PHYSICIAN KNOWLEDGE AND ATTITUDES CONCERNING BREAST CANCER GENETICS

by

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ABSTRACT

The discovery of the breast and ovarian cancer predisposition genes, *BRCA1* and *BRCA2*, has led to the development of lifesaving treatments and cancer risk reduction strategies in families who carry pathogenic variants. Genetic testing techniques have improved over the years and decreased in cost so that many who meet widely accepted testing guidelines based on family and personal histories of cancer are able to afford testing after appropriate counseling. It has been suggested that all women should be offered genetic testing for these genes, regardless of family or personal cancer history. To implement a population-based screening program, primary care physicians would need to know about the *BRCA* genes as well as understand how best to use genetic test results based on an individual's medical history; these providers would also need to be willing to incorporate an additional service into their practice. A questionnaire was developed to assess the knowledge and opinions of individuals, within the UPMC network, in the medical specialties of obstetrics/gynecology and family medicine with regard to *BRCA1/2* and offering *BRCA1/2* testing to patients. The average number of knowledge questions that were answered correctly, across all 64 participants was 9.5 correct out of 13 questions, for an average score of 73.4%; only one individual correctly answered all 13 questions. The question that providers

most often answered incorrectly concerned testing policies for variants of uncertain significance; only 29.8% (25/84) correctly answered that they would not test a patient for an unclear genetic finding that was found in a relative. With regard to what would motivate those surveyed to incorporate population-based *BRCA1/2* testing into their practice, 70.2% (59/84) indicated that evidence-based professional society guidelines would be their greatest motivator, while only 4.8% (4/86) indicated they were not interested or motivated to offer *BRCA1/2* testing to their patients. The results of this study will help to guide future educational programs for physicians as the *BRCA* genes are considered for population-based screening. The public health significance of this work is that the public will receive proper counseling and consistent care with regard to their *BRCA* testing, if physicians are trained properly.

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PREFACE

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1.0 INTRODUCTION

1.1 BACKGROUND

1.1.1 Breast Cancer Genetics

Hereditary breast and ovarian cancer (HBOC) syndrome is a dominantly inherited cancer predisposition syndrome of variable penetrance, which is characterized by multiple family members having breast, ovarian, or both cancers, often at an early age <50 years[1,2]. A single-gene predisposition is the suspected cause for an estimated 10% of all breast cancer diagnoses, with the predominant pathogenic variants occurring in the *BRCA1* and *BRCA2* genes, although these are not the only breast cancer predisposition genes; thirty to fifty percent of hereditary breast cancer cases are due to pathogenic variants in the *BRCA* genes. Additionally, pathogenic variants in the *BRCA* genes are responsible for 10% of all ovarian cancers[1].

The *BRCA* genes are tumor suppressors, meaning their protein products are utilized in the DNA repair process[1]. *BRCA1* was discovered in 1994, is located on chromosome 17, and more than 1,200 different variants within it have been reported to cause increased risks of cancer. *BRCA2* was discovered in 1995, is located on chromosome13, and more than 1,300 variants have been found within it. Inherited *BRCA* pathogenic variants cause an increased risk of cancer when the second copy of the gene gains a pathogenic variant (loss of heterozygosity) allowing a

cell to replicate without DNA repair resulting in an accumulation of additional pathogenic variants, causing cancer; this is known as the "two-hit hypothesis.[1]"

With regard to common pathogenic variants or those known to be associated with certain populations, there are three pathogenic variants that are associated with individuals of Ashkenazi Jewish descent, in *BRCA1* c.68_69delAG and c.5266dupC and in *BRCA2* c.5946delT[3]. In the Ashkenazi Jewish population the incidence of *BRCA* pathogenic variants is 1 in 40; the general population incidence of *BRCA* pathogenic variants is not exactly known, but is suspected to be between 1 in 300 and 1 in 800[1]. There are also specific pathogenic variants that are more commonly found in the French Canadian population and Icelanders, as well as others; these are all called "founder pathogenic variants" as they have been passed down in these populations from small ancestral origin groups[1,3].

Women in the general population are at an 8 to 12% lifetime risk of developing breast cancer, while pathogenic variants in the *BRCA* genes contribute a lifetime risk of 60-80% for developing breast cancer and a 20-40% lifetime risk of developing ovarian cancer[2]; *BRCA1* has traditionally been found to cause a higher risk for ovarian cancer than *BRCA2*[4]. These genes also carry risks for other cancers: a second or contralateral breast cancer, male breast cancer, pancreatic cancer, melanoma (only *BRCA2*), and prostate cancer. Other cancer risks have been suggested to have an association with the *BRCA* genes, but these are controversial and not found to be increased in all studies[4,5].

Individuals can be assessed for their individual likelihood to carry a *BRCA* pathogenic variant based on their own personal and family histories of cancer. These factors can then be compared to nationally accepted, standard guidelines, and/or used in a risk model. These models have been created based on pathogenic variant frequencies and cancer penetrance; these models

were developed to help clinicians determine a numerical estimate for the likelihood that an individual carries a pathogenic variant in one of their *BRCA* genes and if that individual is at a high risk to develop breast cancer. If an individual meets set criteria, then she/he is eligible for genetic testing and should be counseled appropriately[1].

When an individual is found to carry a pathogenic variant in one of the *BRCA* genes, there are a variety of surveillance, chemoprevention, and risk reducing surgical strategies available for consideration[1]. Women are recommended to begin breast self-awareness at the age of 18, get clinical breast exams every 6 to 12 months starting at age 25, and start annual breast MRI's between the ages of 25 and 29 depending on the breast cancer history within the family. After the age of 30 women with *BRCA* pathogenic variants are recommended to undergo annual mammograms and MRIs, preferably one every 6 months; over the age of 75 women should be screened based on their provider's recommendation[6]. For comparison, women who are at general population risk to develop breast cancer begin mammograms at the age of 40 or ten years prior to the earliest diagnosis of breast cancer in their family[7]; women who carry a variant of uncertain significance (VUS) should be managed based on their family history. Women with *BRCA* pathogenic variants are also given the option of risk reducing prophylactic mastectomies which can reduce the risk of developing breast cancer by at least 90%[8]. Women with pathogenic variants are also given the option of taking Tamoxifen, a chemopreventive agent, which may reduce breast cancer risk by 62%[1]. To reduce her ovarian cancer risks, a woman who has a *BRCA* pathogenic variant is recommended to have her ovaries and fallopian tubes removed after 40 years of age or after she has completed her family; another screening possibility, that is not the standard of care, is to screen for ovarian cancer through the use of a blood test looking for the tumor marker, CA-125, and transvaginal ultrasounds[1,6]. Men with *BRCA* pathogenic variants

should begin self-breast exam training and education at age 35, in addition to a clinical breast exam annually. At age 40, men with *BRCA2* pathogenic variants are recommended to begin annual prostate screening, while those with *BRCA1* pathogenic variants should only consider prostate screening at that time[6]. Anyone who carries a *BRCA* pathogenic variant should be educated on the signs of pancreatic cancer and melanoma; they should also establish care with an ophthalmologist and a dermatologist[6].

To provide informed consent, individuals should be educated on the possible risks, benefits, implications of, and limitations associated with any genetic testing. Risks may include: psychosocial and emotional impacts, incidental findings such as misattributed paternity, and the possibility of being denied life or disability insurance. Some benefits associated with genetic testing include: being better educated about one's health, having an answer or explanation for a family history of a cancer, being able to develop a personalized medical management plan, and having peace of mind that increased cancer risks were not passed on to one's children should a person tests negative. Implications associated with genetic testing include: increased cancer risks, risk to family members, and having to inform at-risk family members of their chance to carry a cancer predisposing pathogenic variant. Some limitations of genetic testing include: receiving an ambiguous result known as a variant of uncertain significance or VUS, not finding a pathogenic variant to explain a family cancer history, that not all tests are the same or equally reliable, and that genes are not the only factors that contribute to cancer[9].

1.1.2 Genetic Testing Guidelines

Genetic testing for breast cancer predisposition is most often ordered and then subsequently covered by insurance if an individual meets a set of criteria. There are a number of published

guidelines that are used to determine eligibility for *BRCA1/2* testing. Including: the National Comprehensive Cancer Network (NCCN), the American Cancer Society (ACS), and the United States Preventative Services Task Force (USPSTF). These guidelines rely on personal and family cancer histories, of blood relatives only, to determine if an individual is a candidate for genetic testing.

An example of some, but not all, of the *BRCA1/*2 testing criteria that an individual can meet to receive a cancer risk assessment and genetic testing, from the NCCN, are as follows[6]:

- A person with a known familial pathogenic variant in *BRCA1* or *BRCA2*
- A person with a personal history of breast cancer diagnosed at the age of 45 or younger
- A person diagnosed with breast cancer between the ages of 45 and 50 with one of the following:
    - An additional primary breast cancer
    - At least one blood relative with a breast cancer at any age
    - At least one relative with pancreatic or prostate cancer
    - An unknown or limited family history
- A person diagnosed with breast cancer at an age with at least one of the following:
    - Of Ashkenazi Jewish ancestry, or any other ethnicity associated with high pathogenic variant frequencies
    - Two additional relatives on the same side of the family with breast cancer at any age or one relative with breast cancer at or before the age of 50
    - A close relative with ovarian cancer or male breast cancer at any age

    - Two close relatives with pancreatic and/or prostate cancer at any age
- Individuals who have had ovarian cancer or male breast cancer
- For an individual who is unaffected but has a family history of the following:
    - A first or second degree relative who would meet criteria
    - A third degree relative who has had breast cancer and/or ovarian cancer who has an additional two relatives with breast cancer, one of which must be at the age of 50 or younger, and/or ovarian cancer

1.1.3 Prior Physician Knowledge Studies

Physician knowledge studies exist within the literature and appear to be conducted with a variety of goals in mind. In preparation for a new wide-spread medical initiative, such as population *BRCA* gene testing, the base-line knowledge of physicians should be assessed. By determining what an average population of physicians knows about a topic, focused education programs and support tools can be developed and implemented in preparation for these changes. A literature search of previous studies assessing physician knowledge of breast cancer and breast cancer genetics was performed to better understand topics that have been previously assessed in order to develop a survey that would include questions that may provide additional information in this area.

Teng, et.al in 2014 assayed 161 physicians including: oncologists, other specialists, and general practitioners to examine physicians' knowledge of cancer genetics, patient family history assessment, and attitudes about genetic testing for cancer predisposition using a questionnaire[10]. Although overall knowledge was found to be "suboptimal," the study found that

breast and ovarian cancer specialists were most proficient in genetic testing knowledge, followed by gastrointestinal specialists, "other specialists," and lastly the general practitioners. While general practitioners had the lowest knowledge scores, they were the most likely to want to receive further education on the subject. Over 90% of the responders thought it was their duty to inform a patient about being at high-risk for a hereditary cancer predisposition, prompting them to inform those patients that there was testing available and to refer them to a genetic counselor. An additional aim of this study was to examine the referrals and referral rates of their study population. Unfortunately, referrals and referral rates could not be measured due to a number of factors[10].

An Italian study by Marzuillo and colleagues in 2013 assessed a random sample of physicians regarding their knowledge of and attitudes toward predictive testing for the genes *BRCA1/2* and *APC*[11]. Many of the surveyed physicians thought genetic testing should be performed without efficacy or cost-effectiveness data. A limitation of this study is its lack of specialty data on the physician participants. However, the study found physicians were more likely to refer a patient for genetic testing if the patient had asked for the testing. They also found that greater than 90% of the physicians wanted to improve their knowledge of cancer genetics and 80% thought they currently had inadequate knowledge. The study found that physicians often over-referred for breast and colorectal cancer because they perceived the prevalence of pathogenic variants in predisposing genes to be much higher than in reality. From these data the researchers concluded that physicians are not yet ready to provide cancer genetic testing[11].

In a study by Dhar, et.al from 2011, a random sample of physicians which included: family medicine specialists, OB/Gyns, general surgeons, internal medicine specialists, and

hematology/oncology specialists, all of whom were members of the Texas Medical Association, were given hypothetical HBOC patient cases from which they had to identify the correct management and recommendations for the patient based on their genetic test results and family history. Results revealed that only 16% of physicians followed NCCN guidelines for management of a pathogenic variant positive, unaffected woman. Family and internal medicine practitioners were more likely to recommend too little breast cancer screening; these practitioners under-recommended MRIs, prophylactic mastectomies, and bilateral salpingo-oophorectomies in pathogenic variant-positive women. OB/Gyns and hematology/oncology practitioners were more likely to over-recommend surveillance for pathogenic variant-negative women; only 43% of these physicians correctly managed a patient in this situation. This study highlighted the need for specialty related education to ensure that both pathogenic variant positive and pathogenic variant negative patients receive appropriate cancer screening and management. [12].

In 2005, Wideroff, et.al surveyed 1,251 licensed members of the American Medical Association[13]. Random physicians of differing specialties were given a questionnaire which attempted to assess their knowledge of cancer genetics, predictive genetic testing, and the benefits and limitations of genetic testing. The specialties surveyed were general internal medicine, general practice, family practice, obstetrics/gynecology, oncology, general surgery, urology, and gastroenterology. The topic of paternal inheritance of the *BRCA* genes was of particular interest to this group who found that overall, only 33% of the surveyed physicians agreed with the possibility of paternal inheritance, 50% were unsure and 10% thought it didn't happen; oncologists and OB/Gyns had higher awareness of the possibility of paternal inheritance of *BRCA* genes than family or general practitioners. Also, only 33% of the surveyed physicians

accurately responded that 10% of breast cancers are caused by *BRCA* pathogenic variants, 25% overestimated the number of carriers, and 33% were unsure; again oncologists, general surgeons, and OB/Gyns had a higher likelihood of an accurate response than general or family practitioners. This survey also found a trend between decreases in accuracy when answering genetic testing questions and the physician's age but this finding was not statistically significant. Generally, this survey showed inconsistent genetics knowledge across specialties, though slight correlations were seen between how recent cancer genetics services were provided and accuracy of answering. The strength of this study stems from the fact that it was a national sample of physicians and the researchers were able to achieve a response rate of 71%; a limitation is that not all of the specialties were equally represented. Wideroff, et.al concluded with the recommendation that provider knowledge of cancer genetics should continue to be improved and that motivations of providers to incorporate cancer risk assessment into clinical practice should be investigated[13].

A study from Cohn, et.al (2014) assessed the association between prior genetics training or knowledge and the rate of patient referral to genetics[14]. One-hundred and forty physicians from the NYIT College of Osteopathic Medicine database and the American College of Osteopathic Family Medicine were recruited to fill out a questionnaire regarding their knowledge of HBOC, Lynch syndrome, and familial adenomatous polyposis, this particular paper only included analysis of the answers to HBOC questions. The data from this group indicated a correlation between genetics training and increased HBOC knowledge, as well as a correlation between increased referrals of high-risk patients and knowledge of HBOC. Limitations of this study include possible reporting biases of the participants on referral frequency, inability to compare specific genetics training, and the possibility that the 89% who were invited to, but did

not respond to the questionnaire may have been less engaged in genetics. The authors recommended that additional physician knowledge studies be conducted to further define the knowledge deficiencies and aid in developing genetics training[14].

A 2013 study from Pal et.al also described physician knowledge and application of *BRCA* genetic testing[15]. Their study population encompassed physicians from the state of Florida offering *BRCA* testing who were identified from the Myriad Genetics website. Of 386 providers who were invited to participate, there were 87 respondents. Providers most often responded correctly to questions involving inheritance and pathogenic variant prevalence. Deficiencies were observed in knowledge of management and correct usage of testing; particularly for VUS discoveries and when rearrangement testing is warranted. Based on their findings and due to the liabilities associated with inadequate knowledge and training about *BRCA*, the authors recommended an increase in regulations for those ordering cancer genetic testing[15].

In contrast to many of the above studies which indicated a need for more provider education, Douma, et.al (2015) found that non-genetics healthcare professionals who are currently ordering cancer gene testing are adequately educated and often comfortable with obtaining informed consent[16]. The clinicians who participated in this study were selected because each had self-identified as a provider of cancer genetic services and were members of either the Myriad Genetics 'Find a Healthcare Provider' database or the National Cancer Institute's Cancer Genetics Services Directory. Using this method of recruitment, this study had a response rate of 11% for a total study population of 44 physicians. The question that was answered incorrectly most often concerned VUS results and the protocol for subsequent testing in other family members of a patient. An additional topic that non-genetics healthcare professionals believed to be difficult and that they were uncomfortable addressing were the

emotional needs of the patient. A limitation of this study was the limited response rate, which could mean those who did respond were those most interested in and confident with cancer genetic testing. This group thought these physicians had adequate knowledge to provide testing, but needed to be better educated on the emotional needs of patients[16].

Review of the literature consistently reveals that practitioners have deficiencies in their knowledge of the inheritance of the *BRCA1/2* genes, management based on genetic test results and the protocols for VUS testing in other family members. Fortunately, the studies have also consistently shown that health care providers are interested in or willing to participate in advanced genetics education, which gives hope for future education directives. However, none of the studies aimed to identify the factors that would motivate physicians to incorporate cancer genetic testing into their practice.

1.1.4 Research Supporting Population *BRCA1/2* Screening

In the past several years a number of papers supporting the institution of population-based BRCA screening have been published[17–20]. These studies have been designed to provide a better foundation for implementation of a screening program by trying to answer the points needed for fulfillment of criteria for population-based *BRCA* screening. One such group designed a study designed to answer the question of whether the cancer risks were the same in a random population based study as they are in a selected population. Gabai-Kapara, et.al (2014) genotyped more than 8,000 cancer-free Ashkenazi Jewish men, in Israel, for the three *BRCA1/2* founder pathogenic variants in that population[17]. After genotyping, those men who had pathogenic variants were asked to invite their families to participate and to provide a pedigree. The relatives were genotyped and new cumulative incidences of cancer were determined based

on these family histories. This study found the incidence of breast cancer by age 60 was 0.41(± 0.06) for *BRCA1* pathogenic variant carriers and 0.26 (± 0.08) for *BRCA2* pathogenic variant carriers; the incidences of breast cancer by age 80 were 0.60 (± 0.10) and 0.40 (± 0.11) for *BRCA1* and *BRCA2* respectively. This study found the cumulative incidences of ovarian cancer among pathogenic variant carriers by age 80 to be 0.53 (± 0.11) and 0.62 (± 0.18) for *BRCA1* and *BRCA2* respectively. This high risk of ovarian cancer in *BRCA2* pathogenic variant carriers is suspected to be due to the location of the c.5946delT pathogenic variant within the gene which is located in an "ovarian cancer cluster region." Combined cancer incidence values for breast and ovarian cancer, by age 80, were also provided and were 0.83 (± 0.07) for *BRCA1* pathogenic variant carriers and 0.76 (± 0.13) for *BRCA2* pathogenic variant carriers. Interestingly, 51% of the families that were identified to carry a pathogenic variant would not have met traditional family history criteria for genetic testing. The authors concluded that though this study was performed within an Ashkenazi Jewish cohort, the findings are applicable to the global population of *BRCA* pathogenic variant carriers. There are a number of reasons that the authors formed the conclusion that these results were broadly applicable; first, the finding that 50% of the pathogenic variant carriers identified in their cohort would not have been identified if family history was assessed, so they would not have been managed for their high risk of developing breast and ovarian cancer. Second, the authors found that the reported frequency of breast cancer in their study population matched the rates of breast cancer documented in population registries for the birth cohort, so individuals without an apparent family history of breast cancer have the same risks as those with family histories. Third, a population-based program would allow a person to receive *BRCA1/2* genetic testing regardless of family history or a physician referral, when a physician may incorrectly assess a patient's family history. These authors

believe a *BRCA* screening program should be developed to reduce the incidences of breast and ovarian cancer[17].

Additional population-based *BRCA* screening trials have compared the quality of life outcomes experienced by Ashkenazi Jewish individuals who have been tested for the founder pathogenic variants on either a population basis or selected based only on traditional family history requirements[18]. Manchanda et.al (2014) studied an Ashkenazi Jewish cohort of 1,017 people in the United Kingdom and using randomization placed them either in a group who would be genotyped if they met family history criteria or in a group where all would be genotyped, regardless of history. This research team detailed two main findings; first they found 56% more pathogenic variant positive individuals in the population screen group than in the family history-based group (13:9), the family history based screening missed 5 pathogenic variant positive participants. Second, through post-counseling questionnaires filled out at seven days and three months, they found that there was no statistically significant difference between the quality of life outcomes between *BRCA* pathogenic variant carriers and non-carriers and that counseling led to a decrease in anxiety and uncertainty[18]. Of note, the UK maintains more stringent family history testing criteria than the U.S. and this requirement may have affected how many noncarriers and family history negative participants were identified.

Manchanda et.al (2015) also performed a cost-effectiveness analysis of population- versus family history-based genetic testing in Ashkenazi Jewish women aged 30 years and older[19]. This group compared relative health outcomes using quality-adjusted life-years (QALYs) and costs of interventions based on known cancer incidences in their population from the aforementioned study. A population-based screening program was calculated to save 0.090 more life years and 0.101 more QALYs when compared to only utilizing family history-based

testing; this is associated with a monetary decrease of £2,079/QALYs, or roughly $2,935/QALYs, and a decrease in cancer incidence of 0.34% for ovarian cancer and 0.62% for breast cancer. Costs not included in this analysis comprise the costs of educating the public and healthcare professionals, community involvement, and any media campaigns necessary to institute a population-based screening program. This group maintains introducing a population-based screening program for Ashkenazi Jewish women would save lives and resources; this data cannot be extrapolated to a general population due to the high testing costs associated with complete gene sequencing and deletion/duplication studies required due to an absence of founder pathogenic variants, so further research is necessary[19].

An assessment of clinicians' views and opinions regarding population screening for *BRCA* pathogenic variants has already been conducted, as clinicians will play a large part in the implementation of a new screening program. A study by Shkedi-Rafir, et.al (2013) surveyed the opinions of family practice physicians, geneticists, and genetic counselors in Israel regarding population screening within the Ashkenazi-Jewish population[20]. Most of their questions focused on the amount of agreement or disagreement with statements about benefits and drawbacks as well as false reassurance or screening neglect of pathogenic variant negative individuals; additional questions sought opinions on optimal age of genetic testing and counseling requirements. Approximately 50% of the surveyed clinicians were in favor of population *BRCA* screening in the Ashkenazi-Jewish population. An interesting finding was that individuals who would wish that they could be tested for a *BRCA* pathogenic variant, even without family history, were more likely to be in favor of population *BRCA* testing. Most clinicians surveyed thought genetic counseling should occur before genetic testing; but a portion of the family practitioners thought genetic counseling should not be compulsory and/or should only be a post-test option for

pathogenic variant carriers. Limitations of this study include its sample size of 204 participants due to low response rate, a homogeneous and possibly unrepresentative sample, and no test of clinician knowledge of breast cancer genetics. The lack of heterogeneity stemmed from the fact that the majority of their population was young, female responders, which is not representative of all of the family practice physicians, geneticists, and genetic counselors in Israel. The authors concluded that more evaluation and research is required before a population screening program should be implemented[20].

Future studies need to assess genetic counseling strategies for large scale testing and outcome testing of population screening initiatives[21]. Additional studies to duplicate the findings of the studies presented are indicated as well. Also, these studies were all performed within the Ashkenazi Jewish population or with regard to the Ashkenazi Jewish population, since specific pathogenic variants could be targeted and costs contained; using similar protocols, these studies should be repeated within a broader, general population. Pilot studies of general population-based *BRCA* screening will be critical to investigate the methods of counseling and the understanding of patients of their test results[22]. These studies are also needed to better understand the costs of providing counseling and testing services.

1.1.5 Opinions on Population *BRCA* Screening

Dr. Mary-Claire King, a researcher who played a major role in identifying the *BRCA* genes, has argued that because a number of studies suggest that cancer risks are similar in women with a *BRCA* pathogenic variant, regardless of family history, and genetic sequencing is readily available, a population-based screening effort should be implemented[21]. Additionally she contends that discovering that a person has a pathogenic variant after they have already been

diagnosed with a cancer is a failure of cancer prevention[21]. Dr. Mary-Claire King, Dr. Ephrat Levy-Lahad, and Dr. Amnon Lahad proposed screening parameters include initiating *BRCA* testing into the standards of care before a woman would need to begin intensive breast surveillance and before a risk reducing salpingo-oophorectomy became recommended, preferably in her early 30s[21,23,24]. Additionally, it is recommended that VUS calls should not be reported until they are reclassified; a reference list of known disease-causing pathogenic variants should be developed and updated as needed, and only these pathogenic variants should be reported in population screening to eliminate the confusion for both providers and the patients[23,25]. This opinion on VUS reporting is supported by the American College of Medical Genetics which recommends only "unambiguous loss-of-function mutations" be reported when they are identified as incidental findings on exome sequencing[26]. Other plans for population cancer genetic screening, include the eventual inclusion of other cancer predisposition genes[26].

There are also arguments against the proposed population *BRCA* screening. The primary argument involves logistics, ethical, and legal aspects of not reporting VUS calls. In addition, there has not been a study to learn the opinions of the public, physicians, or the laboratories on not reporting this data[22]. There is also the fact that these unreported variants, which may later be reclassified as pathogenic alterations, will then be false-negatives and will be heavily prevalent in minority populations. Another argument against population-based *BRCA* screening regards the availability of *BRCA1/2* pathogenic variant testing for all women. This sentiment is also true where follow-up care and surveillance after genetic testing is concerned, preventative measures recommended as a result of a finding a *BRCA* pathogenic variant may not be readily available to all women. Additionally, not all of the recipients of population-based *BRCA* testing will be able to receive genetic counseling services, thus new informed consent and counseling models will

need to be developed to accommodate all of the women who will need these services[27]. Another opinion in favor of waiting to implement population-based screening, expressed by Joy Larsen Haidle when she was President-elect of the National Society of Genetic Counselors, indicates the need for providers and the general public to be better educated on the risks of hereditary cancer so the proper genetics referrals can be made[28]. She states: "it is premature to suggest that the medical system is prepared to implement general population screening of *BRCA1* and *BRCA2* mutations, and more harm than good can happen as a result[28]." In other terms, these nay-sayers believe further research and the proper safeguards need to be put in place before population-based *BRCA* screening can be implemented.

1.1.6 Population Screening Guidelines

There are well established screening guidelines to detect chronic and prevalent diseases early, which were created by Wilson and Junger in 1968[29]. The principles were developed to provide a process for deciding which conditions should be screened for due to the complexities involved with and maintaining screening practices[30]. The ten principles are as follows[29]:

> "(1) The condition sought should be an important health problem.
>
> (2) There should be an accepted treatment for patients with recognized disease.
>
> (3) Facilities for diagnosis and treatment should be available.
>
> (4) There should be a recognizable latent or early symptomatic stage.
>
> (5) There should be a suitable test or examination.
>
> (6) The test should be acceptable to the population.

(7) The natural history of the condition, including development from latent to declared disease, should be adequately understood.

(8) There should be an agreed policy on whom to treat as patients.

(9) The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.

(10) Case-finding should be a continuing process and not a "once and for all" project."

These principles were created during a time of significant medical advancement when screening was controversial and a process was needed to maintain consistent care for the public[30].

Current genetic population-based screening programs generally focus on autosomal recessive conditions and include examples such as newborn screening programs and pre-conception cases to identify Tay Sachs carriers in the Jewish population[30]. As these principles are considered for genetic diseases, some have suggested that Wilson and Junger's criteria need to be reevaluated and updated. For example, Andermann et.al (2008) developed modifications to Wilson and Junger's criteria which is geared toward genetic screening, based on a review of the literature and practitioner consults of what criteria and changes to the criteria had been utilized since 1968. They are as follows[30]:

"(1) The screening program should respond to a recognized need.

(2) The objectives of screening should be defined at the outset.

(3) There should be a defined target population.

(4) There should be scientific evidence of screening program effectiveness.

(5) The program should integrate education, testing, clinical services and program management.

(6) There should be quality assurance, with mechanisms to minimize potential risks of screening.

(7) The program should ensure informed choice, confidentiality and respect for autonomy.

(8) The program should promote equity and access to screening for the entire target population.

(9) Program evaluation should be planned from the outset.

(10) The overall benefits of screening should outweigh the harm."

These adapted criteria are intended to be seen as updates and additions to the original criteria, to better reflect Westernized medicine and new societal views, as well as to better encompass genetic screening concerns. Andermann, et.al stated, "This approach to screening policy-making encourages documentation of evidence, trade-offs, and the reasoning underpinning recommendations, thus promoting greater transparency, and allowing decisions to be revisited over time[30]."

1.2 SPECIFIC AIMS

1.2.1 First Aim

The first aim of this study was to survey the breast cancer genetics knowledge of primary care physicians, specifically family practice physicians and OB/Gyns in the UPMC system.

1.2.2 Second Aim

The second aim of this study was to elicit the opinions of primary care physicians on who they believe would be the best health care specialist to discuss, order, disclose, and manage patients with regard to their *BRCA1/2* gene testing.

1.2.3 Third Aim

The third aim of this study was to assess what would motivate the study population to incorporate new testing or procedures into their practice, in this case, population-based *BRCA1/2* screening.

1.3 SIGNIFICANCE

1.3.1 Significance of the First Specific Aim

It is assumed that these two groups of providers, obstetrics and gynecology and family practice professionals will be the practitioners women will visit most often for their medical care. Should this assumption be correct, then these physicians are the best candidates to implement population-based *BRCA* screening in all women over the age of 30 and will need to have the proper knowledge and counseling tools to provide the public with the best care.

1.3.2 Significance of the Second Specific Aim

It is suggested that the providers in question may be the expected ones to implement screening. However, their perceptions regarding the best care provider to implement a population-wide screening program may be at odds with this expectation. Knowing who these providers believe to be the most qualified to provide population screening may be useful in the implementation of a program.

1.3.3 Significance of the Third Specific Aim

By illuminating the specific factors that providers consider motivational, these factors can then be manipulated and used as focal points to help ensure a more consistent up-take of educational materials and an overall smoother transition into population-based screening.

2.0 MATERIALS AND METHODS

This study has been approved as an exempt study by the University of Pittsburgh Institutional Review Board, approval number: PRO15030332. Please see the approval letter in Appendix C.

2.1 QUESTIONNAIRE DESIGN

This questionnaire was developed using the surveying tool Qualtrics Survey System (Qualtrics LLC), as required by the University of Pittsburgh Institutional Review Board. A consent form educating study participants was developed and was shown before participants initiated the questionnaire; the consent form can be found in Appendix A. The questions used were developed, edited, and piloted by individuals in the fields of cancer genetics, public health, obstetrics/gynecology, and family medicine. The process used in the development of some of the questions were guided by the physician knowledge surveys previously discussed, as well as others[10,11, 16,31 ,32]. Additional questions were developed similarly to those on a survey from the National Cancer Institute which gave physicians patient scenarios to analyze[33]. Furthermore, review of research from Boulton, et.al (1996) that assessed providers' knowledge and thoughts with regard to population-based cystic fibrosis screening, gave rise to many of the opinion-based questions created for the questionnaire[34]. A published literature review by Mikat-Stevens, et.al

(2014) based on primary-care provider's perceived barriers to integrating genetic testing services was utilized in the development of some opinion-based questions[35].

Three types of questions were constructed: knowledge, opinion, and demographic. The knowledge-based questions were designed to test the participants basic knowledge of the *BRCA1/2* genes; topics regarding inheritance, genetic testing, and results interpretation. Thirteen questions were created to assess the participant's knowledge. The goals of the opinion questions were to gauge participants' feelings toward population genetic screening and its implementation. Finally, the demographic questions were designed to gain a variety of information from the study participants in an effort to discover if any defining qualities affect knowledge and opinions of breast cancer genetics, genetic testing, and opinions concerning population-based *BRCA* screening.

This questionnaire was designed specifically for OB/Gyns and family practice or general physicians. Physicians employed at the University of Pittsburgh Medical Center (UPMC) in family practice or obstetrics and gynecology were selected as the study population for ease of access. Because healthcare providers are busy, the questionnaire was designed to take no more than fifteen minutes of the participant's time. No incentive was provided to participants and all responses were anonymized. The questionnaire can be found in Appendix B.

2.2 QUESTIONNAIRE DISTRIBUTION

This questionnaire was distributed by Dr. Robert Edwards, Chairman of the Department of Obstetrics and Gynecology at Magee-Women's Hospital of UPMC to the OB/Gyn physicians, residents and advanced practice providers of UPMC and by Dr. Mylynda Massart, family

practice physician, to the Family Practice physicians, residents, and advanced practice providers of UPMC. Email distribution lists were utilized in the dissemination of the questionnaire. A total of 342 providers were invited to participate; two hundred and forty-five OB/Gyn providers and 97 Family Practice providers. Drs. Edwards and Massart were asked to redistribute the questionnaire, using the same mailing lists, a few weeks after the initial distribution in an attempt to increase the number of responses.

2.3 DATA ANALYSIS

Initial descriptive analyses of the questionnaire data were performed using either Microsoft Excel version 14.0.7166.5000 (Microsoft Corporation, Redmond, WA) or the reporting functions of Qualtrics. Participants were only included if they completed the entire questionnaire and selected OB/Gyn or Family Medicine as their practice specialty. Questions which included an open response option were reported as is.

Comparative or analytical statistics were performed using Minitab Express version 1.2.0 (Minitab Inc., State College, PA). Comparisons of number of correct responses between the two surveyed groups were made utilizing 2-sample t-tests which reported the statistical significance of knowledge differences between the OB/Gyn and family medicine groups; comparisons were also made between genders and prior experience providing *BRCA* testing. Comparisons for statistically significant differences between the selected opinions of practice specialties were checked by utilizing the Mann-Whitney nonparametric test.

3.0 RESULTS

Three hundred and forty-two healthcare providers received the questionnaire and a total of 104 individuals began the questionnaire resulting in an initial response rate of 30.4%. Eighteen participants declined to complete the questions resulting in a drop-out rate of 17%. Thus, the data analyzed will encompass the 86 practitioners who elected to complete the questionnaire, unless otherwise specified, resulting in a response rate of 25.2%.

3.1 DEMOGRAPHIC INFORMATION

The survey was completed by 53 females and 33 males. The majority of participants, 47%, have been in the medical field for more than 15 years. Those who have been practicing for 10 to 15 years make up 15% of the surveyed population. Participants who have been practicing 5 to 10 years made up 13% of the survey group. Those who have been in practice for less than 5 years made up 16% of those surveyed and there were eight residents who took the questionnaire, making up 9% of the sample. Gender distribution of the participants, broken down by years of experience, can be visualized in Figure 1, below. Unsurprisingly, based on the selected population, when asked about practice setting 53% reported that they worked in an academic facility. Additionally, 22% reportedly work in a private practice, 19% work in a hospital-based practice, and 6% reported to work in “other” which some reported to mean FQHC (Federally

Qualified Health Center) or a community-based facility. When the participants were asked what their practice specialty was 62% reported obstetrics and gynecology, 27% reported family practice, one person identified themselves as working in internal medicine, and nine individuals responded with "other." "Other" was then reported to mean advanced practice provider/certified nurse midwife (four participants), gynecologic oncologist (two participants), maternal-fetal medicine or MFM (two participants), and a single reproductive endocrinologist. Of, note, for ease of further analyses, the two gynecologic oncologists will be excluded from the data as they are not directly in the target population. Additionally, all other participants will be sorted into either the OB/Gyn specialty or the family practice specialty for future analyses; the participant who selected "internal medicine" will be added to the family practice grouping and those who identified as advanced practice providers, MFM, and the reproductive endocrinologist will be added to the OB/Gyn group. For exact numbers of participants in the previously mentioned categories, please see Table 1, below. Two hundred and forty-five individuals were sent questionnaires using the OB/Gyn email list and 60 responded. The response rate for the OB/Gyn group is 24.5%. Ninety-seven questionnaires were sent out using the family medicine emailing list and 24 responded for a response rate of 24.7%.

Participants were also asked some questions regarding their personal experience with genetics, *BRCA* testing specifically, and breast or ovarian cancer. When asked if the participant had received any formal genetics training, outside of their schooling, 87% responded that they had not. Participants were then asked if their current group or practice provides *BRCA* testing to its patients; 20% indicated that they did, 30% responded that they did not, and 50% reported that they refer such patients to genetics. Additionally study participants were asked if they personally had ever provided *BRCA* genetic counseling to a patient and 60% reported that they had not,

while 40% indicated that they had provided genetic counseling. Participants were also asked if they had a personal or family history of breast cancer; 77% said no, 2% were unsure, and the remaining 21% indicated they did have a personal or family history. Study participants were then asked if they personally have or would wish to receive *BRCA* gene testing, 84% indicated they would not wish to receive *BRCA* gene testing and an additional 14% indicated they were unsure of their interest, leaving only two individuals who have already or would wish to be tested for pathogenic variants in the *BRCA1/2* genes.

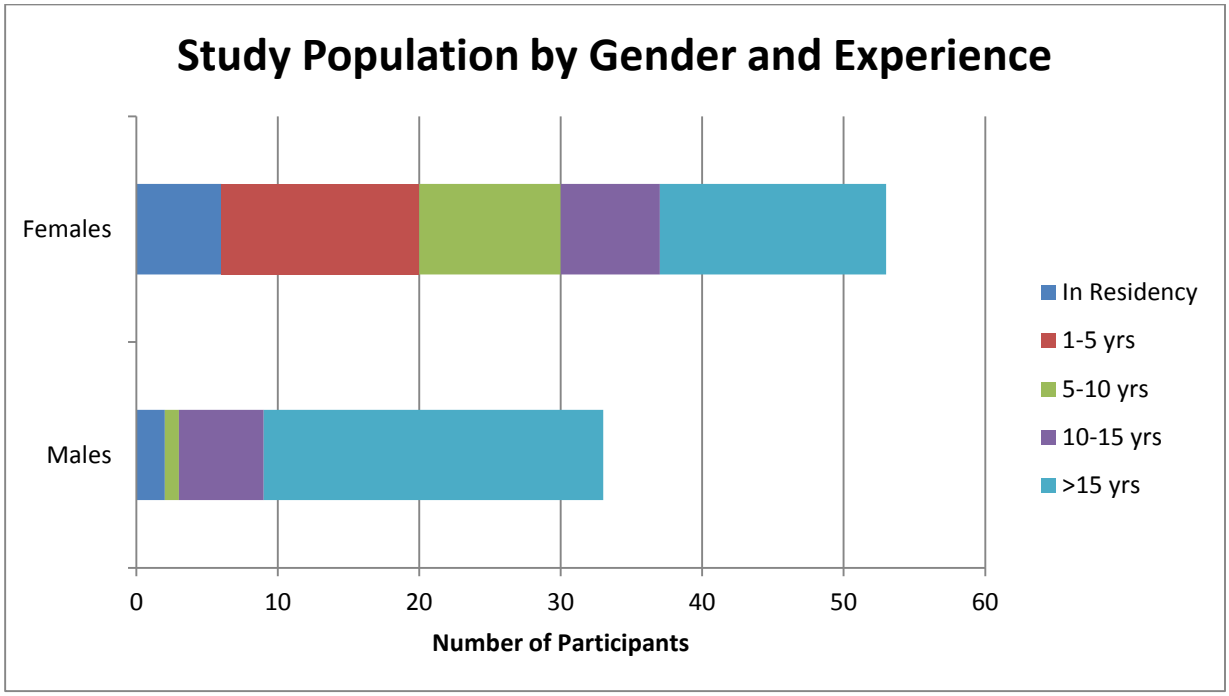

Figure 1: Participants by Gender and Years of Experience

Table 1: Characteristics of the Study Population

Demographics	**N (%)**
Gender	
Male	33 (38)
Female	53 (62)
Length of time in profession	
Currently a Resident	8 (9)
<5 years	14 (16)
5-10 years	11 (13)
10-15 years	13 (15)
>15 years	40 (47)
Type of practice setting	
Private	19 (22)
Hospital-Based	16 (19)
Academic	46 (53)
Other (FQHC, Community)	5 (6)
Practice Specialty	
OB/Gyn	53 (62)
Family Practice	23 (27)
Internal Medicine	1 (1)
Advanced Practice Provider	4 (4)
Other (Gyn Onc, Reproductive Endo, MFM)	5 (6)
Do you/your practice currently provide *BRCA* testing?	
Yes	17 (20)
No	26 (30)
Referred to genetics	43 (50)
Have you personally provided *BRCA1/2* genetic counseling?	
Yes	34 (40)
No	52 (60)
Have you received formal genetics education, outside of medical school/training?	
Yes	11 (13)
No	75 (87)
Do you have a personal/family history of breast or ovarian cancer?	
Yes	18 (21)
No	66 (77)
Unsure	2 (2)
Have you or would you wish to undergo *BRCA1/2* testing?	
Yes	2 (2)
No	72 (84)
Unsure	12 (14)

3.2 KNOWLEDGE BASE ANALYSIS

The average score of all participants was 73.4%, or 9.5 questions correct out of 13 total knowledge questions. The average score of the OB/Gyn group was 75.9%, with an average number correct of 9.9. The average score of the family medicine group was 67%, which means they, on average got 8.7 questions correct. A summary of all questions and how the participants answered can be found in Table 2, below.

The first question the participants were asked to answer is how the *BRCA1/2* genes are inherited, 49 (58.3%) correctly answered autosomal dominant, 14 (16.7%) chose autosomal recessive, 2 (2.4%) chose x-linked inheritance, and 19 (22.6%) were unsure how these genes are inherited. All but two of respondents (98.8%) knew that the *BRCA* genes were not the only breast cancer predisposition genes. Regarding the high *BRCA* pathogenic variant carrier rate in the Ashkenazi Jewish population, 62 (73.8%) respondents knew this population had a higher carrier rate than the general population, the remaining respondents either thought this was false or were unsure. Concerning paternal inheritance of the *BRCA* genes, 81% agreed that a patient could inherit a pathogenic variant from their father. Forty-four participants (52.4%) correctly identified that the highest lifetime breast cancer risk associated with the *BRCA1* gene is 87%. The majority of respondents (97.6%) also correctly agreed that the *BRCA* genes are also associated with increased risks for ovarian cancer; however only 48.8% of participants knew which gene carried a higher lifetime risk of developing ovarian cancer. Furthermore, all but one of the respondents (98.8%) also correctly identified the definition of a VUS.

Regarding testing pathways, the majority of participants (76.2%) knew that an unaffected individual is not the best person to initiate testing in a family, unless the other family members who have had cancer are no longer living or if they are unwilling to be tested. Additionally,

when a patient has a family member who is identified to carry a VUS, only 25 (29.8%) participants correctly indicated a healthy patient does not need to be tested for that variant; 30 (35.7%) respondents were unsure if that patient should receive genetic testing and 29 (34.5%) respondents thought that patient should receive testing for the variant. When asked about the mode of testing for a patient whose family has been found to carry a known pathogenic *BRCA* pathogenic variant, 55 (65.5%) participants correctly identified that site-specific or single-site analysis for the familial pathogenic variant would be warranted; 23.8% thought the patient should receive complete *BRCA1/2* sequencing, 9.5% thought the patient should receive *BRCA1/2* sequencing and deletion/duplication studies, and one participant selected whole exome sequencing as the best genetic testing option for the patient.

Regarding management based on test results, the majority of participants (86.9%) agreed that a patient with a VUS should receive treatment based on her family history. Similarly, 88.1% correctly identified that a patient who is found to not carry a familial pathogenic variant would have the risk to develop breast cancer similar to that of the general population.

To best analyze the knowledge of the participants, a t-test was performed to show the differences between the numbers of correctly answered questions of participants in the OB/Gyn specialty versus those in the Family Practice specialty. The OB/Gyn group received significantly overall higher knowledge scores than the family practice group ($p=0.016$). A box-plot of the distribution of scores in each of the two groups is shown in Figure 2; group 1 represents the OB/Gyn participants and group 2 represents the family practice physicians. The maximum score from the OB/Gyn group was 12/13 and the lowest score was 6/13. The maximum score from the family practice group was 13/13, only one individual answered all 13 questions correctly, and the minimum score was also 6/13. Additional findings of interest, there was no significant

difference in knowledge between genders (average scores equaled 9.5 and 9.6 in women and men respectively), but unsurprisingly, individuals who had previously provided *BRCA* testing and counseling were found to have increased knowledge of *BRCA* testing (average scores equaled 10 and 9.2, respectively; p= 0.042).

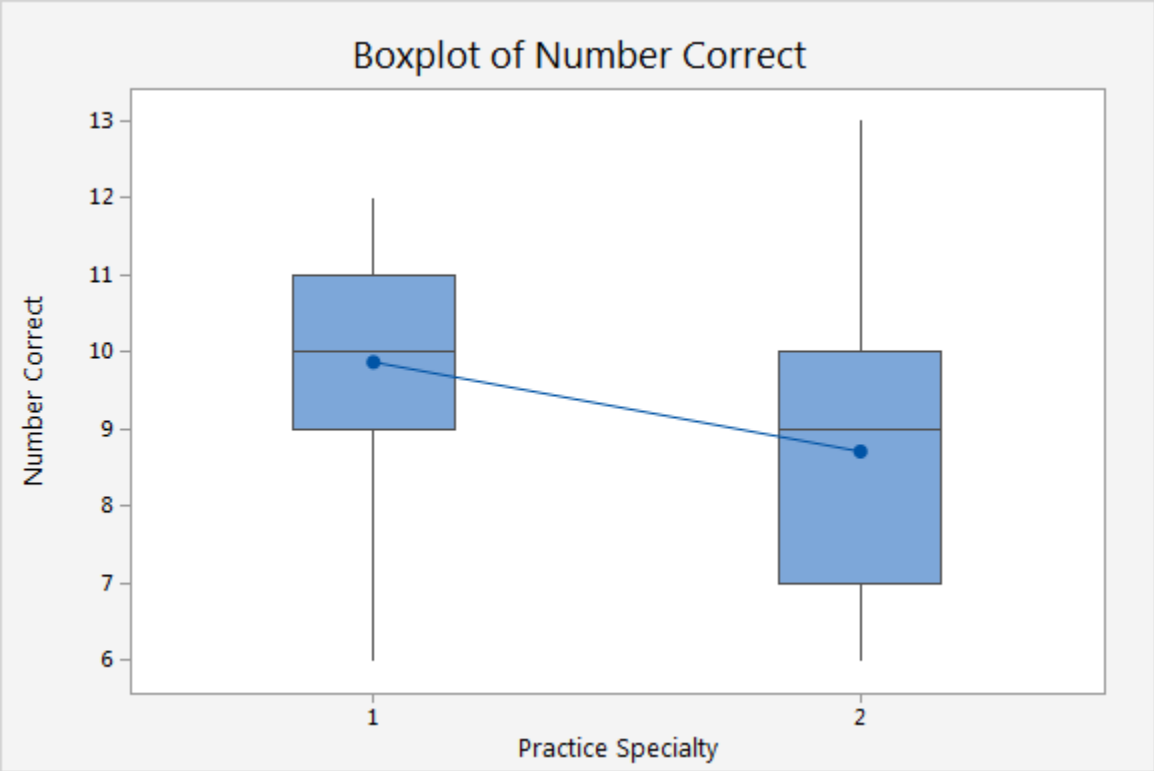

Figure 2: Boxplot of Correctly Answered Questions by Specialty

Table 2: Frequency of Correct Responses to each Knowledge Question

Question	Correct n (%)	
What is the mode of inheritance for pathogenic variants in the BRCA genes?	49 (58)	
True or false, BRCA1/2 pathogenic variants account for all hereditary breast cancers.	83 (99)	
The BRCA pathogenic variant carrier rate in individuals of Ashkenazi Jewish (Eastern European Jewish) ancestry is higher than the carrier rate of the general population.	62 (74)	
Your patient has an aunt on her father's side who is a carrier of a BRCA1 pathogenic variant. Is it possible that your patient could also carry this pathogenic variant?	68 (81)	
Your 35 year old female patient tests positive for a BRCA1 gene pathogenic variant. What is her highest lifetime risk of developing breast cancer?	44 (52)	
Your healthy patient tests positive for a BRCA pathogenic variant. She has an increased risk for breast and ovarian cancer. True or false?	82 (98)	
Your patient's maternal family history is significant for breast cancer diagnosed prior to age 50 in several women. Several of the affected women are still living but have not been tested for pathogenic variants in BRCA1/2. Your patient asks to be tested. Is she the best person to initiate testing in this family?	64 (76)	
Your unaffected patient undergoes BRCA1/2 testing and is found to have a variant of uncertain significance (VUS) in the BRCA1 gene. What does this mean?	83 (99)	
The same patient asks how the VUS result will affect her care. You tell her that her management will be based on her family history. True or false?	73 (87)	
Your patient's sister carries a VUS in the BRCA1 gene, should you test your healthy patient for this BRCA1 variant?	25 (30)	
Your patient's maternal family has a known BRCA1 pathogenic variant; there is no history of cancer in her father's family. What type of testing would you choose to offer your patient?	55 (65)	
This same woman undergoes testing and does not carry the known familial pathogenic variant. What is your interpretation of her risk of developing breast cancer?	74 (88)	
Which gene pathogenic variant carries a higher lifetime risk of developing ovarian cancer?	41 (49)	

3.3 OPINION ANALYSIS

All of the responses to the opinion questions were compared between the obstetricians/gynecologists and family practice physicians, using the Mann-Whitney test and no statistically significant differences of opinion were identified between the two groups.

The first opinion-based question asked the respondents about their confidence in their ability to provide information regarding breast cancer genetics; the respondents were asked to select whether they felt not confident, somewhat confident, or completely confident. Fifty participants (59.5%) indicated they were somewhat confident with *BRCA* cancer risks, while only 3 participants (3.6%) indicated they were completely confident. With regard to *BRCA* inheritance, 37 (44%) respondents indicated they were somewhat confident and 6 (7.1%) participants were completely confident. Thirty-seven participants (44.1%) were somewhat confident with medical management after *BRCA* testing, and no participants indicated they were completely confident. Thirty-five (41.7%) respondents were somewhat confident with *BRCA* genetic test result interpretation and one participant indicated he/she was completely confident. Participants were least confident with the many *BRCA* testing methods, 30 participants (35.7%) were somewhat confident and 2 (2.4%) were completely confident. Figure 3 is summarized bar graphs of the participant's confidence levels.

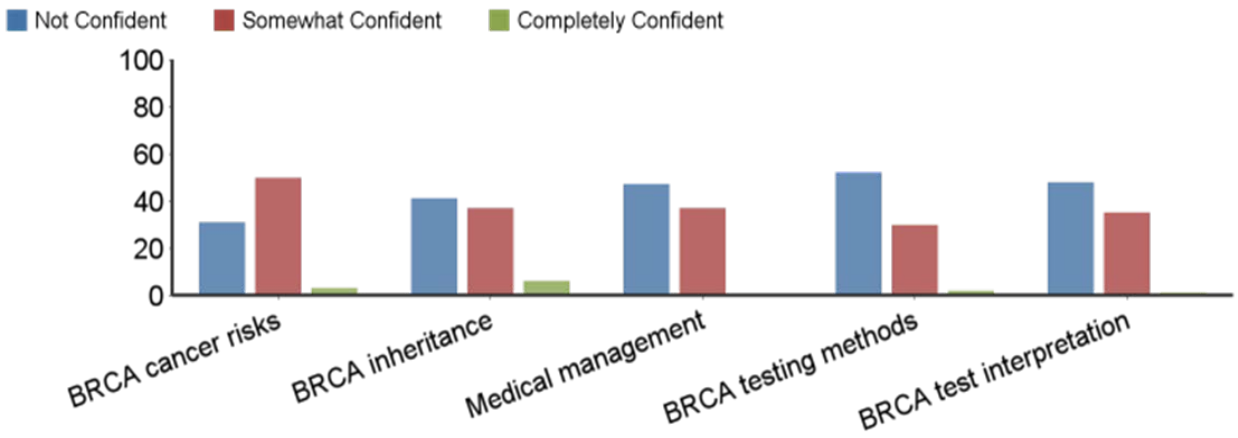

Figure 3: Participants' Confidence with Providing Breast Cancer Genetics Information

Participants were asked which fellow health care professionals would be best qualified to provide genetic testing and counseling services. The vast majority of participants, 97.6%, 83.3%, and 97.6%, respectively, thought that medical geneticists, genetic counselors, and oncologists were the best professionals to address these concerns for the patient. Respondents were split fairly evenly on their opinions regarding the qualifications of Obstetrician/Gynecologists and Nurse Specialists to provide *BRCA* testing and risk assessment to patients. The respondents were also given the option to input additional professionals who they deemed were qualified to address patient's risks, testing, and counseling; all additional responses were regarding trained family practice and primary care physicians. Please see Figure 4 below for a graphical representation of all responses.

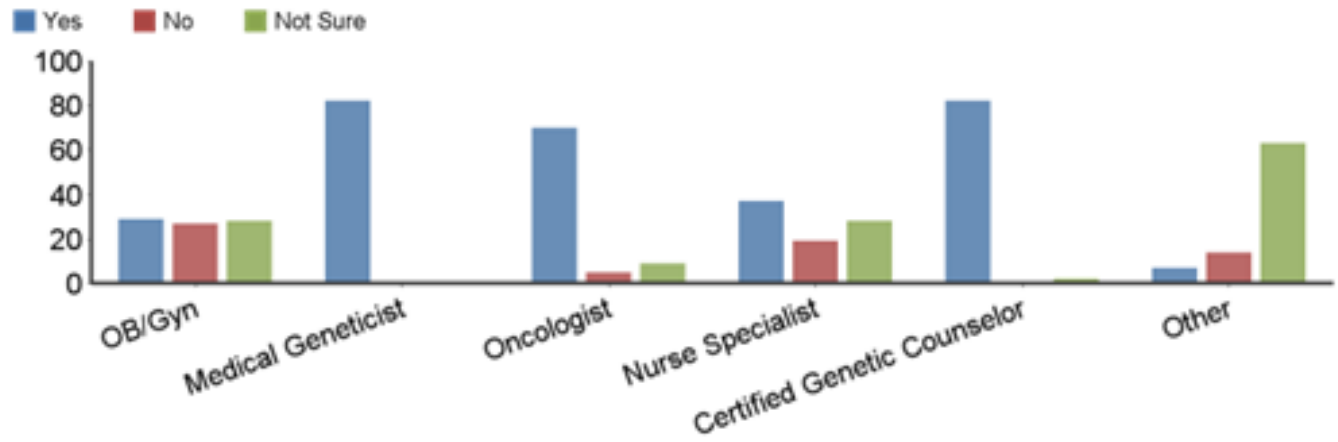

Figure 4: Participants' Beliefs on Provider's Qualifications

When queried about whether they felt a population-based testing program would be cost effective, 85.7% of respondents did not believe it would be. The majority of respondents, 79.8%, indicated that they did not have adequate time or resources to provide *BRCA* testing to every female patient, over the age of 30. However, when asked if they would be interested in future medical genetics and cancer risk assessment education, 75 (89.3%) participants indicated some level of interest.

Participants were also asked to specify what factors would motivate them to incorporate *BRCA* gene testing into their practice (Table 3). Forty-three participants, 51.2%, indicated they would be more motivated if there was population-based evidence that their patient population was at risk of carrying a pathogenic variant. Thirteen respondents, 15.5%, would be motivated by being personally affected or having a family member affected by breast cancer. Thirty respondents, 35.7%, would be motivated to incorporate testing if they had a patient with a *BRCA* pathogenic variant. Forty-four participants, 52.4%, would be motivated to offer testing if their patients requested testing. Forty-five respondents, 53.6%, indicated cost-benefit data would motivate them. Thirty-one participants, 36.9%, indicated incorporation of cancer risk assessment

in electronic records to help red-flag appropriate patients would be a motivating factor to incorporate testing into their practice. Fifty-nine participants, 70.2%, indicated their greatest motivator would be evidence-based professional society guidelines indicating the utility of population-based testing. Finally, 4 individuals, 4.8%, indicated they were not interested or motivated to incorporate *BRCA* testing into their practice.

Table 3: Motivators to Incorporate *BRCA* Testing into Practice

Proposed Motivator	Participants n (%)
Population evidence that your patient population is at increased risk for carrying a BRCA pathogenic variant.	43 (51)
Being personally affected by breast cancer or having a close family member or friend with breast cancer.	13 (15)
Having a patient with a BRCA pathogenic variant.	30 (36)
Patients requesting testing.	44 (52)
Cost/benefit data.	45 (54)
Evidence-based professional society guidelines.	59 (70)
If the electronic health record provided a cancer risk assessment to flag appropriate patients.	31 (37)
Not interested or motivated to incorporate this testing into my practice.	4 (5)

The final opinions collected from the participants were answered on a scale, strongly disagree, disagree, neutral, agree, and strongly agree; the participants were given a number of statements with which they had to state agreement or disagreement (Table 4). Fifty respondents, 59.5%, disagreed with the statement that the benefits of population *BRCA* screening outweigh the risks; 8.3% agreed. Thirty-four respondents, 42.7%, disagreed with the statement that population screening will reduce breast cancer morbidity and mortality, 38.1% were neutral on the matter. Fifty-four participants, 64.3%, felt that pathogenic variant carriers would feel like

they can better protect themselves from the future cancers; 10.7% disagreed with this statement. Thirty respondents (35.7%) believe *BRCA* testing will lead to stigmatization or discrimination, while 39.3% disagree with that statement. Fifty-three respondents (63.1%) agree that a negative test result will lead to false reassurance of cancer risks. Twenty-seven respondents, 32.1%, agree that a negative test result will lead to neglect of routine breast health surveillance; but 32 participants (38.1%) disagree. Forty-two respondents (50.0%) agree that pathogenic variant carriers will experience significant, long-term psychological and emotional distress; thirty-two participants (38.1%) felt neutral about the subject.

Table 4: Provider Opinions on Population *BRCA* Screening

Statement	Strongly Disagree n (%)	Disagree n (%)	Neither Agree nor Disagree n (%)	Agree n (%)	Strongly Agree n (%)
The benefits of population BRCA screening outweigh the risks.	7 (8)	43 (51)	27 (32)	6 (7)	1 (1)
Population screening will reduce breast cancer morbidity and mortality.	4 (5)	31 (37)	32 (38)	17 (20)	0 (0)
Pathogenic variant carriers will feel like they can better protect themselves from future cancers.	0 (0)	9 (11)	21 (25)	48 (57)	6 (7)
Testing will lead to stigmatization or discrimination.	7 (8)	26 (30)	21 (25)	29 (35)	1 (1)
A negative test result will lead to false reassurance of cancer risks.	1 (1)	13 (15)	17 (20)	50 (60)	3 (4)
A negative test result will lead to neglect of routine breast health surveillance.	2 (2)	32 (38)	23 (27)	24 (29)	3 (4)
Carriers will experience significant, long-term psychological and emotional distress.	0 (0)	10 (12)	32 (38)	40 (48)	2 (2)

4.0 DISCUSSION

4.1 ANALYSIS OF QUESTIONNAIRE DATA

The participation rate in this questionnaire was similar to, if not better than, similar physician knowledge studies[14–16,20]. The fact that 47% of the respondents had more than 15 years of experience may mean this population may not be entirely representative of all OB/Gyns and family practice professionals. The majority of the participants, 87%, indicated they had not received additional formal genetics training, this may be because physicians, midlevel providers and nurses were all included in this sample and they may not all have the same opportunities for genetics educational advancement Additionally, more women than men responded to the questionnaire and therefore, it is unknown if this is representative of providers in the UPMC system, as gender distribution of the email lists were not available. It may be possible that more women responded because the topic under study was of more personal interest to the female population and motivated them to complete the questionnaire. The responses from each specialty group were equally representative when response rates were compared; Obstetrics/Gynecology responded at a rate of 24.5% and the family medicine group responded at a rate of 24.7%. Although there were more OB/Gyn responses, the percentages of the total populations are comparable.

As shown by Wideroff et.al (2005), the OB/Gyns in this study also demonstrated statistically more accurate *BRCA* knowledge than the family practice individuals (p-value= 0.016). The questions that almost all respondents answered correctly were related to knowledge that *BRCA* genes are not the only breast cancer predisposition genes and the definition of a VUS. Only 73.8% knew that the Ashkenazi Jewish population had a higher prevalence of *BRCA* pathogenic variants; it is unclear if prior knowledge studies asked this question specifically.

Also, in general, participants were not overly confident in their capabilities to provide patients with information about the *BRCA* genes. A question that participants struggled to answer was how the *BRCA* genes are inherited, less than 60% indicated autosomal dominant inheritance, but 81% knew a child could inherit a *BRCA* pathogenic variant from their father. Based on the inheritance pattern question, however, it is not surprising that only about 50% of participants indicated a level of confidence in explaining *BRCA* inheritance to patients. The study by Wideroff et.al (2005) found deficiencies with physician knowledge of inheritance, while Pal et.al (2013) indicated their physician population responded best to questions of *BRCA* inheritance; the data found by this questionnaire falls somewhere in between these two studies which may be attributed to the different populations and specialties that were assessed.

Three questions were asked with regard to the cancer risks attributed to the *BRCA* genes, one was almost unanimously answered correctly with 97.6% agreeing that the *BRCA* genes are also associated with an increased risk of ovarian cancer as well as breast cancer. However, only 52.8% indicated that the highest lifetime risk associated with the *BRCA1* gene is 87% and only 48.8% knew that the *BRCA1* gene was associated with higher ovarian cancer risks. But when it came to their opinions of their skills associated with cancer risks, over 60% of participants

indicated a level of confidence reporting risks; this seems worrisome considering the proportion of incorrect answers to the risk questions.

Conversely, nearly 87% of respondents would manage a patient correctly if she received a VUS by treating her based on her family history. Additionally, 88% of respondents knew that if a patient did not carry their familial pathogenic variant they should be followed as any member of the general population. Yet, only 44.1% of participants indicated they were somewhat confident with management of individuals who have had *BRCA* testing and 42.9% of respondents felt some level of confidence with *BRCA* gene testing interpretations. Though the specific questions were not the exact questions asked in prior studies[12,15], the accuracy of responses to the management questions in this study was higher than other studies, which, found management to be an area requiring further education.

Similar to past knowledge studies[15,16], participants demonstrated knowledge deficits with regard to management for a patient whose family member carries a VUS. Less than 30% of participants knew not to test the patient when a VUS was found within the family. However, for other testing procedures, more than 65% of respondents knew to order single site testing for a patient whose family has a pathogenic variant. Additionally, 76% knew an unaffected individual was not the most appropriate person to initiate the genetic testing within a family. These questions represented the subject matter that the respondents were least confident answering; less than 40% of respondents indicated confidence in answering questions related to testing methods.

When queried about which providers would be best to consent and inform patients of their risks, testing options, and results, respondents selected medical geneticists and oncologists most frequently, followed by genetic counselors. Interestingly, only 83% of the respondents thought genetic counselors were qualified to perform these duties even though cancer genetic

counselors routinely perform these tasks. The majority of respondents, 85.7%, indicated they did not believe population-based genetic testing could be a cost-effective venture, and since a cost-effectiveness study has not been performed while considering *BRCA* sequencing in a general population, their opinion cannot yet be contradicted. Nearly 80% of respondents indicated they were unable to currently support a population screening program. However, 89% of participants still showed interest in learning more about medical genetics and cancer risk assessment, this has been previously reported by other studies and was supported by the results found from this questionnaire[10,11,15].

Wideroff, et.al (2005), recommended that motivating factors of physicians to incorporate cancer risk assessment into their practice be investigated. This study approached this issue from a different perspective and assessed what factors motivate respondents to consider incorporating a population based screening program into their practice. The majority of respondents, 70%, selected evidence-based professional society guidelines indicating the utility of population-based testing, as the greatest motivator for population –based screening. The next greatest motivator was cost-benefit data, which contradicts the research by Marzuillo, et.al (2013) which revealed that physicians believed genetic testing should be performed regardless of cost-effectiveness data. Patients requesting testing and population-based evidence that their patient population was at risk of carrying a pathogenic variant were selected as the net two motivators for incorporating population-based screening, selected by 52% and 51%, respectively. Also of interest was the finding that four of the 84 participants (4.8%) indicated they would not be motivated to offer population-based *BRCA* screening; this will be important to consider in the future.

The majority of respondents disagreed with the statements that the benefits of population *BRCA* screening would outweigh the risks, that population screening would reduce morbidity

and mortality due to breast cancer, that a negative genetic test will lead to neglect of routine breast health, and that *BRCA* testing will lead to stigmatization or discrimination. Participants generally agreed with the following statements: pathogenic variant carriers would be better able to protect themselves from future cancers, negative genetic testing will lead to a false reassurance of cancer risks, and that pathogenic variant carriers will experience significant, long-term psychological and emotional distress. Some of the opinions expressed in this section contradict themselves, for example, the providers surveyed think a negative *BRCA* test will cause a patient to think she has lower cancer risks than that of the general population, but they do not believe these individuals will neglect their routine breast screening. Also, they reportedly believe pathogenic variant carriers will be able to better protect themselves from cancers, but they do not think that population-based screening will reduce morbidity and mortality rates from breast cancer. Perhaps some of these statements were either not worded well or were not well understood, leading to the contradictions mentioned.

4.2 LIMITATIONS OF STUDY AND FUTURE DIRECTIONS

One limitation of this questionnaire relates to the ordering of the questions. There are two perspectives that suggest demographic questions should be placed at the end of the survey. One perspective contends that participants will be more likely to complete demographic questions at the end if they are personal and not complex. The second perspective is that participants, who disclose demographic information before completing a survey, may answer a question based on how they think someone in that demographic should answer, rather than how that participant, as an individual, actually feels[36]. Unfortunately, individuals who did not complete the survey did

not get to the demographic questions and therefore their knowledge and opinion data could not be incorporated into the analysis.

Another limitation to consider would be the population that was invited to participate in this study. First, these physicians and advanced practice providers were all associated with the UPMC system, an academic medical center. Although this provider population was selected based on ease of accessibility, it is not possible to know if these providers are representative of all clinicians, only OB/Gyn and Family Practice clinicians, or only the OB/Gyn and Family Practice clinicians of Western Pennsylvania.

A future direction that is worthy to pursue is to further explore why 84% of the surveyed medical professionals specified they would not wish to undergo *BRCA* testing. One possibility is that the participants are an informed population and feel that testing is not necessary based on their assessment of their personal risk. Additional studies could determine whether this opinion is localized to this population or more wide spread. It is possible that providers may feel this way because they are knowledgeable of the extensive management associated with having a *BRCA* pathogenic variant, and/or because they are concerned about stigmatization and discrimination. Clarification of the participants' reasoning for indicating they would not want to know their own *BRCA* pathogenic variant status is warranted to ensure their aversion to being tested would not affect their views on offering population screening to their patient population.

As a future study it would be interesting to compare the beliefs of this study population on their own confidence levels with breast cancer genetics before and after answering the knowledge questions. Alternatively, the survey could have individuals report their confidence levels and opinions before the knowledge section, at random, while other individuals complete the knowledge portion first, as it was in this study. This may allow for more insight into the

depth of the provider's beliefs on population-based *BRCA* screening since their opinions may be affected by their knowledge and this may be seen by reordering the questionnaires.

Furthermore, now that a number of studies have demonstrated the important areas of cancer genetic testing that physicians are either uncomfortable with or have consistently answered incorrectly, future research should focus on effective training strategies to utilize in advance of the implementation of *BRCA* population screening. Research has already shown education geared toward general practitioners was feasible, satisfactory, and a clinically applicable way to improve cancer genetics consultations[37]. There are already provider educational programs in place to enhance provider knowledge of HBOC, such as the one facilitated by the National Coalition for Health Professionals Education in Genetics (NCHPEG). Some additional programs covering all aspects of breast cancer genetics are available through the Medical College of Wisconsin, the Oncology Nursing Society, and the Jackson Laboratory; Wisconsin, NCHPEG, and Jackson are all free programs offering CME credit. Perhaps future ventures should focus on adapting old programs and making providers aware of the educational opportunities available to them to further their knowledge about HBOC and to earn CME/CEU credits. No matter which route is utilized to prepare providers for population-based *BRCA* screening, the outcomes of physician education efforts should be monitored for efficacy.

Future directions also need to include the developments of educational programs for the general public. It may be beneficial to take direction from studies performed during the implementation of Cystic Fibrosis Carrier Screening. Clayton et.al (1995), found no difference between the knowledge obtained from educational materials based on their form, print vs. recording, despite designing a video to be able to reach individuals who were less comfortable with reading information[38]. Additionally, Myers, et.al (1994) found discordances between what

providers believed the general public would want to know about CF screening, and what members of the general public wanted to know[39]. When educational programs for population *BRCA* screening are developed for the general public, the opinions of the public on what information is most important to them should be determined and included in the educational materials. General public knowledge should also be assessed over time.

4.3 PUBLIC HEALTH SIGNIFICANCE

This questionnaire aimed to assess the readiness of physicians to implement a population-based *BRCA* screening protocol and therefore, this research has public health relevance. By understanding the baseline knowledge of providers, information is gained to facilitate provider education to improve their clinical performance[40]. Additionally, determining physician motivation to incorporate population screening into their practice is of use to increase compliance with the employment of a new protocol in their practice. Moreover, it is hoped that any research that aims to provide additional services for patients, especially population screening, that has the potential to decrease the number of breast and ovarian cancer diagnoses and related death is of public health significance. This has been shown in the population-based screening of the Ashkenazi Jewish population, where it was estimated to result in 276 fewer ovarian cancer cases and 508 fewer breast cancer diagnoses[19].

In a broader sense, there are additional public health concerns associated with a population wide *BRCA* screening program, many of which have already been raised by individuals in the medical and genetics communities[22,27,28]. One such concern is VUS reporting and the proposed plan to not report VUS findings, however VUS results are found more often in

non-Caucasians. A study from Ambry Genetics reports VUS rates for *BRCA1/2* upwards of 9% in the Asian population, 6 to 7% in the African American population, and about 5% in the Hispanic population; this is compared to approximately a 3% chance of finding a VUS in a Caucasian individual[41]. The overarching concern is that these variants will be reclassified to pathogenic variants and the individuals who were found to carry them will not be notified of their cancer predisposition. An additional concern is disparities between individuals of different ethnicities and socioeconomic status with regard to the availability of health care; women included in these groups (African Americans and Hispanics) often do not have access genetic counselors, may not be aware of genetic testing or may not be referred for genetic testing, and may be unable or unwilling to pursue risk-reducing interventions when found to carry a pathogenic variant[27]. One additional concern is cultural acceptance of genetic testing, studies have shown certain cultural, ethnic, and religious beliefs have varying opinions on the utility and acceptability of genetic testing[27,42]. If a significant proportion of the population does not participate in a population-based screen, then any estimated or potential benefits to the overall population will no longer be applicable.

4.4 CONCLUSIONS

The knowledge of OB/Gyns and family medicine providers was assessed using a questionnaire which asked them to answer *BRCA*-based knowledge questions in addition to sharing their opinions on who the best provider would be to implement population-based *BRCA* screening and which factors would influence them to incorporate population-based *BRCA* screening into their own practice. The present study supports previous practitioner knowledge surveys which

showed specialists had better overall knowledge of breast cancer genetics; providers within obstetrics and gynecology had overall better knowledge scores as compared to family medicine. This may be due to the fact that the specialty of OB/Gyn focuses on women's care and information about *BRCA* tends to be skewed toward women. All participants showed knowledge deficits with testing protocols for variants of uncertain significance in addition to the inheritance of the *BRCA* genes. It is concerning that those surveyed were over-confident, meaning they scored poorly but indicated they were confident, with regard to their abilities to inform patients of the cancer risks associated with *BRCA* pathogenic variants. Also, the respondents indicated a lack of confidence with their abilities to communicate patient management after *BRCA* testing. The respondents specified two professional groups who would best be able to inform and consent patients for population *BRCA* screening, they were medical geneticists and oncologists. If the respondents of this questionnaire were to start offering *BRCA* testing to their patients, however, it would seem that they would be more motivated to do so if there were professional society guidelines indicating the utility of population-based *BRCA* screening.

The results obtained from this questionnaire identify previously unrecognized pitfalls in provider knowledge about breast cancer genetics, specifically *BRCA* cancer risks. This study was also able to confirm prior research on other areas of knowledge, specifically VUS testing and *BRCA* inheritance. New information was also obtained from this questionnaire in the form of provider beliefs on who should provide population-based screening, in addition to elucidating motivating factors of physicians to implement *BRCA* population-based screening. These findings may, over time, help to guide the involvement and education of clinicians in implementing population-based screening of the *BRCA* genes. There is significant research left

to be completed before population-based *BRCA* screening becomes a wide-spread program due to concerns that have been raised from the medical and genetics communities..

APPENDIX A: CONSENT SCRIPT

You are being invited to complete a questionnaire as part of a Masters level research study being conducted by a genetic counseling graduate student at the University of Pittsburgh.

The purpose of this study is to gauge the level of knowledge and current practices of physicians and mid-level providers in the UPMC network on the topic of breast cancer genetics *BRCA*1/2 testing. The findings of this study will help to determine the readiness of health care providers to offer *BRCA* gene screening and to identify areas where more education may be needed in the event that population based *BRCA*1/2 gene screening is initiated.

This questionnaire is intended to measure the extent of your "off the cuff" knowledge, so there is no need to look-up any of the answers to these questions. This questionnaire is intended to take 10 to 15 minutes to complete. This is an anonymous questionnaire and your responses will not be identifiable in any way.

By submitting this questionnaire, you are consenting to participate in this research study. Your participation is voluntary and may be terminated at any time by exiting the questionnaire. Your participation will help to identify knowledge gaps and current practice of *BRCA*1/2 gene testing. Thank you in advance for your participation. Your time and input are appreciated. To begin the questionnaire, please click the "Arrow" button below.

Contact Information

There are no foreseeable risks to you in completing this questionnaire, but should you have any questions or concerns about this research study please feel free to contact:

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APPENDIX B: STUDY QUESTIONNAIRE

POPULATION *BRCA* SCREENING QUESTIONNAIRE

Knowledge Questions (correct answers are bolded):

Q1 What is the mode of inheritance for pathogenic variants in the *BRCA* genes?

☐ **Autosomal Dominant**
☐ Autosomal Recessive
☐ X-Linked
☐ Mitochondrial
☐ Unsure

Q2 True or false, *BRCA*1/2 pathogenic variants account for all hereditary breast cancers.

☐ True
☐ **False**

Q3 The *BRCA* pathogenic variant carrier rate in individuals of Ashkenazi Jewish (Eastern European Jewish) ancestry is higher than the carrier rate of the general population.

☐ **True**
☐ False
☐ Unsure

Q4 Your patient has an aunt on her father's side who is a carrier of a *BRCA*1 pathogenic variant. Is it possible that your patient could also carry this pathogenic variant?

☐ **Yes**
☐ No
☐ Unsure

Q5 Your 35 year old female patient tests positive for a *BRCA*1 gene pathogenic variant. What is her highest lifetime risk of developing breast cancer?

☐ 39%
☐ **87%**
☐ 100%
☐ Unsure

Q6 Your healthy patient tests positive for a *BRCA* pathogenic variant. She has an increased risk for breast and ovarian cancer.

☐ **True**
☐ False

Q7 Your patient's maternal family history is significant for breast cancer diagnosed prior to age 50 in several women. Several of the affected women are still living but have not been tested for pathogenic variants in *BRCA*1/2. Your patient asks to be tested. Is she the best person to initiate testing in this family?

☐ Yes
☐ **No**
☐ Unsure

Q8 Your unaffected patient undergoes *BRCA*1/2 testing and is found to have a variant of uncertain significance (VUS) in the *BRCA*1 gene. What does this mean?

☐ A pathogenic variant was identified that causes hereditary breast and ovarian cancer syndrome.
☐ **A change was identified for which there is insufficient information to determine if it is harmful or benign to gene function.**
☐ A benign variation was identified.
☐ The test needs to be repeated.

Q9 The same patient asks how the VUS result will affect her care. You tell her that her management will be based on her family history.

☐ **True**
☐ False

Q10 Your patient's sister carries a VUS in the *BRCA*1 gene, should you test your healthy patient for this *BRCA*1 variant?

☐ Yes
☐ **No**
☐ Unsure

Q11 Your patient's maternal family has a known *BRCA*1 pathogenic variant; there is no history of cancer in her father's family. What type of testing would you offer your patient?

☐ **Site-specific *BRCA*1 pathogenic variant analysis**
☐ Complete sequencing of *BRCA*1/2
☐ Complete sequencing, plus deletion/duplication studies of *BRCA*1/2
☐ Whole Exome Sequencing

Q12 This same woman undergoes testing and does not carry the known familial pathogenic variant. What is your interpretation of her risk of developing breast cancer?

☐ She has an increased risk of developing breast and ovarian cancer.
☐ She has an increased risk of developing breast cancer.
☐ **She has a risk similar to that of the general population of developing breast cancer.**
☐ She should be tested again to verify her cancer risks.

Q13 Which gene pathogenic variant carries a higher lifetime risk of developing ovarian cancer?

☐ ***BRCA*1**
☐ *BRCA*2

Opinion Questions:

Q1 How confident are you in your ability to provide information to patients on the following components of breast cancer genetics? Please answer for each component.

	Not Confident	Somewhat Confident	Completely Confident
BRCA cancer risks	☐	☐	☐
BRCA inheritance	☐	☐	☐
Medical management	☐	☐	☐
BRCA testing methods	☐	☐	☐
BRCA test interpretation	☐	☐	☐

Q2 Cancer risk assessment and genetic counseling provides patients with information about genetic testing and their risk of inherited cancer predisposition. Which of the following health care providers would you consider to be qualified to provide these services to your patients? Please make a selection for each profession.

	Yes	No	Not Sure
OB/Gyn	☐	☐	☐
Medical Geneticist	☐	☐	☐
Oncologist	☐	☐	☐
Nurse Specialist	☐	☐	☐
Certified Genetic Counselor	☐	☐	☐
Other	☐	☐	☐

Q2.1 If you selected 'yes' for "Other," who else do you believe is qualified?

Q3 Have you or would you wish to undergo *BRCA* testing?

☐ Yes
☐ No
☐ Unsure

Q4 In the general population the chance to have a *BRCA*1/2 pathogenic variant is less than 1%. Do you think population based *BRCA* testing would be a cost-effective venture, meaning the cost of testing every woman outweighs or is equal to the cost of treating and managing the women who are found to have *BRCA* pathogenic variants?

☐ Yes
☐ No
☐ Unsure

Q5 Do you feel you have adequate time and resources to test every woman over the age of 30 that comes to your practice?

☐ Yes
☐ No
☐ Unsure

Q6 How interested would you be in furthering your medical genetics and cancer risk assessment education?

☐ Very Interested
☐ Somewhat Interested
☐ Not Interested
☐ Unsure

Q7 What is or would be the strongest motivator to incorporate *BRCA* gene testing into your practice? Please select all that apply to you.

☐ Population evidence that your patient population is at increased risk for carrying a *BRCA* pathogenic variant.
☐ Being personally affected by breast cancer or having a close family member or friend with breast cancer.
☐ Having a patient with a *BRCA* pathogenic variant.
☐ Patients requesting testing.
☐ Cost/benefit data.
☐ Evidence-based professional society guidelines.
☐ If the electronic health record provided a cancer risk assessment to flag appropriate patients.
☐ Not interested or motivated to incorporate this testing into my practice.

Q8 To what extent do you agree or disagree (strongly disagree, disagree, neither agree nor disagree, agree, or strongly agree) with the following statements regarding population *BRCA* screening? Please make a selection for each statement.

The benefits of population *BRCA* screening outweigh the risks.
Population screening will reduce breast cancer morbidity and mortality.
Pathogenic variant carriers will feel like they can better protect themselves from future cancers.
Testing will lead to stigmatization or discrimination.
A negative test result will lead to false reassurance of cancer risks.
A negative test result will lead to neglect of routine breast health surveillance.
Carriers will experience significant, long-term psychological and emotional distress.

Demographic Questions:

Q1 Gender:

☐ Male
☐ Female

Q2 How long have you been practicing medicine?

☐ Still in residency
☐ < 5 years
☐ 5-10 years
☐ 10-15 years
☐ >15 years

Q3 What type of practice setting do you currently work in?

☐ Private
☐ Locum tenens
☐ Hospital Based
☐ Academic
☐ Other _____

Q4 What is your practice specialty?

☐ OB/Gyn
☐ Family Practice
☐ Internal Medicine
☐ Mid-level provider (Nurse Practitioner, Physician's Assistant, etc.)
☐ Other _____

Q5 Does your office/practice currently provide *BRCA* testing to your patients?

☐ Yes
☐ No
☐ I refer them to genetics

Q6 Have you personally provided genetic counseling about *BRCA*1/2 to a patient?

☐ Yes
☐ No

Q7 Have you received any formal genetics training, outside of medical school/training?

☐ Yes
☐ No

Q8 Do you have a personal or family history of breast or ovarian cancer?

☐ Yes
☐ No
☐ Unsure

APPENDIX C: 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: Erin Winchester

From: IRB Office

Date: 6/15/2015

IRB#: PRO15030332

Subject: Physician Knowledge of Breast Cancer Genetics

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.

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