERING

The participants who indicated at the end of the survey that they would either want to take a genetic testing like this at some point (either immediately or possibly in the future) were asked what their preferred way of ordering this test would be. The options were "Direct to Consumer," "Through my Primary Care Physician," and "Through a Genetic Counselor." The majority of participants (50.77%, n = 778) indicated that they would prefer to order this test through their

PCP. A similar number of participants indicated that they would prefer to order this test Direct-to-Consumer (25.32%, n = 778) as through a genetic counselor (23.91%, n = 778).

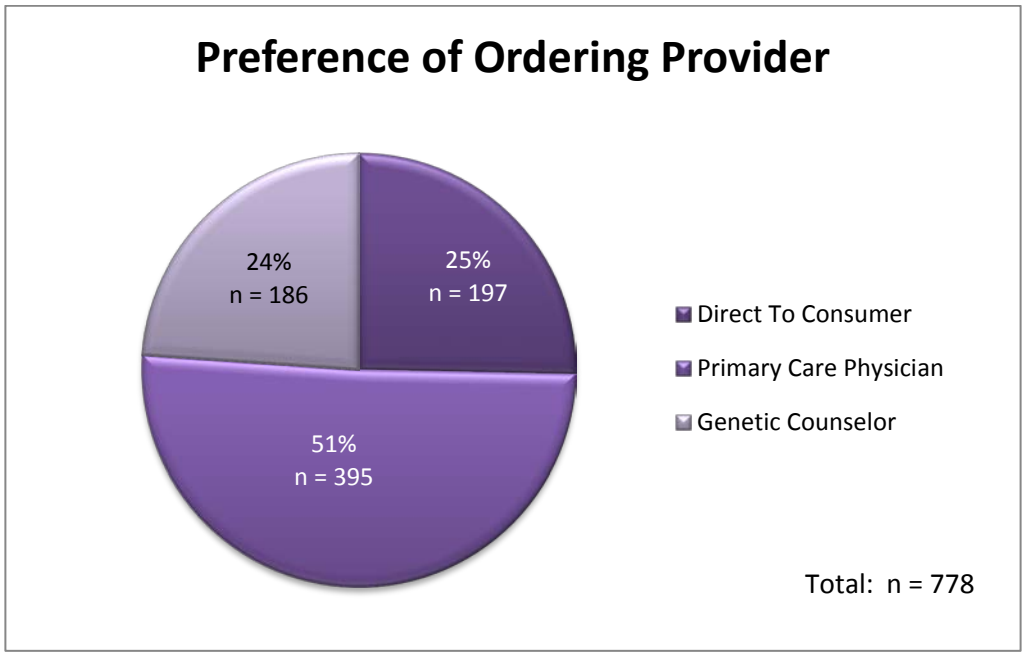

Figure 2: Preference of Ordering Provider

4.5.1 Thematic Analysis of Ordering Method

Some of the participants interpreted the last question of "why would you want to take a genetic test like this" as why they would want to order the test through DTC, PCP, or GC (depending what answer option they chose. This was not the original intent of the question, but incidentally provided a different aspect to the data to analyze and explained the through processes of why they would want to order a genetic test like this through direct to consumer testing, through their primary care physician, or through a genetic counselor. In total, 201 participants obviously interpreted the question this way and referred to either the ordering of the test or the test method

itself and why they chose their answer. These answers were coded separately than the other responses to identify themes specific to that specific interpretation of the question.

Thematic analysis was performed on these coded answers. Major themes identifed relating to ordering preference were: 1) trust/relationship with provider, 2) desire for a specialist or expert in the field, 3) privacy, 4) convenience/time, 5) cost, and 6) accuracy. Prevalence of each theme was calculated (Table 15). Quotes from survey respondents exemplifying each theme are illustrated in Table 16.

Table 21: **Prevalence of Identified Themes**

Theme	n (%), n = 201
Trust and/or relationship with provider	54 (26.87)
Desire for specialist and/or expert in the field	51 (25.37)
Privacy	17 (8.46)
Convenience/Time	40 (19.90)
Cost	15 (7.46)
Accuracy	18 (8.96)

Table 22: **Participant Quotes**

Theme	Quote
Trust and/or relationship with provider	“I know my primary care physician and we have a good relationship. Doing this test with them would make me feel comfortable, and I know my doctor would do a nice job explaining the results of the test to me.”
Desire for specialist and/or expert in the field	“This is specialized data that requires interpretation. A professional who has practice reading this data would be more able to properly explain the results.”
Privacy	“It would be more private and no insurance involved to label me”
Convenience/Time	“It’s easy, I don’t have to go anywhere to get it done. I can do it on my time.”
Cost	“Because it’s probably cheaper by bypassing the doctor”
Accuracy	“It seems to have the least chance for any errors or variables to skew/alter the results.”

5.0 DISCUSSION

This study was designed to collect data on the interest level and motivations of individuals from Amazon Mechanical Turks regarding genetic testing for hereditary cancer syndromes. The interest level and motivations were elicited from participants both before and after more information about the possible result of a test like this were divulged. In addition, the second objective of the study was to collect data on possible psychosocial impacts of a program of genetic testing in the general population. This study's findings, along with future studies, will aid in filling a gap in the literature about the interest of individuals in the general population for population-based cancer genetic testing. The findings also point out other elements that need to be considered when implementing such a program.

5.1 INITIAL INTEREST LEVEL FOR CANCER GENETIC TESTING

The first aim of the study was to examine the interest level of individuals in the Amazon Turks Community in taking a genetic test for hereditary cancer. Analysis of the survey data indicate that the majority of participants were initially interested in personally taking a genetic test for hereditary cancer genes at this point in time. Only 6% of participants initially indicated that they would never be interested in taking a genetic test for hereditary cancer genes.

The survey question eliciting initial interest referred to all known cancer genes in order to make the test applicable to all, though *BRCA1/2* would most likely be the only genes first offered in a population-screening approach based on current discussion in the literature. It was decided to include all known cancer genes instead of focusing on only *BRCA1/2* so as to make the survey more obviously applicable to all participants, specifically men. There was also a simplicity factor in not having to go into detail about specific genes. It would be an interesting follow-up study to focus specifically on interest and attitudes towards *BRCA1/2* testing.

It was interesting that most of the individuals in the study desired to take a genetic test like this simply because they want to know or are curious about this information. Additionally, many respondents were also interested in knowing this information so they could possibly take preventative measures or indicated that they would make lifestyle changes if they knew they were at a higher risk of a certain type of cancer. Other studies have found that members of the general population are interested in genetic testing for similar reasons[71,72]. A study by Henneman *et al*., 2006[72] surveyed the Dutch population and found that 52% of their participants would want to know their risks of certain diseases in order to prevent them and 34% of participants would want genetic testing because they are curious about their "genetic make-up"[72].

5.2 COMPARING THE SCENARIOS

The second aim of the study was to identify some possible psychosocial implications in the context of a population-screening program for hereditary cancer. The scenarios were presented to participants immediately after the initial question of interest.

5.2.1 Risk Level Scenarios

In comparing the three mutation-positive results, one where the lifetime risk of a certain cancer was increased to 15 – 25%, one where the lifetime risk was increased to 50%, and one where the lifetime risk was increased to 80%, the percentage of participants who agreed/strongly agreed with the psychosocial implication statements almost follow an exponential curve (Figure 3). For each of the statements, the lowest percentage of participants who agreed/strongly agreed with the psychosocial implication statement was found at the 15 – 25% level, and the highest percentage of participants who agreed/strongly agreed with the psychosocial implication statement was found at the 80% level. This intuitively makes sense, as one would expect a positive result to possibly affect one's life more, if the lifetime risk of cancer is higher.

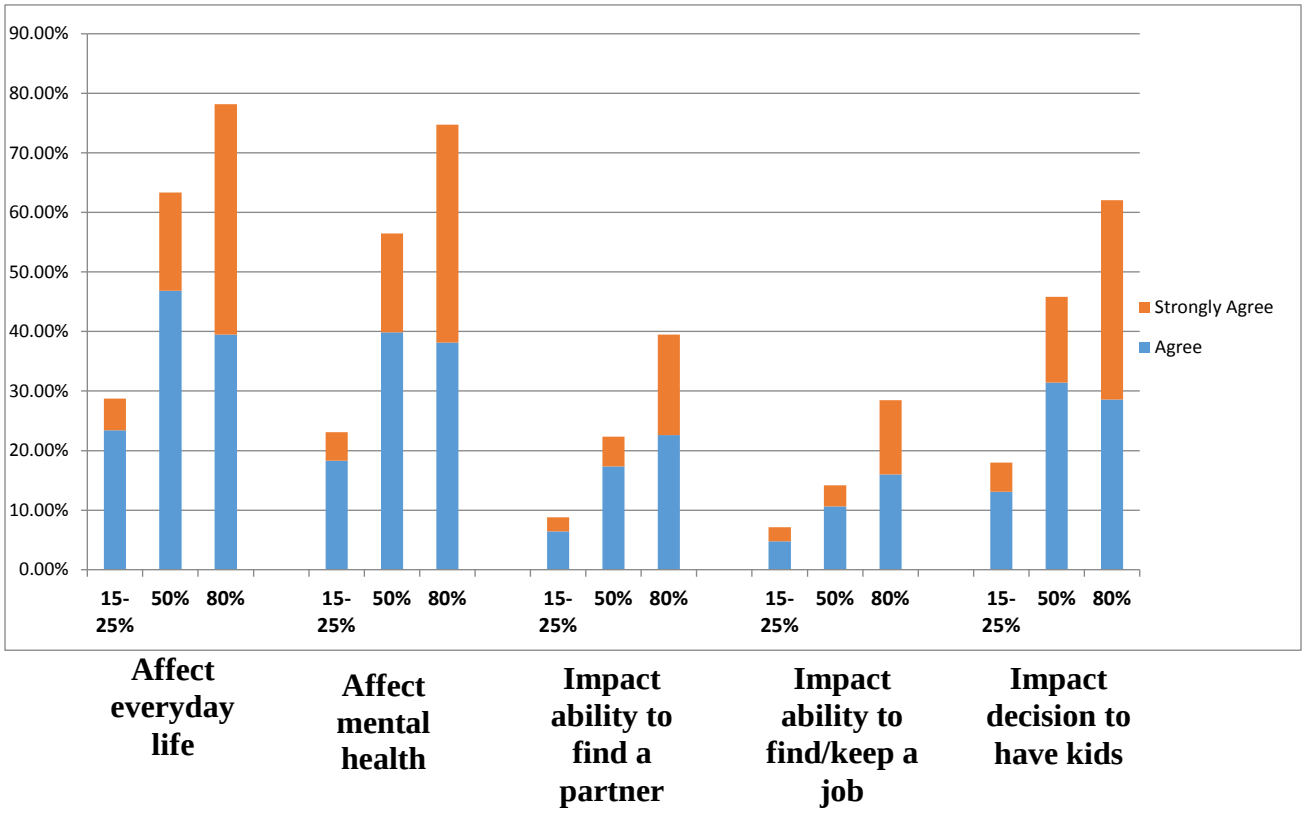

Figure 3: Comparing the 5 psychosocial implication statements between risk level scenarios

5.2.2 VUS Scenario

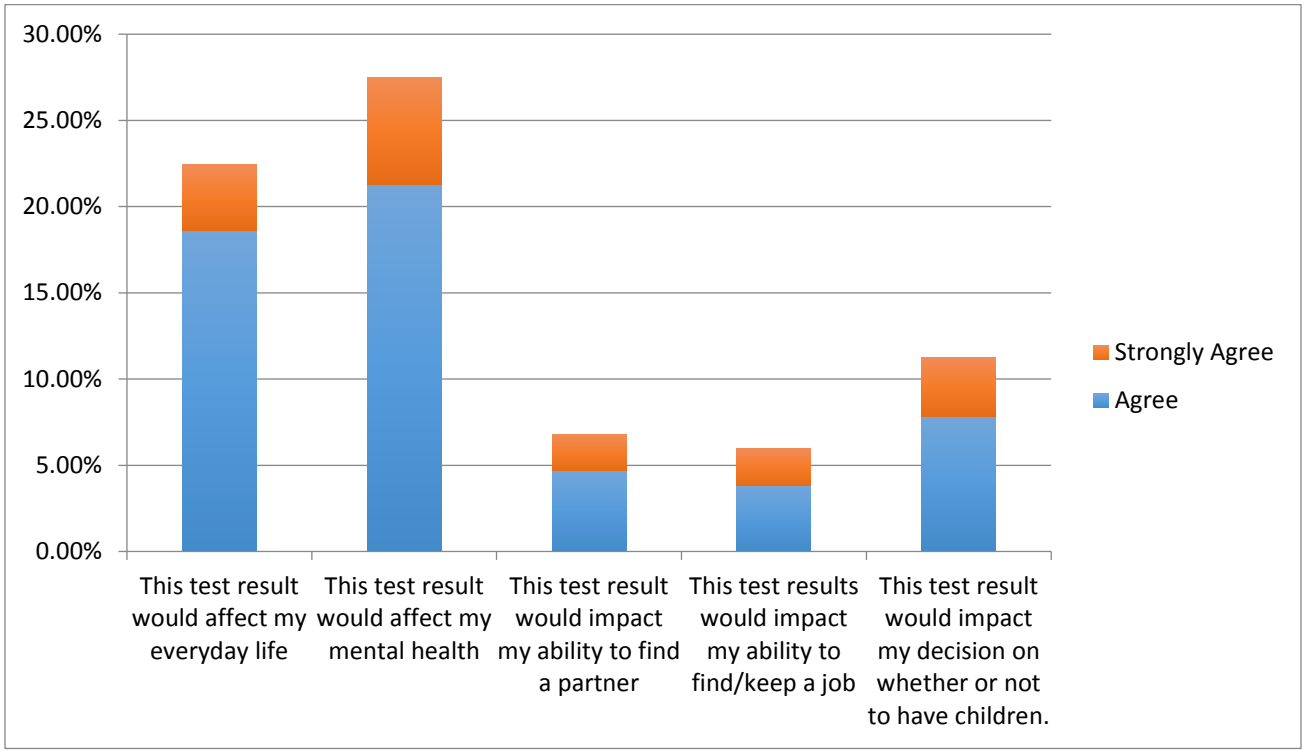

Figure 4: VUS Scenario Results

The likert-scale results of a variant of uncertain significance in a gene associated with an increased risk in hereditary cancer are depicted in Figure 4. These results followed a similar pattern as the 'increased risk of a certain cancer to 15 - 25%,' though the percentage of participants who agreed or strongly agreed with each of these statements was slightly less than the 15 - 25% increased risk scenario. Approximately 22% of participants agreed or strongly agreed that a VUS result would affect their everyday life and approximately 27% of participants agreed or strongly agreed that this test result would affect their mental health. This may be concerning for a population-based screening program as currently at least 1.6% of participants in a program such as this would have a result of a VUS in *BRCA1/2*. These results are somewhat

consistent with reported data. A study by Vos *et al*., 2008[73] was conducted of patients with a VUS and found that a third (n = 24) of their participants reported "large changes in specific life domains." There is some evidence to suggest that carriers of a VUS in a hereditary cancer gene may have a misperception and make radical medical decisions based on this VUS[41]. This is greatly concerning as it is a recommendation that patients should not make medical decision based on a VUS[74]. Hopefully attempts to make surgical decisions based on a VUS would be halted by either physicians or insurance companies, but it may prove difficult to ensure this.

5.2.3 Negative Result Scenarios

5.2.3.1 Negative Genetic Testing Results

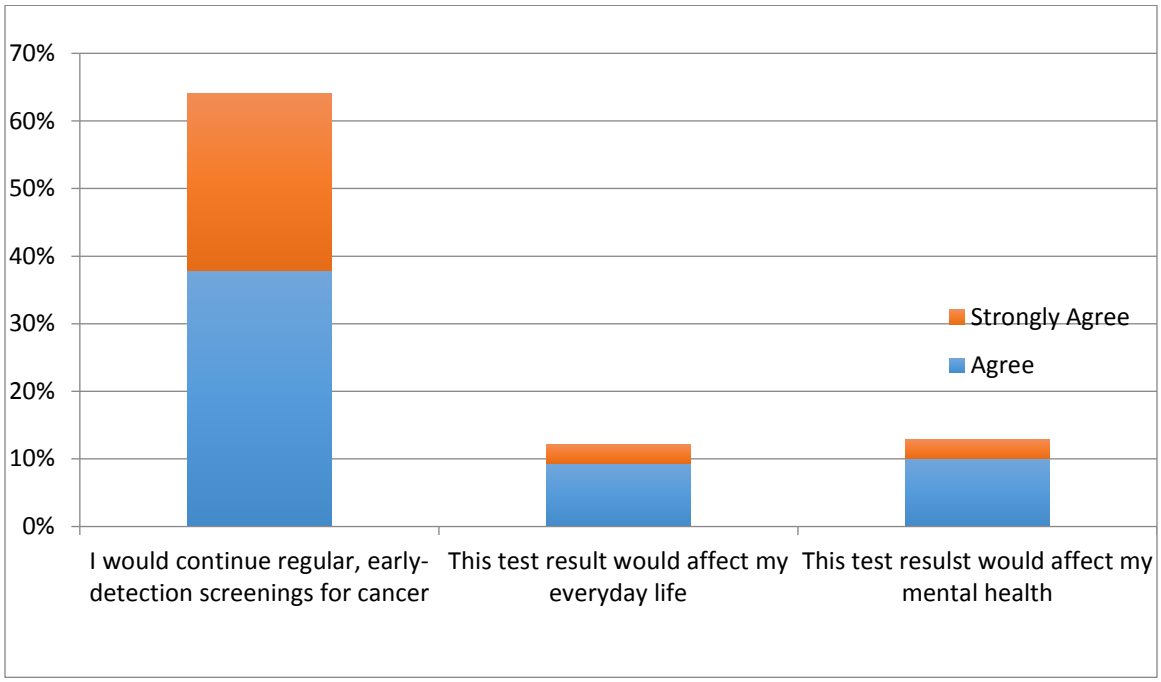

Figure 5: Negative Test, Likert-Scale Result

Figure 5 demonstrates the percentage of participants who agreed or strongly agreed on a likert-scale to three of the statements given. One of the more concerning findings of this study would be that only 64% of participants agreed or strongly agreed with the statement “I would continue regular, early-detection screenings for cancer (mammograms, prostate exams, pap smears, etc.).” This is an important point to consider when weighing the benefits and risks of a population-based screening program. If a substantial number of participants of such a program are going to decide to not have the recommended cancer screenings if they test negative for hereditary cancer genes, the positive effects of a program may be negated or the effects may prove to be harmful overall for cancer prevention. However, it is important to note one of the limitations of the study, which is that this is a hypothetical question. Faced with an actual test result and physician recommendations, this data may not prove to be an accurate representation of what would happen.

5.2.3.2 Negative Genetic Testing Result, Diagnosis of Cancer 15 Years Later

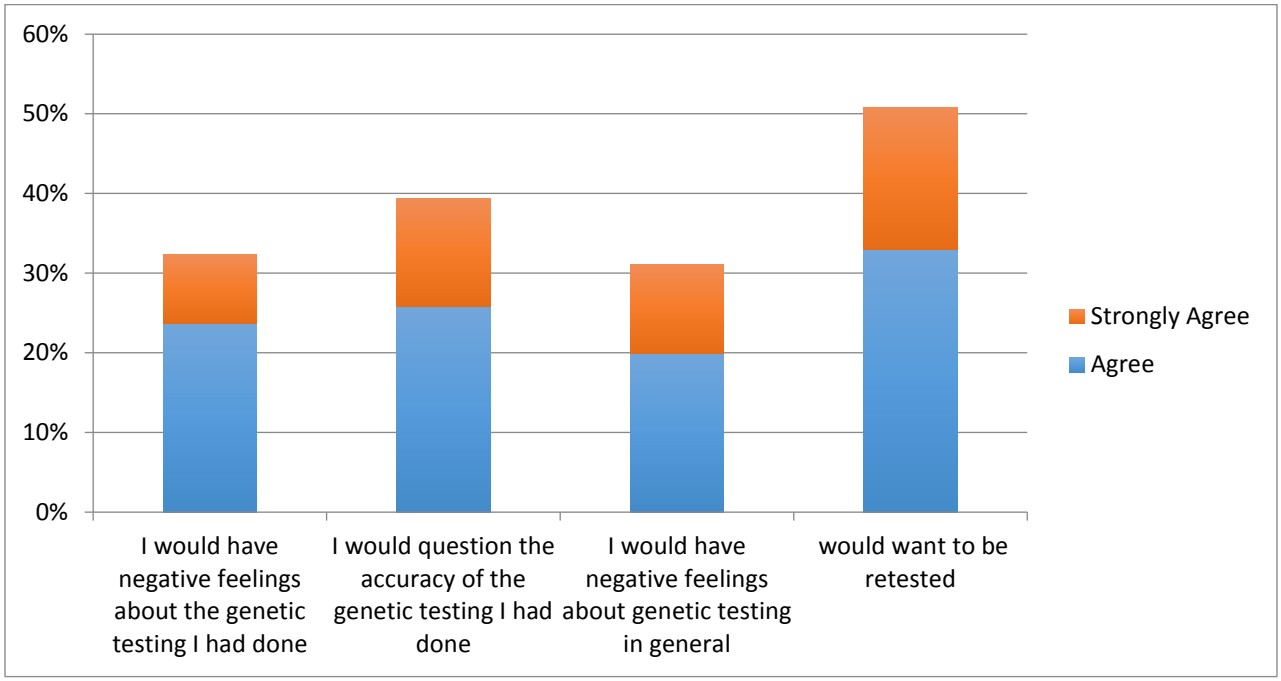

Figure 6: Negative Genetic Test, Cancer Diagnosis Later - Likert Scale Results

This scenario described the participant testing negative for mutations in the known hereditary cancer genes, but then getting a diagnosis of cancer 15 years later. The results of the likert-scale statements show a concerning trend of possible negative feelings about genetic testing. There may be additional negative emotions towards healthcare providers and the medical field in general. This is speculation, as these specific questions were not asked. More than half of participants agreed or strongly agreed that they would want to be retested, which illuminates the need of education and explanation in the world of genetics as to the benefits and limitations of genetic testing.

5.3 INTEREST LEVEL AFTER THE SCENARIOS

When comparing the interest level in taking a genetic test such as this after the participants answered questions related to the six scenarios to the initial interest level question, there were more participants who answered (9.64%, n = 861) that they would "never take a test like this" and answered (25.44%, n = 861) "currently not interested, but would consider it in the future" and less who answered (64.92%, n = 861) "yes, I would take this test today if I could." The majority of participants were still interested in taking a test like this either immediately if possible or at some point in the future (90.36%, n = 861).

5.4 STUDY FINDINGS IN THE CONTEXT OF PREVIOUS WORK

The vast majority of studies that have collected data on the possibility of population screening for hereditary cancer genes, specifically *BRCA1/2* have focused on the prevalence of mutations in families with unremarkable cancer history or on cost-effectiveness of population-screening compared to a family-history based approach[75,76].

Based on an extensive literature search, this appears to be the first reported data on whether individuals in the general population in the United States would be interested in being offered a genetic test like this. There was a study conducted in the Dutch population that assessed interest in genetic testing for cardiovascular disease, cancer, dementia, and diabetes[71]. This data fills part of a gap in the literature relating to the desire of individuals in the general population to have this type of genetic testing available on a broader scale than current methods allow.

5.5 IMPORTANCE OF GENETIC COUNSELING

One of the primary aims of genetic counseling in a cancer setting is to ensure that the informed consent elements previously discussed in the background are present and understood by the individual considering genetic testing for cancer susceptibility. Many of these basic elements would be difficult to establish in a population-screening based approach and may pose an ethical barrier for a population-screening program for cancer susceptibility. This may be an ethical barrier because informed consent has been shown to be an important aspect of patient autonomy. This study showed that the majority of our participants were interested, but that the interest level changed in some individuals after more information was gained about possible results. It may be beneficial to study if interest levels in genetic testing change with a formal informed consent process.

Genetic counselors have specialized training to ensure that the proper informed consent is present in a session as well as the ability to assess how well the patient is understanding the information related to genetic testing. In a face-to-face session, genetic counselors are also able to ask questions relating to the psychological state of the patient and his/her social support and provide referrals and resources. Given the current limited number of genetic counselors, pre-test counseling by genetic counselors would not be plausible for a population-screening program. Genetic counseling outcomes been reported on in the literature and has been shown to be valuable in terms of patient satisfaction, knowledge, and understanding[55]. Specific outcomes found in the ABOUT study by Armstrong *et al*.[55] show the increased satisfaction of patients who had pre-test counseling by genetic counselors compared to physicians.

5.6 STUDY LIMITATIONS

One of the study limitations was a lack of robust qualitative data. In the open-ended qualitative questions, many respondents used a few words or a sentence to answer the question. Because of the nature of a survey rather than a focus group or an interview, robust qualitative data is typically difficult to obtain. This made thematic analysis difficult as broader themes outside of the codes themselves were not exactly feasible.

It was revealed through data analysis that the order of the open-ended question of Q54:“why did you decide you would want to take a genetic test like this?” was poorly placed after Q50: “what would your preferred way of ordering this test be?” instead of Q54: “after going through the various scenarios of possible outcomes for genetic testing, would you be interested in taking a comprehensive genetic test that could identify a hereditary risk of cancer?” This mis-ordering of questions caused participants to not consistently interpret the question. Many interpreted it as it was intended as to elicit an elaboration on their interest level, however, many other interpreted as to why they chose their preferred ordering method. However, this mistake led to the gathering of useful and interesting data, and if the survey were repeated, participants would be asked to elaborate on their preferred ordering method.

Amazon Mechanical Turks was a convenience sample and not perfectly representative of the general population of the United States. While other studies on the demographics of Amazon Mechanical Turks have shown it to be more representative than other convenience samples of college students, it is still a convenience sample and certain groups are underrepresented while other groups are overrepresented. This is a limitation of the findings of this study may not be fully applicable to the actual general population.

An additional limitation of this study is that it asked about a hypothetical situation and there are studies that show that individuals may have different opinions or ideas when presented with an actual genetic test. Further studies could calculate interest levels and motivations in a real-life situation and possibly compare these to the hypothetical findings from this study.

5.7 FUTURE STUDIES

A future study eliciting the interest level of taking a genetic test for only *BRCA1/2* would be interesting to see if there are differences than the interest level in this study. If possible, another study relating to the interest level and psychosocial implications on a sample more representative of the general population may be useful to compare to the findings of this study.

More research needs to be conducted in the form of studies with large sample sizes to work out the proper infrastructure needed for a population-screening program of cancer genes. These studies could specifically collect data on possible forms of informed consent (ex. Video, quizzes, interactive website, etc.) that are the most effective, best way to disclose results, how to best triage participants based on results for future medical care, and specific resources for participants.

Future studies should also focus on how best to properly convey the results of the genetic test to participants in order to ensure proper understanding of these results in the context of their future medical management, in the case of the possible results of a positive, negative, or VUS. Part of the results disclosure may also need to be able to assess the psychological state of the participant and have the ability to offer appropriate resources such as support groups or therapists and follow up with the participant as needed. Long-term studies could track participants and

collect data regarding the adherence to medical management recommendations concerning appropriate cancer screening procedures in the case of all possible test results as well as any psychosocial implications.

5.8 BASIC ELEMENTS NEEDED BEFORE THE IMPLEMENTATION OF A POPULATION SCREENING PROGRAM

The significant reductions in cancer risks associated with preventative measures[1] offered to those known to be at a high-risk of cancer highlights the importance of identifying mutation carriers. However, several problems present themselves when posing a program of population screening. The benefits and risks should always be weighed before the implementation of such a program. Future clinical research studies should take place to determine what specific extensive infrastructure is necessary to have in place before a population-screening program for hereditary cancer genes is implemented. Examples of the specific extensive infrastructure would most likely include the following: how results would be communicated, how to manage participants appropriately based on results, how to provide education on what their results mean for them and how to communicate with family members about results, what testing laboratory would be used, and resources such as support groups and hotlines for questions from participants. This infrastructure will be necessary in order to ensure that the possible benefits of such a program outweigh the possible risks. Streamlined mechanisms for the clinical management of *BRCA1/2* mutation carriers would be essential for the success of a population-screening program.

The elements and current standards for informed consent prior to cancer susceptibility testing should still be part of a population screening approach to genetic testing. This informed

consent would most likely need to look differently than a genetic counseling pre-test session currently does, simply because of the lack of manpower. Recent reports in the media have specifically highlighted this shortage. National Public Radio (NPR) summarized the shortage of genetic counselors and discussed how there are currently approximately 650 job openings for less than 300 new genetic counseling graduates[77]. This study showed the importance of informed consent as part of any genetic testing, as a subset of the participants indicated a different level of interest after learning more about possible results and processing how this could affect their life.

Given the possibility of reclassification of a VUS to a pathogenic mutation, strong consideration should be given to whether these results are reported or not. Medical, ethical, and legal issues arise if these results are not reported, while psychosocial and possible medical issues arise if these results are reported. A reliable system for re-contacting in the case of a VUS when it is reclassified is necessary in either case, particularly for those VUS results that are reclassified as positive. In the case a population screening program that does not report out VUS results, negative results would not need to be called out to patients as they were already told they were negative. This study shows that there is at least a subset of individuals may experience psychosocial effects such as an impact on mental health due to a VUS result.

5.9 PUBLIC HEALTH IMPACT

Population-based screening for hereditary cancer syndromes would have the ultimate goal of eventually eliminating the portion (5-10%) of the cancer burden that consists of hereditary cancers. This could have a substantial impact on multiple aspects of healthcare. Population-based screening has the potential ability to prevent cancer entirely or detect it at an early stage. This

prevention and early detection of hereditary cancer could both save lives and improve the quality of life for those that may have otherwise had to endure substantial medical bills and/or extensive treatment in the form of chemotherapy, radiation, surgery, etc.

If it were possible to appropriately manage all hereditary cancer syndrome mutation carriers through prevention and early detection in the general population, there may be a significant public health impact in terms of cost-effectiveness, patient waitlists for oncology clinicians, quality adjusted life years (QALYs) of the patients, rates of hospitalization, measurement of disability, and others. Some of these public health impacts may be difficult to measure, particularly in the case of hereditary cancer gene mutations, which are not 100% prevalent. Long-term studies would most likely be needed to truly measure the public health impact in meaningful ways.

There is also a possibility of negative public health impacts should a population-based screening program be implemented. The possible negative effects could include a false sense of security of mutation-negative patients, increased psychological distress in patients with variants of uncertain significance or pathogenic mutations, an increased patient load for certain clinicians, the possibility of the mismanagement of patients due to infrastructure problems or misinformation on the part of healthcare providers and/or patients. It would also be very difficult to measure overall cost-effectiveness as those that may have died from cancer would most likely have other health-related costs as they age.

6.0 CONCLUSION

Overall, this study found that the majority of participants were interested in taking a genetic test that could identify a hereditary predisposition to cancer. However, the interest levels changed somewhat after the presentation of the scenarios, implying that individuals may have different opinions about such testing when more information is learned about the test one would be undergoing. Motivations for why an individual would be interested in testing either now or possibly in the future were identified using thematic analysis. The largest proportion of participants (59.81%) simply wants to know this information. Motivations for why an individual would not be interested in testing were also identified using thematic analysis and the largest proportion (34.38%) of participants stated psychological stress/anxiety as the reason why they would not want this test. Even at the lowest risk level of an increased risk of 15 – 25% of a certain cancer, a negative result, and a result of a variant of uncertain significance (VUS), participants noted psychological and psychosocial implications of these results. The ultimate benefit of a population-based screening program would be to have the ability to identify more mutation-carriers and manage them appropriately. Appropriate management of mutation-carriers to prevent cancer and save lives should be weighed against the risks of the psychological, medical, legal, economic and ethical issues that currently surround such a program. More studies with large sample-sizes are needed in the general population to work out these issues before a program like this is implemented on a clinical, state or nation-wide scale.

APPENDIX A: LETTER OF IRB APPROVAL

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: Laura Cross
From: IRB Office
Date: 4/8/2015
IRB#: PRO14100612
Subject: Population Screening for Hereditary Cancer: Opinions from the General Public

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The above-referenced project has been reviewed by the Institutional Review Board. Based on the information provided, this project meets all the necessary criteria for an exemption, and is hereby designated as "exempt" under section
45 CFR 46.101(b)(2)

Please note the following information:

- Investigators should consult with the IRB whenever questions arise about whether planned changes to an exempt study might alter the exempt status. Use the "**Send Comments to IRB Staff**" link displayed on study workspace to request a review to ensure it continues to meet the exempt category.
- It is important to close your study when finished by using the "**Study Completed**" link displayed on the study workspace.
- Exempt studies will be archived after 3 years unless you choose to extend the study. If your study is archived, you can continue conducting research activities as the IRB has made the determination that your project met one of the required exempt categories. The only caveat is that no changes can be made to the application. If a change is needed, you will need to submit a NEW Exempt application.

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

APPENDIX B: SURVEY

Duplicate questions are due to survey flow. Text highlighted in yellow are explanations about survey flow.

University of Pittsburgh

Default Question Block

Q1. This survey is anonymous and takes approximately 10 minutes to complete. There will be compensation in the amount of $0.50 for those who fill out the survey in its entirety.

Q2. Dear Participant,

The purpose of this research study is to study the opinions from the general public on the topic of offering population-wide screening for hereditary cancer genes (genes that are passed down through generations in a family). For this reason we will be surveying Amazon's Mechanical Turks and asking them to complete a brief questionnaire (approximately 10 minutes). Our goal is to have approximately 1000 responses. All participants must be 18 years old or older and located in the United States. If you are willing to participate, our questionnaire will ask about your background (e.g. age, gender, and family background) and your opinions on genetic testing and related topics.

There are no foreseeable risks associated with this project, nor are there any direct benefits to you.

This is an anonymous questionnaire, and as such your responses will not be identifiable in any way. All responses are confidential, and results will be kept in password-protected files.

Your participation is voluntary, and you may stop completing the survey at any time.

This study is being conducted by Laura Cross, who can be reached at pscstudy@pitt.edu, if you have any questions.

Q3. Are you over the age of 18?

- Yes
- No

[Anyone who answered "no" was not eligible to take the survey and taken to a "thank you" page]

Q4.
Hereditary cancer is cancer that is caused by a single gene that is not working how it should. This single gene can be passed down through generations in a family. Approximately 10% of cancer is hereditary.

If it were available, would you be interested in taking a comprehensive genetic test that could identify a hereditary risk of cancer?

- ○ Yes, I would take that test today if I could.
- ○ Currently not interested, but would consider it later in life
- ○ No, I would never take a test like that

Q5. Why would you want to take a test like this?

[Only asked to participants who answered "Yes, I would take this test today if I could"]

Q6. Why would you never take a test like this?

[Only asked to participants who answered "No, I would never take a test like that"]

Q7. Why would you consider taking this test in the future?

[Only asked to participants who answered "Currently not interested, but would consider it later in life"]

Q8. In each of the following scenarios, you have a saliva or blood sample taken and all of the currently known cancer genes are analyzed. There are three possible test results:

Negative: meaning no cancer genes were found to be changed and you have no increased genetic risk for cancer. Your cancer screening would be the same as the rest of the general population.

Positive: meaning that a change in a gene was found that is hurting that gene (mutation), and you are at an increased risk of cancer. Different screening and management guidelines could apply. Examples of these differences could be starting mammograms at earlier ages, more frequent colonoscopies, or the removal of the organ at risk (for example the surgical removal of the uterus/ovaries or of part of your colon or stomach).

Uncertain: Meaning that a change was found in one of the cancer genes, but it is unclear whether that change is benign (not harmful) or whether the change actually hurts the function of the gene.

Q9. SCENARIO: You go through comprehensive genetic testing for cancer genes and are found to have a changed gene that is harmful and increases your risk of a certain type cancer (for example, colon cancer) to 50%. This would mean that over the course of your lifetime, there is a 1 in 2 chance that you would develop that certain type of cancer.

Q10. In your own words, what would this mean to you?

Q11. What do you think you would be feeling after receiving this news?

Q12. What would you do differently based on this result, if anything?

Q13. Please indicate the degree to which you agree or disagree with the following statements.

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
This test result would affect my everyday life.	○	○	○	○	○
This test result would affect my mental health.	○	○	○	○	○
This test result would impact my ability to find a partner (assuming you did not have a partner at the time).	○	○	○	○	○
This test result would impact my ability to find and/or keep a job.	○	○	○	○	○
This test result would impact my decision on whether or not to have children. (Each child would have a 50% chance of inheriting the harmful gene from you)	○	○	○	○	○
I would talk to my family about this gene and my test result	○	○	○	○	○

Q14. Why would you not talk about this gene and your test result with your family?

[Only asked to participants who answered "Strongly Disagree" to the statement "I would talk to my family about this gene and my test result]

Q15. Why would you not talk about this gene and your test result with your family?

[Only asked to participants who answered "Disagree" to the statement "I would talk to my family about this gene and my test result]

Q16. SCENARIO: You go through comprehensive genetic testing for cancer genes and are found to have a broken gene that increases your risk of a certain type of cancer (for example, colon cancer) to 80%. This would mean that over the course of your lifetime, there is a 4 in 5 chance of developing that type of cancer.

Q17. In your own words, what would this mean to you?

Q18. What do you think you would be feeling after receiving this news?

Q19. What would you do differently based on this result, if anything?

Q20. Please indicate the degree to which you agree or disagree with the following statements.

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
This test result would affect my everyday life.	○	○	○	○	○
This test result would affect my mental health.	○	○	○	○	○
This test result would impact my ability to find a partner (assuming you did not have a partner at the time).	○	○	○	○	○
This test result would impact my ability to find and/or keep a job.	○	○	○	○	○
This test result would impact my decision on whether or not to have children. (Each child would have a 50% chance of inheriting the harmful gene from you)	○	○	○	○	○
I would talk to my family about this gene and my test result	○	○	○	○	○

Q21. Why would you not talk about this gene and your test result with your family?

[Only asked to participants who answered "Strongly Disagree" to the statement "I would talk to my family about this gene and my test result]

Q22. Why would you not talk about this gene and your test result with your family?

[Only asked to participants who answered "Disagree" to the statement "I would talk to my family about this gene and my test result]

Q23. SCENARIO: You go through comprehensive genetic testing for cancer genes and are found to have a broken gene that increases your risk for a certain type of cancer to 15-25%. This would mean that over the course of your lifetime there is approximately a 1 in 5 chance of developing that type of cancer.

Q24. In your own words, what would this mean to you?

Q25. What do you think you would be feeling after receiving this news?

Q26. What would you do differently based on this result, if anything?

Q27. Please indicate the degree to which you agree or disagree with the following statements.

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
This test result would affect my everyday life.	○	○	○	○	○
This test result would affect my mental health.	○	○	○	○	○
This test result would impact my ability to find a partner (assuming you did not have a partner at the time).	○	○	○	○	○
This test result would impact my ability to find and/or keep a job.	○	○	○	○	○
This test result would impact my decision on whether or not to have children. (Each child would have a 50% chance of inheriting the harmful gene from you)	○	○	○	○	○
I would talk to my family about this gene and my test result	○	○	○	○	○

Q28. Why would you not talk about this gene and your test result with your family?

[Only asked to participants who answered "Strongly Disagree" to the statement "I would talk to my family about this gene and my test result]

Q29. Why would you not talk about this gene and your test result with your family?

[Only asked to participants who answered "Disagree" to the statement "I would talk to my family about this gene and my test result]

Q30. Scenario: You go through comprehensive genetic testing for cancer genes and are found to have an uncertain result. This means that there was a change found in a gene that is associated with a certain cancer. However, it is unclear whether that change is harmless, or if that change causes an increased risk for a certain type of cancer.

Q31. In your own words, what would this mean to you?

Q32. What do you think you would be feeling after receiving this news?

Q33. What would you do differently based on this result, if anything?

Q34. Please indicate the degree to which you agree or disagree with the following statements.

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
This test result would affect my everyday life.	○	○	○	○	○
This test result would affect my mental health.	○	○	○	○	○
This test result would impact my ability to find a partner (assuming you did not have a partner at the time).	○	○	○	○	○
This test result would impact my ability to find and/or keep a job.	○	○	○	○	○
This test result would impact my decision on whether or not to have children. (Each child would have a 50% chance of inheriting the harmful gene from you)	○	○	○	○	○
I would talk to my family about this gene and my test result	○	○	○	○	○

Q35. Why would you not talk about this gene and your test result with your family?

Q36. Why would you not talk about this gene and your test result with your family?

Q37. SCENARIO: You go through comprehensive genetic testing for cancer genes and are found to be negative for any changes in the genes that we can test for at this time. Although the test indicates that you are likely not at an increased risk for cancer, it is important to remember that most cancers are not hereditary, meaning that they are not caused by a change in a gene that can be passed down through families.

As a result, you still could develop cancer in the future, but your risk is likely similar to other people in the general population.

Q38. In your own words, what would this mean to you?

Q39. What do you think you would be feeling after receiving this news?

Q40. What would you do differently based on this result, if anything?

Q41. Given these test results, what would you think your lifetime chance of cancer is?

- 0%
- <10%
- 10-25%
- 25-50%
- 50-75%
- 75-100%

Q42. Please indicate the degree to which you agree or disagree with the following statement.

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
This test result would affect my everyday life.	○	○	○	○	○
This test result would affect my mental health.	○	○	○	○	○
I would continue regular, early-detection screenings for cancer (mammograms, prostate exams, pap smears, etc.)	○	○	○	○	○
I would talk to my family about my test result	○	○	○	○	○

Q43. Why would you not talk about this test result with your family?

Q44. Why would you not talk about this test result with your family?

Q45. Why would you not continue regular, early-detection screenings for cancer?

Q46. Why would you not continue regular, early-detection screenings for cancer?

Q47. SCENARIO: You go through comprehensive genetic testing for cancer genes and are found to be negative for any changes in the genes that we can test for at this time. (0% increased risk for hereditary cancer, your risk is likely similar to the general population). However, 15 years later, you are diagnosed with cancer.

Q48. Please indicate the degree to which you agree or disagree with the following statements.

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
I would have negative feelings about the genetic testing I had done.	○	○	○	○	○
I would question the accuracy of the genetic testing I had done.	○	○	○	○	○
I would have negative feelings about genetic testing in general	○	○	○	○	○
I would want to be retested	○	○	○	○	○

Q49. After going through the various scenarios of possible outcomes for genetic testing, would you be interested in taking a comprehensive genetic test that could identify a hereditary risk of cancer?

- Yes, I would take this test today if I could
- Currently not interested, but would consider it later in life
- No, I would never take a test like that

Q50. What would your preferred way of ordering this test be?

- Direct to consumer (You would order the test directly through the company and they would ship you a DNA kit, bypassing all healthcare professionals)
- Through my Primary Care Physician (Your primary doctor would coordinate the testing)
- Through a Genetic Counselor (Healthcare professional who specializes in Genetics would coordinate the testing)

[Only asked to participants who answered "Yes, I would take this test today if I could" to Q49.]

Q51. What would your preferred way of ordering this test be?

- Direct to consumer (You would order the test directly through the company and they would ship you a DNA kit, bypassing all healthcare professionals)
- Through my Primary Care Physician (Your primary doctor would coordinate the testing)
- Through a Genetic Counselor (Healthcare professional who specializes in Genetics would coordinate the testing)

[Only asked to participants who answered "Currently not interested, but would consider it later in life" to Q49.]

Q52. Why did you decide you would not want to take a genetic test like this?

[Only asked to participants who answered "No, I would never take a test like that" Q49.]

Q53. Why did you decide that you would consider taking a genetic test like this in the future?

[Only asked to participants who answered "Currently not interested, but would consider it later in life" to Q49.]

Q54. Why did you decide you would want to take a genetic test like this?

[Only asked to participants who answered "Yes, I would take this test today if I could" to Q49.]

Q55. What is your sex?

- Female
- Male

Q56. What is your age?

Q57. Do you have a significant family history of cancer?

- Yes
- No

Q58. Have you personally ever had cancer?

- Yes
- No

Q59. Have you ever had genetic testing?

- Yes
- No

Q60. What genetic testing have you had?

[Only asked to participants who answered "Yes" to Q59.]

Q61. How would you rank your knowledge/understanding of genetics

- Excellent
- Good
- Average
- Poor

Q62. What is the highest level of education completed or the highest degree you have received?

- Less than 12th grade/no diploma
- High School or GED
- Some college/no degree
- Associates Degree
- Bachelors Degree
- Graduate/Professional Degree

Q63. What is your race/ethnicity?

- White
- Black or African American
- Hispanic or Latino
- Asian
- Native Hawaiian or Pacific Islander
- American Indian or Alaska Native
- Other

Q64. Have you ever worked in healthcare?

- Yes
- No

Q65. Which category represents the total combined income of all members of your family in your household during the past 12 months?

This includes money from jobs, net income from business, farm or rent, pensions, dividends, interest, social security payments and any other money income received by members of this family who are 15 years of age or older?

- less than $10,000
- $10,000 - $19,999
- $20,000 - $29,999
- $30,000 - $39,999
- $40,000 - $49,999
- $50,000 - $74,999
- $75,000 - $99,999
- $100,000 - $149,999
- $150,000 or more

Q66. Are you currently married, widowed, divorced, separated, or never married?

- Married
- Widowed
- Divorced
- Separated
- Never Married

Q67. Please indicate the degree to which you agree or disagree with the following statement:

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
Religion is an important part of my life	○	○	○	○	○

Q68. How would you define your political views?

- Liberal
- Moderate
- Conservative

Q69. Did you ever serve in the military?

- Yes
- No

Q70. What region do you currently live in?

- Northeast (PA, MD, DE, NJ, CT, RI, MA, NH, ME, VT, NY, DC)
- Southeast (WV, VA, NC, SC, GA, FL, AL, MS, LA, AR, TN, KY)
- Midwest (OH, MI, IN, IL, WI, MN, IA, MO, ND, SD, NE, KS)
- Southwest (OK, TX, NM, AZ)
- West (WA, OR, ID, MT, WY, CO, UT, NV, CA)
- Alaska or Hawaii
- US Territory (American Samoa, Guam, Northern Mariana Islands, Puerto Rico, US Virgin Islands)

Q71. Thank you for taking our survey. Please copy the following code and hit submit after entering the code into the Amazon Turks verification box.

PSCSTUDY **6237**

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