EXPLORING OB-GYN PROVIDERS' EXPERIENCE WITH AND KNOWLEDGE OF MULTI-GENE PANELS FOR HEREDITARY BREAST AND OVARIAN CANCER

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ABSTRACT

Genetic testing for hereditary risk factors for breast and ovarian cancer initially focused on the *BRCA1* and *BRCA2* genes. Ob-Gyns have been involved in making this testing accessible to patients. With recent advancements in genetic testing technologies, multi-gene panels are being used to test a group of cancer genes simultaneously. Prior studies focused on the *BRCA* genes showed that Ob-Gyn providers and other non-genetics professionals can sometimes misinterpret genetic test results and are often uncomfortable counseling patients about testing implications. The use of cancer panels introduces additional complications, as these tests include many more genes that each have their own cancer risk profile. Literature regarding how Ob-Gyn providers are using these panels is currently lacking. In this study, 67 Ob-Gyn providers (physicians, gynecologic oncologists, PA-Cs/CRNPs/midwives, residents/fellows) in Western Pennsylvania were surveyed about their current practices regarding breast and ovarian cancer panels.

About 61% of providers reported using results from cancer panel testing to help manage patients. Responses to theoretical clinical management scenarios varied by provider type and experience level. Ob-Gyns and individuals with more clinical experience were more likely to refer the theoretical patients to discuss prophylactic bilateral mastectomy at moderate breast cancer risks (20% and 40%). About 30-80% of providers outside of gynecologic oncologists failed to recommend RRSO for the 5% and 10% risk categories, although RRSO is indicated for genes with

similar associated risks. Further, 70% of all providers indicated incorrect risk assessment for an individual testing negative for a known familial pathogenic variant in a moderate risk breast cancer gene. Most providers excluding gynecologic oncologists also indicated discomfort interpreting positive/inconclusive test results and reported inadequate cancer genetics formal education.

This study identified several concerning findings that could have public health significance. Some providers selected inappropriate management recommendations based on current NCCN guidelines for multi-gene breast/ovarian panel testing and other providers reported inadequate genetics training. These concerns must be addressed to ensure that individuals seeking cancer genetic testing are receiving consistent, appropriate, and evidence-based care based on their results.

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PREFACE

I would like to offer my gratitude to my committee members for their guidance and the many hours of work that they dedicated to this project. Thank you to my committee chair Maureen May and Dr. Andrea Durst for their expertise in clinical cancer genetics, to Dr. Todd Bear for guidance with survey design, distribution, and statistical analysis, and to Dr. Robin Grubs for her help finessing the structure of the survey and the manuscript document.

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1.0 INTRODUCTION

The *BRCA1* and *BRCA2* genes were the first identified genetic risk factors for breast and ovarian cancer. In the 1990s, pathogenic variants in the DNA sequence of these two genes were found to substantially increase an individual's risk to develop breast and ovarian cancer. [1] Since *BRCA* genetic testing was first introduced, Ob-Gyn providers have been involved in making this testing clinically accessible. These providers often refer patients to cancer genetics specialists and sometimes order genetic testing on their own. Numerous studies have been conducted throughout the years surveying Ob-Gyns and other non-genetics providers about their cancer genetic testing practices. Several concerning trends have been identified from these studies, including inappropriate ordering patterns, incomplete pre- and post-testing counseling, and errors in results interpretation. [2]

More recently, simultaneous testing of *BRCA* and other, more recently identified genes linked to breast or ovarian cancer risk has become available through multi-gene panel testing. Since the introduction of these panel tests in the clinical setting, there has been a lack of research about the ways in which Ob-Gyn providers are using and interpreting these tests. Learning more about Ob-Gyn provider use of cancer panels is important to ensure consistent care between patients and to help identify any potential problems arising from this new testing.

This study aims to gather data about how different providers working in the obstetrics/gynecology field manage patients with different hereditary cancer risks. This data will help to determine whether patient care varies based on provider role or level of clinical experience. Further, as previously noted, there are many examples in the medical literature of non-genetics providers misinterpreting *BRCA* test results.[3–5] Multi-gene cancer panels analyze many genes that are each associated with unique cancer types and levels of risk. This variability further complicates results interpretation. Identifying whether Ob-Gyns are misinterpreting cancer panels and for what reasons is essential to ensuring that patients are being provided with appropriate cancer risk assessment and prevention measures.

This study consists of a survey of Ob-Gyn providers within two Pittsburgh, PA-based major healthcare systems. For this study, Ob-Gyn providers included Ob-Gyn physicians, gynecologic oncologists, midwives, Ob-Gyn residents/fellows, and physicians' assistants/nurse practioners working in this setting. The two large healthcare systems involved were the University of Pittsburgh Medical Center and Allegheny Health Network. These systems both include large urban hospitals located within the Pittsburgh area, as well as suburban and rural wellness centers and hospitals spread across western and central Pennsylvania. The Ob-Gyn providers working for each of these healthcare systems were sent the survey via email through the Qualtrics survey system.

The **specific aims** of this study were as follows:

- To identify how often Ob-Gyn providers are using cancer gene panel testing
- To gather data about how providers would manage patients at varying genetic risk levels for breast and ovarian cancer
- To ascertain Ob-Gyn provider perspectives about their role in panel testing

To achieve these aims, the survey included sections asking providers about prior ordering practices, theoretical management and risk assessment scenarios simulating different panel results, and their opinions about cancer panel testing processes. The surveys were emailed to over 400 Ob-Gyn providers from both healthcare systems, with the intent that responses from this population may provide initial findings that may later be corroborated in a larger population across a wider geographic range.

2.0 LITERATURE REVIEW

2.1 EARLY HISTORY OF HEREDITARY BREAST AND OVARIAN CANCER

The recognition that certain families share a strong predisposition for cancers has long been described in the medical literature. Researchers and clinicians proposed that specific types of cancer may trend within families because family members share both environmental and genetic risk factors. However, it has only been within the last few decades that researchers have started identifying the specific genes that confer an inherited predisposition to cancer.

Initial efforts to identify specific cancer susceptibility genes focused on a cohort of families that shared a strong predisposition for breast and/or ovarian cancer.[1] These families shared similar characteristics, including a high prevalence of these cancers within the family, early ages of onset, and the tendency to develop multiple or bilateral cancers.[6–8] In the 1990s, genetic linkage studies were performed on this cohort to determine the location of genetic markers tracking with the cancer predisposition in these families. These studies found that markers near the chromosomal locations 17q and 13q appeared to segregate with disease in some of these families.[9–12] Researchers were eventually able to map a gene to each of these chromosomal locations. The gene mapped to 17q was later named *BRCA1* for breast cancer 1 and the gene mapped to 13q was named *BRCA2* for breast cancer 2.[9–12]

After these genes were mapped, further studies of the *BRCA* genes were used to help translate this research into clinical applications. Functional studies confirmed that the *BRCA* genes are tumor suppressor genes that prevent cells from dividing if the DNA replication process

produces errors.[13,14] By preventing the proliferation of cells with DNA errors, these genes help protect against unregulated cell division processes that can lead to the formation of tumors.[15]

Gene analyzing technologies were then used to decipher the DNA sequence of these genes and started to highlight the variability that can be seen in the sequence.[16–18] Some individuals were found to carry a sequence change that disrupted the normal functioning of one *BRCA1* or *BRCA2* allele.[16–18] These disease-causing sequence changes are referred to as pathogenic variants or likely pathogenic variants. Individuals carrying these pathogenic variants in the *BRCA* genes were said to have hereditary breast and ovarian cancer, or HBOC. HBOC is inherited in an autosomal dominant manner, indicating that inheritance of a pathogenic variant in one *BRCA1* or *BRCA2* allele is enough to cause an increased breast and ovary cancer risk. For autosomal dominant conditions, an individual has a 50% chance of passing a disease-causing pathogenic variant on to each child.

All individuals harbor unique sequence changes that do not affect gene function or health. Such changes are referred to as benign variants and are generally not reported on clinical testing. When a sequence change is identified with unclear consequences for protein function and/or health, it is referred to as a variant of uncertain significance (VUS). These are reported by clinical testing laboratories, leaving the clinician to determine how and whether to use the information for management. These results are often reclassified as either benign or pathogenic over time as more data is gathered about their function.

2.1.1.1 Associated Cancer Risks

Many studies were then initiated to clarify the cancer risks for carriers of a *BRCA* pathogenic variant.[19,20] Both *BRCA1* and *BRCA2* are considered highly penetrant, indicating that they

significantly increase breast and ovarian cancer risks over those of the general population. In the general population of women in the United States, the lifetime risks to develop breast cancer and ovarian cancer are 12.5% and 1-2% respectively. [21] The median ages at which breast and ovarian cancer are diagnosed are 62 years and 63 years respectively. [21]

A series of prospective studies of *BRCA* carriers were conducted to determine the cumulative lifetime risks, age-specific risks, and average ages of diagnosis for breast and ovarian cancer. A meta-analysis of these studies in 2007 found that the lifetime breast cancer risk ranges from 47-66% for *BRCA1* and 40-57% for *BRCA2*.[19,22] More recently, a prospective study of *BRCA* pathogenic variant carriers published in the *Journal of the American Medical Association (JAMA)* in 2017 estimated breast cancer risk by age 80 for *BRCA1* and *BRCA2* positive women to be 65-79% and 61-77% respectively.[20,23]For *BRCA* positive individuals, the risk of developing a second, contralateral breast cancer after an initial diagnosis is also elevated. The 2017 *JAMA* study found that the 20-year contralateral breast cancer risk is 35-45% for *BRCA1* positive individuals and 20-33% for *BRCA2* positive individuals.[20] For *BRCA1* and *BRCA2* respectively, the average age of breast cancer diagnosis is 40-43 years.[16,24,25]

The meta-analysis also estimated lifetime ovarian cancer risk to be 35-46% for *BRCA1* and 13-23% for *BRCA2* .[19,22] The 2017 *JAMA* study found the cumulative ovarian cancer risk by age 80 to be 36-53% and 11-25% for *BRCA1* and *BRCA2* respectively. [20,23] The average age of ovarian cancer diagnosis is around 50-55 years. [16,24,25] Both *BRCA* genes have also been linked to an increased risk for male breast cancer, prostate cancer, and pancreatic cancer. *BRCA2* has been linked to an increased risk for melanoma as well.[16,26] Once the risks associated with these genes were elucidated, it opened up the opportunity to use genetic testing for cancer risk assessment and medical management.

2.1.1.2 Clinical Implications of a Pathogenic Variant in *BRCA*

For women considered to be at average risk of developing breast cancer, the American Cancer Society (ACS) screening guidelines recommend initiating annual mammograms starting at age 40-45.[27] The ACS states that annual mammograms should continue until age 55, at which point they can occur every 2 years.[27] The U.S. Preventative Services Task Force guidelines vary slightly in that they recommend that mammograms should be initiated by age 50, can be considered as early as age 40, and should occur every 2 years.[28] For ovarian cancer, women are advised to meet regularly with their Ob-Gyn providers and to report any abnormal symptoms, but there are no additional screening guidelines endorsed by the American College of Obstetricians and Gynecologists (ACOG).[29]

Because initial breast cancer risk, risk of a second breast cancer, and ovary cancer risk are elevated in the *BRCA* positive population, different management guidelines apply for these individuals. In the United States, the National Comprehensive Cancer Network (NCCN) reviews existing literature and expert consensus to issue regular guidelines regarding the most effective management for these elevated risk individuals. [30] For *BRCA* , the current NCCN guidelines (V. 1.2018) suggest that prophylactic bilateral mastectomy should be considered.[30] Individuals who pursue prophylactic bilateral mastectomy are 90% less likely to be diagnosed with breast cancer compared to those who do not choose this procedure.[31–33] The recommendation for women who choose not to undergo surgery is to pursue breast MRI screening in addition to their regular mammograms. Annual breast MRIs should be instituted from ages 25-29, with the addition of mammograms starting at age 30.[34] For populations at increased breast cancer risk, breast MRIs are more sensitive than mammograms in detecting invasive breast cancer, with a sensitivity estimated at 71-100% compared to 16-40%.[35–37] Although they can have a high false positive rate when

performed on average risk individuals, they are more appropriate for screening individuals with a high risk of developing breast cancer.[34–37]

To manage the increase in ovarian cancer risk, the current recommendation by the NCCN is to undergo risk-reducing salpingo-oophorectomy (RRSO) from ages 35-40 for *BRCA1* and ages 40-45 for *BRCA2*, and after childbearing, if desired, is complete. This procedure reduces ovarian cancer risk by 85-95%.[38–40] Current screening methods for ovarian cancer include transvaginal ultrasound and CA-125 bloodwork. Several recent studies have found that these screening modalities do not appear to lower ovarian cancer mortality for average risk individuals and have an unclear effect for mortality in high-risk individuals.[41–46] Additionally, ovarian cancer has a 5-year mortality rate of 55%, often because it is unlikely to be detected until an advanced stage .[42] For these reasons, surgical removal of the ovaries and fallopian tubes is considered the only reliable risk-reducing procedure for *BRCA* positive individuals.[30,47] However, some guidelines, such as those issued by the NCCN (V.1.2018) and ACOG indicate that individuals who do not receive a RRSO may consider ovarian cancer screening despite its limitations. [29,30,43,47]

2.2 MULTI-GENE BREAST AND OVARY PANEL TESTING

2.2.1 Definition and History of Panel Testing

Within the last five to ten years, genetic testing for hereditary forms of breast and ovarian cancer has expanded to include genes in addition to *BRCA1* and *BRCA2*. As new genes linked to breast and ovarian cancer risk have been discovered, next generation sequencing technologies have also

advanced to be able to quickly analyze a group of genes simultaneously. These changes have led to the development of multi-gene cancer panels, which can simultaneously examine all or a subset of genes currently known to predispose to particular types of cancers. With the expansion of cancer genetic testing, it was found that the *BRCA* genes alone account for only about 50-60% of hereditary forms of breast cancer. About 40% of hereditary breast cancers are attributed to other genes that are now included on multi-gene panels.[48] These panels can vary in size depending on the types of cancer present in a family and the level of cancer risk associated with a group of genes. Cancer genetic counselors have started to use breast or gynecological panels to evaluate individuals with a family history of breast or breast-gynecologic cancer in order to analyze for pathogenic variants in genes in addition to the *BRCA* genes.

2.2.2 Categories Based on Risk Levels and Actionability

Panel composition varies by lab and indication. For the genes on any given panel, there is variability in the types of cancer linked to each gene included, the level of risk conferred by the gene, and gene-specific penetrance and outcomes data published. The diversity of genes on a particular panel complicates results interpretation. The NCCN has crafted definitions to describe these different parameters. It describes clinical validity as the level of evidence supporting the association between a gene and a given cancer risk. Clinical utility is the level of evidence that a particular intervention is effective for individuals carrying pathogenic variants in a particular gene. Clinical actionability describes whether or not a pathogenic variant in a particular gene can change medical management. [30]

The NCCN attempts to delineate different categories based on the clinical validity of a gene and the degree of risk associated with that gene. The high-risk category consists of genes with high clinical validity and an increased cancer risk. Many of these genes are linked to well-established cancer syndromes. Moderate-risk genes have been linked to a particular type of cancer and have a lower cancer risk on average than the high-risk category. Other genes that can be included on a cancer panel may have lower validity and less research on degree of cancer risk, and these are often referred to as "newly researched" or "emerging research" genes. [30]

For genes on a panel test, the NCCN issues appropriate management guidelines for genes considered to be clinically actionable based on validity, utility, and the level of risk for a given cancer that is linked to a particular gene.

2.2.2.1 High Risk Cancer Syndromes

The *BRCA* genes are considered high-risk breast and ovary genes. High-risk or high penetrance breast cancer genes typically confer over a five-fold lifetime risk to develop breast cancer, which corresponds to an absolute risk over 50%.[49] In addition to HBOC, several syndromes with well-characterized features are linked to a significantly increased risk for breast or ovary cancer. Other hereditary breast cancer syndromes that fall into this category include Li-Fraumeni syndrome (*TP53* gene), Cowden syndrome (*PTEN* gene), and hereditary diffuse gastric cancer (*CDH1* gene).[50–52] Although pathogenic variants in these genes confer an increased breast cancer risk, each gene is also linked to a unique spectrum of other cancer types. Similarly, Lynch syndrome, which is caused by pathogenic variants in the mismatch-repair genes (*MLH1, MSH2, MSH6, PMS2, EPCAM)* is a high-risk ovarian syndrome. It is associated with an ovarian cancer risk up to 24%.[53]

Pathogenic variants identified in this category of genes are considered largely contributory to the cancer history within a family. While other risk factors may adjust cancer risk, much of the family risk can be attributed to a high-risk pathogenic variant alone. An unaffected individual who does not carry a known familial pathogenic variant in one of these genes is generally considered to be at general population risk to develop cancer, in the absence of any significant exposures or other personal risk factors.[54]

2.2.2.2 Other Clinically Actionable Genes

Breast and ovarian panels have recently expanded even further to include non-syndromic clinically actionable genes, which includes NCCN's moderate-risk category. A pathogenic variant identified in one of these genes is viewed as a risk factor that likely interacts with other shared risk factors, either genetic or environmental, to cause an increased cancer risk within a family. [54] Increased cancer risk within a family therefore cannot be solely attributed to a pathogenic variant in one of these genes. [54] Accordingly, individuals who test negative for a known pathogenic variant in their family are still considered to be at increased risk compared to the general population because other shared risk factors are likely at play.[54]

Breast Cancer Genes

Moderate-risk or moderate penetrance breast cancer genes increase breast cancer risk by about two-to-five-fold. Genes within this category include *ATM, CHEK2,* and *PALB2*, although more recent studies suggest that *PALB2* may actually elevate breast cancer risk over the threshold defining this category of genes.[48] Moderate risk genes are also associated with other cancer types. The *ATM* gene has been linked to pancreatic, prostate, colorectal, and gastric cancers.[55–59] The

PALB2 gene has been previously linked to increased ovarian cancer risk.[55,60,61] *CHEK2* has been linked to colorectal cancer, prostate cancer, gastric cancer, thyroid cancer, melanoma, and leukemia.[55–57,62,63] Current research suggests that *CHEK2* pathogenic variant carriers have a two-fold increased risk for colon cancer over general population risk.

Ovary Cancer Genes

Several genes, including *BRIP1, RAD51C,* and *RAD51D* have been associated with a clinically actionable increase in ovarian cancer risk. Current estimates project that *BRIP1* confers a lifetime risk from 4.06-12.7%, while *RAD51C* and *RAD51D* confer 6.12% and 13.56% risks respectively.[64–66] Some breast cancer panels include *RAD51C* and *RAD51D* based on preliminary data. Recent studies have suggested that *BRIP1* is not linked to breast cancer risk.[60,61,65,67]

2.2.2.3 Newly Researched Genes

Many of the largest breast and ovarian panels also include a group of preliminary evidence genes. These genes have been linked to breast or ovarian cancer risk in some studies, but the level of risk conferred by each gene is not well established.[48] Some of these genes include *BARD1, MRE11A,* and *RAD50.*[68,69]

2.2.3 Interpretation of Positive Breast and Gynecologic Panel Results

2.2.3.1 Breast Cancer Management Implications

About 5-10% of people with breast cancer are thought to carry a pathogenic variant in a known breast gene.[70] High-risk syndromic genes and moderate-risk breast genes are considered clinically actionable, but the guidelines for how best to manage these patients varies by the level of risk

associated with each gene and the level of evidence supporting the effectiveness of a specific intervention in reducing that risk. Breast cancer risk for individuals who test positive for Li-Fraumeni or Cowden syndrome are managed similarly to *BRCA*-positive individuals. [30] This includes consideration of prophylactic bilateral mastectomy. [30] Screening options would include adding breast MRI, considering tomosynthesis use during mammograms, and starting screening at a younger age influenced by family history (as early as age 20 for Li-Fraumeni and as late as age 35 for Cowden).[48] For individuals with hereditary diffuse gastric cancer, the recommended management is to start breast screening at age 30, to add breast MRI screening, and to consider tomosynthesis with mammograms.[71] The current NCCN guidelines (V.1.2018) indicate that prophylactic surgery may be indicated if the family history of breast cancer is strong.[30] For each of these syndromes, there are management recommendations for the other cancers associated with the particular gene. For instance, individuals who test positive for a *PTEN* pathogenic variant are to receive regular renal and thyroid screening and can consider prophylactic hysterectomy, individuals with Li-Fraumeni may consider full body MRIs considering their elevated risk for a wide range of different cancers, and *CDH1* positive individuals receive regular endoscopies to screen for gastric cancer.[30,72,73]

For moderate-risk genes, there are insufficient data to recommend surgical intervention.[48] The clinical utility of surgery for these genes is unclear. [48] However, the guidelines indicate that surgery may be considered in the context of a strong family history.[30] These recommendations acknowledge the fact that moderate risk cancer genes likely interact with other shared risk factors to determine cancer risk in a given family. The presence or absence of breast cancer in the family provides some insight into the degree of other shared risk factors within the family. [48] Currently, there are screening recommendations for moderate risk breast-genes. These involve pursing annual

breast MRIs along with mammograms (with consideration of tomosynthesis) starting at age 30 for *PALB2* and 40 for *ATM* and *CHEK2*.[30,48] Further, the NCCN recommends that *CHEK2* carriers pursue colonoscopies every 5 years starting at age 40 or earlier based on family history. [30]

The NCCN does not outline specific surveillance or management recommendations for newly researched breast cancer genes. [30] The suggestion is to consider a pathogenic variant in one of these genes as one component of breast cancer risk assessment in combination with other personal and family risk factors.

2.2.3.2 Ovary Cancer Management Implications

For syndromic genes like *BRCA* and some Lynch syndrome genes, the NCCN indicates that individuals can consider risk-reducing salpingo-oophorectomy (RRSO). [30] Transvaginal ultrasound and CA-125 can be considered but they do not clearly decrease mortality rate.[73,74] Because screening via transvaginal US and CA-125 is not reliable, the recommended management for all other clinically actionable ovarian cancer genes (*RAD51C, RAD51D, BRIP1*) is to consider RRSO between ages 45-50.[48]

The NCCN does not have outline specific surveillance or management recommendations for newly researched ovary cancer genes. The suggestion is to consider a pathogenic variant in one of these genes as one component of ovary cancer risk assessment in combination with other personal and family risk factors.

2.2.4 Negative Multi-Gene Panel Result

Negative panel test results must be interpreted in the context of panel composition and the relationship of the tested individual within the family. When interpreting a negative panel in the context of family risk assessment, the result can only be considered a true negative when the affected individuals most likely to carry a hereditary risk factor test negative. If an unaffected family member tests negative, their remains the possibility that affected family members carry a hereditary risk factor that the unaffected family member did not inherit. When a true negative panel result is identified for a family with a strong cancer history, the history is described as familial. [70] The presence of a familial cancer predisposition is considered multifactorial, indicating that the interaction of shared environmental and/or currently undetectable genetic risk factors is likely influencing cancer risk. About 20% of breast cancer cases are familial.[70] In these cases, appropriate cancer risk management is determined by personal and family history risk factors.

Cohort studies on the Utah Population Database were used to estimate how a family history of breast or ovary cancer influences individual risk based on degree of relationship.[6–8] These studies suggested that having one first-degree relative with breast cancer increases lifetime cancer risk to about 20% and having one first-degree relative with ovarian cancer increases risk to about 3-5%.[6–8] Adding in additional family members with breast or ovarian cancer can increase risk further. [6–8] Various risk models have been developed to quantify breast cancer risk based on personal risk factors and/or family history. Models such as *BRCAPro,* Tyrer-Cuziak, and BODICEA use varying levels of personal and family history information to estimate a lifetime breast cancer risk. [35] Current guidelines by the ACS recommend considering screening via breast MRI in addition to mammograms for individuals with a lifetime risk of breast cancer exceeding

20-25%.[35] For families with early onset breast cancers, they also recommend initiating screening 5-10 years prior to the youngest breast cancer diagnosis in the family. [8] Risk-reducing medications like tamoxifen can also be considered if an individual's 5-year risk to develop breast cancer exceeds 1.66%, as calculated by the Gail Breast Cancer model. [35] Tamoxifen has been estimated to reduce breast cancer risk by 49%, but can also have accompanying side effects including a small elevation in risk for endometrial cancer.[75]

2.2.4.1 Inconclusive Panel Genetic Testing Result

Current estimates suggest that for each gene examined on a test, there is about a 1% chance of identifying a VUS.[48] In 2015, the American College of Medical Genetics (ACMG) issued systematic guidelines for classifying variants into five categories, including pathogenic, likely pathogenic, variant of uncertain significance, likely benign , and benign. [8] Criteria used in this classification process include allele frequencies, functional studies, modeling software, and segregation studies among others. [8]

The ACMG guidelines state that "a variant of uncertain significance should not be used in clinical decision-making."[76] The guidelines do indicate that "efforts to resolve the classification of the variant to 'pathogenic' or 'benign' should be undertaken" and "while this effort to reclassify the variant is underway, additional monitoring of the patient for the disorder in question may be prudent."[76] Further, it has been estimated that as many as 90% of VUS results are downgraded over time.[77] In the cancer genetics field, current practice is to refrain from using these results to influence a patient's medical management. Like negative genetic test results, management typically depends on personal risk factors and family history.

2.3 CANCER GENETIC TESTING AND OB-GYN PROVIDERS

Ob-Gyn providers play a vital role in the prevention of breast and gynecological cancers in women. Their role in breast and ovarian cancer prevention has been laid out and regularly updated in practice bulletins by the American College of Obstetricians and Gynecologists (ACOG).[41,78–80] A 2010 survey of 289 Ob-Gyn fellows who were members of ACOG found that 98% reported having performed clinical breast exams, 28% had performed fine needle aspiration of suspicious breast lumps, and 2.4% had performed breast biopsies.[81] They are also commonly involved in the ordering of screening mammograms and the identification of individuals at high risk of developing breast cancer.[78,79] Although ovarian cancer screening via transvaginal ultrasound and CA-125 levels is not recommended for average risk individuals, Ob-Gyns play a role in ovarian cancer prevention by regularly monitoring their patients for early symptoms of ovarian cancer.[45]

Because Ob-Gyn providers have a clearly defined role in breast and gynecologic cancer prevention, the development of clinical *BRCA* testing had an immediate impact on their practice. With the development of *BRCA* testing, a field of genetic counseling dedicated to hereditary cancer predisposition arose. The major roles of cancer genetic counselors are to obtain a complete cancer family history, to assess the family history and establish differential diagnoses, to explain testing options and implications to patients, to obtain informed consent for testing, to facilitate testing, to explain testing results, and to use all acquired data to perform cancer risk assessment.[82] However, other professionals, including Ob-Gyn providers, gynecologic oncologists, and breast surgeons also became involved in the ordering of *BRCA* testing for their patients.

2.3.1 Ob-Gyn Use of BRCA1/2 Testing

Many surveys of various physicians have been conducted to try to quantify how often each provider type orders genetic testing. From 2009-2011, the estimated range of Ob-Gyn providers who had ordered *BRCA* testing varied from 43-61%.[2,3,83] The likelihood that an Ob-Gyn provider had previously ordered *BRCA* testing was more than double that of an internal medicine physician ($p<0.01$).[83] Further, a 2010 survey of 65 Ob-Gyn residents across Texas found that 67% of the providers had referred a patient for genetic counseling over the last year.[81] As cancer genetic testing options continue to expand, it is likely that these numbers will continue to increase. However, because Ob-Gyns and other primary care providers are not specifically trained in genetics and have many competing priorities, some complications with their use and interpretation of this testing have been identified.

2.3.2 Complications of *BRCA* Testing by Non-genetics Providers

Non-genetics provider use of genetic testing has been shown to stray from current guidelines is several key ways. Major areas in which practice can differ include ordering tendencies, counseling techniques, and results interpretation.[84] The following sections outline data regarding some of these problems, their possible causes, and intervention steps that have been taken for testing of the *BRCA* genes. This serves as a framework for surveillance of similar problems with gene panel testing.

2.3.2.1 Ordering Practices

Ordering Practices

One source of error that arose when non-genetics professionals began ordering *BRCA* testing was determining when testing should be ordered. Initially, there were concerns that providers were not following national guidelines for testing and that testing was being ordered for patients who were at low risk of having a pathogenic variant. [2] In 2011, a group 1500 primary care physicians, internists, pediatricians, and Ob-Gyns across the United States were surveyed and asked to determine whether different theoretical patients were at high or low risk of carrying a *BRCA* pathogenic variant.[2] Some of these scenarios met national guidelines for *BRCA* testing while others did not. The study found that 45% of the surveyed providers suggested testing for at least one patient who did not meet testing guidelines.[2]

One initial barrier to appropriate ordering practice noted in the literature was non-genetics professionals' knowledge and interpretation of genetic non-discrimination laws. In 2008, a survey of 611 non-genetics providers from non-academic centers who had ordered *BRCA* testing was conducted. [85] It found that less than 40% knew about these genetic discrimination protections and that about 75% had the perception that patients would not be interested in genetic testing without them.[85] An additional factor suggesting that non-genetics professionals may not be initiating testing themselves is that the likelihood of testing being ordered was linked to the patient prompting the genetics discussion ($p=0.08$).[83]

There are also many accounts of non-genetics professionals recommending that family members be tested for an identified variant of uncertain significance. [86–88] The American College of Medical Genetics indicates that testing for these variants in unnecessary because they should

not impact patient care.[76] However, a wide range of surveys found that between 60-90% of non-genetics providers indicated that they would recommend that other family members be tested for a VUS.[4,5,86–88] One of these studies identified that genetics providers were significantly less likely to order this testing ($p<0.001$).[87] Testing for a VUS does not provide clinically valuable information, because it is unclear whether these results increase cancer risks. Providers ordering this type of testing may not understand the implications of a VUS result and may therefore recommend inappropriate management based on this result.

Another concern is that non-genetics professionals may not be aware of genetic testing updates. Analysis of the *BRCA* genes was eventually updated to include BART testing, which looks for more rearrangements in the genes. In 2013, only 39% of Florida providers who had ordered *BRCA* testing previously indicated that a patient with previously negative *BRCA* testing should receive this updated test.[86] Further, some non-genetics providers choose suboptimal testing for patients. In 2011, 225 Texas-based family medicine, internal medicine, Ob-Gyn, general surgery, and hematology-oncology physicians were surveyed and asked which testing they would select for patients in different clinical scenarios. [4] One of these clinical scenarios included a patient whose mother carried a known *BRCA1* pathogenic variant. In this scenario, in which single-site testing was most appropriate, only 20-35% of physicians ordered this test. [4] Many others ordered full analysis of *BRCA1/2* instead.[4,89] This study reported that this led to a "9-fold increase in unnecessary genetic testing costs."[4]

A final area of concern with ordering by non-genetics professionals is that they may be more likely to test an individual under the age of 18. Currently, the ACMG recommends that individuals should not be tested under age 18 unless the results could change clinical management.[90] One 2016 study found that in a population of 91 Florida-based nongenetics

providers who had previously ordered *BRCA* testing, 35% of respondents would test a minor for a known familial *BRCA* pathogenic variant. [87] None of the 10 genetics providers surveyed indicated that they would test a minor, and the difference between the two groups was significant (p=0.02).[87]

Trends Correlated with Ordering Practices

Physicians who order genetic testing more often seem to share several characteristics. Multiple surveys found that physicians were more likely to order cancer genetic testing if they believed that they had adequate genetics training during their schooling or through continuing education opportunities.[91] Increased ordering practices were also correlated with provider attitude towards genetic testing. Providers who believed genetic testing could impact medical management and who tended to be open to innovation were more likely to order testing.[91,92] Other factors that increased the likelihood of testing were access to genetic counselors, knowledge of the ordering procedures, knowledge of non-discrimination laws, and patient-prompted discussions about testing.[91–93]

Some barriers preventing genetic testing by non-genetics professionals included lack of confidence in genetics communication skills and knowledge, inadequate training programs, concerns about potential genetic discrimination for patients, and a lack of support resources for the providers.[91–93] Some providers also feared that they would not be able to manage a patient's emotional response to a result. [91–93] One analysis found that providers who had graduated most recently and those who graduated the longest ago were both less likely to order genetic testing. [91–93] Factors correlating with increased genetics referrals included attendance in genetics conferences, more confidence in training programs, better knowledge of genetics concepts, and being located in an urban environment.[91–93]

2.3.2.2 Counseling

Another area of concern with genetic testing by non-genetics professionals relates to counseling style. Pre-test counseling is essential to including the patient in their own medical decision-making. This process helps the patient to understand how these results may impact their medical care, their emotions, and their family life. Without fully understanding these implications prior to testing, the results may negatively impact a patient's life.

Several aspects of pre-test counseling have been shown to differ significantly between genetics and non-genetics providers. In a 2015 study, 473 patients who had genetic testing were surveyed about their pre-test counseling experience. The study found that 97% of patients who had testing facilitated through a genetics professional remembered that they had pre-test counseling. For those who had testing organized through a non-genetics professional such as an Ob-Gyn, surgeon, oncologist, or nurse practioner, only 59% recalled having pre-test counseling.[89]

Several studies were also aimed at assessing the content included in pre-testing counseling by non-genetics professionals. The American Society of Cancer Oncology and the American College of Medical Genetics issued guidelines outlining topics that should be covered in the informed consent process prior to cancer genetic testing.[94,95] These topics included possible medical implications, psychosocial effects, results implications for family members, and privacy/confidentiality concerns with testing.[87]

A 2016 survey by Cragun et al asked patients about their pre-test genetic counseling experiences. Patients reported that they were significantly less likely to be counseled about employment and insurance discrimination when the counseling was performed by a non-genetics professional ($p<=0.01$).[87–89] Further, they were significantly less likely to receive a summary letter of what had been discussed ($p=0.02$).[89] Non-genetics providers also reported discussing

psychosocial concerns and the possibility of a VUS result significantly less than genetics providers.[88,89] Amongst the Ob-Gyn providers, about 50% indicated that they sometimes or rarely covered all pre-test counseling topics issued by ASCO and ACMG.[96]

One reason non-genetics providers may not cover all the important aspects of pre-test counseling is that they spend less time counseling. The average time spent counseling was 20 minutes for non-genetics professionals compared to 67.5 minutes by genetics professionals.[97] Also, physician's offices that also employed a genetics nurse, PA-C, CRNP, or genetic counselor were significantly more likely to have performed complete pre-test counseling.[96] It is possible that physicians do not have enough time to spend counseling patients without these additional providers, and/or that these providers have more genetics education.

There is additional evidence that non-genetics providers do not feel qualified or comfortable obtaining informed consent for genetic testing. A 2010 survey of Ob-Gyn providers found that 28% of providers felt unqualified and 64% felt only partially qualified to perform cancer genetic counseling.[81] In another study, 20-36% of non-genetics providers indicated that they struggled to provide counseling for emotional responses to test results.[88] About 32% of non-genetics providers indicated that they do not perceive handling long-term psychosocial effects of testing to be part of their professional role.[88]

2.3.2.3 Knowledge and Interpretation

The interpretation of *BRCA* test results by non-genetics professionals can sometimes be clinically problematic. First, there are concerns that *BRCA* positive individuals are not always being managed appropriately. One 2011 survey of non-genetics professionals found that 76% of Ob-Gyn providers recommended that *BRCA* positive patients should consider RRSO. [3,4] National

management guidelines recommend that this surgery should always be discussed, because there are no reliable screening alternatives.[30] Some women with positive *BRCA* test results do not pursue this surgery for various reasons, including possible side-effects. However, rates at which recommendations for RRSO were made by physicians completing this survey still appear lower than would be advised by these national guidelines.

There is also evidence that some non-genetics providers may have difficulty interpreting a negative genetic test result. In 2016, non-genetics professionals were surveyed regarding how to manage a patient with a family history of cancer and a negative *BRCA* result. Of this surveyed group, 19% wrongly indicated that this high risk patient should pursue general population screening recommendations.[87] This suggests that almost one-fifth of surveyed providers would have mis-managed this patient.

Non-genetics providers have been shown to have concerns related to managing patients with variant of uncertain significance (VUS) results. [5] About 60% of the 92 surveyed physicians working at Mayo Clinic in Florida in 2018 reported being uncomfortable interpreting this type of result. [5] This study also found discrepancies in how providers viewed VUS results, with 11.9% indicating that they did not believe the VUS explained their patient's condition, while another 32.1% thought it was very likely that the VUS was responsible for the condition. [5] Only 16% answered all theoretical management questions about VUS results correctly.[5]

These instances serve as indications that there are challenges with non-genetics professionals adhering to national management guidelines and suggests that some patients may not be receiving optimal care.

Factors Impacting Results Interpretation

Many studies have tried to determine what factors are contributing to these mismanagement trends. One potential contributing factor is that some of these providers do not feel comfortable managing these *BRCA* positive patients. In one 2010 study, 26-35% of the 289 surveyed Ob-Gyn ACOG fellows indicated that they did not feel at all qualified to manage breast and gynecologic risk for *BRCA* positive patients.[81] Furthermore, another 60% indicated that they felt only partially qualified to manage each of these cancer risks.[81] Although high risk breast specialists or gynecologic oncologists are sometimes available to help manage these patients, in other cases this responsibility may fall upon Ob-Gyns despite their feelings of discomfort.

Studies also found that individuals who were more confident in their level of genetics knowledge were more likely to correctly interpret results and manage patients.[3,86] One way they gain knowledge is through clinical experience. Those providers who had ordered the most tests tended to manage patients more appropriately. For example, providers who had more experience ordering testing were significantly more likely to recommend RRSO for *BRCA* positive patients.[3]

Formal genetics training also affects knowledge, comfort level, and management. In a 2013 study, 44-55% of 91 responding Florida-based non-genetics providers who had ordered *BRCA* testing reported that they had some form of genetics training. [86,87] About 30-57% of those providers stated that they had been trained by educational materials issued by commercial labs.[86,87] In a 2010 study by Ready et al, 65 Ob-Gyn residents in Texas were surveyed and 76% indicated that they would value improvements in their genetics training.[98] This study echoed findings from a survey of Ob-Gyns conducted in 2000, which found that providers who reported that they had formal training in genetics were more likely to follow management guidelines for theoretical clinical scenarios.[99]

Several interventions centered on improving genetics education are documented in the medical literature. In 2013, Cragun et al surveyed non-genetics physicians about what genetics educational resources they would find helpful. [100] The study offered several possible educational materials, including a formal training program consisting of a three day in-person training and/or monthly webinars, and other education resources, including a resource guide, case scenarios, and newsletters. Over 80% of surveyed physicians identified that they would be interested in formal training with about one third demonstrating interest in in-person training, one fifth demonstrating interest in a regular webinar, and one third demonstrating interest in both. About 64% indicated that they would be interested in receiving other educational resources.[100]

These physicians were asked what factors they felt were preventing them from pursuing further genetics education and 88% identified taking time off work as a barrier to pursuing in-person training. They were also asked what would further motivate them to pursue genetics training, with 77% indicating a desire to receive continuing education credits for the training, 64% seeking specialized training in counseling skills, and 64% requesting a certificate of completion.[100]

Identifying what factors seem to be contributing to problems providers experience with *BRCA* testing will help guide similar intervention strategies in the future. The data collected from *BRCA* testing will help identify potential concerns with newer panel testing and ways to combat these concerns. However, multi-gene panel testing may contribute additional concerns since interpretation of these tests can be complicated.

2.3.3 Multi-Gene Panel Testing

An increasing number of providers are beginning to use multi-gene panel testing instead of *BRCA* testing alone. In 2016, 90% of genetics providers and 42% of non-genetics providers had reported prior use of cancer gene panel testing.[87] With more non-genetic providers starting to order this testing, several new complications may be anticipated.

Previous data has shown that providers are not comfortable interpreting and managing VUS results identified on *BRCA* testing. Because more genes are included on panels, the likelihood of receiving a VUS result is higher. Current estimates suggest that there is at least a 1% chance of getting a VUS per gene studied.[101] Therefore, providers ordering panels will likely have to interpret these types of results more often.

Further, many gene panels now include moderate penetrance genes and newly researched genes. Some guidelines have been issued indicating best practice for the management of moderate penetrance pathogenic variants.[48] However, experience with *BRCA* testing showed that providers do not always follow the management guidelines. One potential concern is that providers may not correctly assess the level of risk associated with each gene and may make inappropriate management recommendations. They may also lack knowledge about the types of cancer associated with each gene and therefore miss opportunities for intervention.

Additionally, for many of these newly researched genes, there is not enough information to establish guidelines. Without a standard of care for these patients, providers have to individualize management plans. This lends itself to management inconsistencies dependent on risk perception by the provider. As more is learned about these genes, recommendations may

change, which puts the responsibility on the ordering provider to stay updated about genetics research.

Overall, the use of cancer genetic testing has helped to prevent cancer diagnoses in individuals born at high risk. Although cancer genetic counselors are specially trained to take on this clinical role, the field is new and not all patients have access to a local counselor. For this and other reasons, many primary care providers, particularly Ob-Gyns, have become involved in cancer genetic testing. Initial data from non-genetics providers' use of *BRCA* testing has identified some areas in need of improvement. Multi-gene panel testing presents some additional potential challenges. The purpose of this study is to learn more about how local providers are using this testing, to assess how results are being managed, and to gather provider perspective on their use of panel testing.

3.0 MANUSCRIPT

3.1 BACKGROUND

3.1.1 Breast and Ovary Cancer Genes

Since the 1990s, the *BRCA1* and *BRCA2* genes have been the most well-known genetic risk factors for breast and ovarian cancer.[9,14] Pathogenic variants in the DNA sequence of the *BRCA1* and *BRCA2* genes increase an individual's lifetime breast cancer risk to 65-79% and 61-77% respectively, compared to the 12.5% general population risk. [20,23] Pathogenic variants in *BRCA1* and *BRCA2* also increase ovarian cancer risk to 36-53% and 11-25% respectively, compared to 1-2% in the general population. [20,23]

Within the last five to ten years, genetic testing for hereditary forms of breast and ovarian cancer has expanded to include genes in addition to *BRCA1* and *BRCA2*. Groups of these genes can be analyzed simultaneously through multi-gene cancer panels.[102] With the expansion of cancer genetic testing, it was found that about 40% of hereditary breast cancers are attributed to other genes that are now included on multi-gene panels.[48]

Panel composition varies by lab and indication. For the genes on any given panel, there is variability in the types of cancer linked to each gene included, the level of risk conferred by the gene, and gene-specific penetrance and outcomes data published. The diversity of genes on a particular panel complicates results interpretation. The NCCN has crafted definitions to describe these different parameters. It describes clinical validity as the level of evidence supporting the

association between a gene and a given cancer risk. Clinical utility is the level of evidence that a particular intervention is effective for individuals carrying a pathogenic variant in a particular gene. Clinical actionability describes whether or not a pathogenic variant in a particular gene can change medical management. [30]

The NCCN attempts to delineate different categories based on the clinical validity of a gene and the degree of risk associated with that gene. The high-risk category consists of genes with high clinical validity and an increased cancer risk. Many of these genes are linked to well-established cancer syndromes. Moderate-risk genes have been linked to a particular type of cancer and have a lower cancer risk on average than the high-risk category. Other genes that can be included on a cancer panel may have lower validity and less research on degree of cancer risk, and these are often referred to as "newly researched" or "emerging research" genes. [30] For genes on a panel test, the NCCN issues appropriate management guidelines for genes considered to be clinically actionable based on validity, utility and the level risk for a given cancer that is linked to a particular gene.

High-risk breast cancer genes include those genes, that like *BRCA1* and *BRCA2*, confer over a five-fold lifetime risk to develop breast cancer.[49] Genes associated with specific hereditary cancer syndromes fall into this category, including Li-Fraumeni syndrome (*TP53* gene), Cowden syndrome (*PTEN* gene), and hereditary diffuse gastric cancer (*CDH1* gene).[50–52] Genes associated with Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM)* can be linked to an increased ovarian cancer risk up to 24%.[53] Pathogenic variants identified in this category of genes are considered largely contributory to the cancer history within a family. While other risk factors may adjust cancer risk, much of the family risk can be attributed to a high risk pathogenic variant alone. An unaffected individual who does not carry a known familial pathogenic variant in one of these

genes is generally considered to be at general population risk to develop cancer, in the absence of any significant exposures or other personal risk factors.[54]

Breast and ovarian panels have recently expanded even further to include clinically actionable moderate risk genes. Moderate-risk breast cancer genes increase breast cancer risk by about two-to-five-fold. Genes within this category include *ATM, CHEK2,* and *PALB2,* although more recent studies suggest that *PALB2* may actually elevate breast cancer risk over the risk threshold defining this category of genes. [48] Pathogenic variants in these genes account for the most cases of hereditary breast cancer outside of the *BRCA* genes.[102] Several genes, including *BRIP1, RAD51C,* and *RAD51D* have been associated with a clinically actionable increase in ovarian cancer risk. Current estimates project that *BRIP1* confers a lifetime ovarian cancer risk from 4.06-12.7%, while *RAD51C* and *RAD51D* confer 6.12% and 13.56% risk respectively.[64–66]

A pathogenic variant identified in one of these genes is viewed as a risk factor that likely interacts with other shared risk factors, either genetic or environmental, to cause an increased cancer risk within a family. [54] Increased cancer risk within a family therefore cannot be solely attributed to a pathogenic variant in one of these genes. [54] Accordingly, individuals who test negative for a known pathogenic variant in their family are still considered to be at increased risk compared to the general population because other shared risk factors are likely at play.[54]

Many of the largest breast and ovary gene panels also include a group of newly researched genes. These genes have been linked to breast or ovary cancer risk in some studies, but the level of risk conferred by each gene is not well established.[48] Some of these genes include *BARD1, MRE11A,* and *RAD50.*[68,69]

3.1.2 Cancer Panel Results Interpretation

For women considered to be at average risk of developing breast cancer, the American Cancer Society (ACS) recommends initiating annual mammograms starting at age 40-45.[27] The ACS states that annual mammograms should continue until age 55, at which point they can occur every 2 years.[27] The U.S. Preventative Services Task Force guidelines vary slightly in that they recommend that mammograms should be initiated by age 50, can be considered as early as age 40, and should occur every 2 years.[28] For ovary cancer, women are advised to meet regularly with their Ob-Gyn providers and to report any abnormal symptoms, but there are no additional screening guidelines endorsed by the American College of Obstetricians and Gynecologists (ACOG).[29]

There are three possible outcomes from all cancer genetic testing. A negative genetic test indicates that no pathogenic variants were identified in the genes examined. Individuals with a negative test result are still considered to be at increased risk for a particular type of cancer if they have a family history of that cancer. [6–8] For individuals with a family history of breast cancer and a negative breast-centered genetic test, specific risk models such as Tyrer-Cuziak, BODICEA, and *BRCApro* can be used to help predict an individual's breast cancer risk. [35] According to the ACS, individuals with a family history of early onset breast cancer can consider initiating mammography screening five to ten years before the earliest breast cancer diagnosis in the family. [8] The ACS also indicates that individuals found to have over a 20% lifetime breast cancer risk using these risk models can consider using breast MRI screening in addition to mammograms. [35]

Individuals with negative ovary-centered genetic testing and a family history of ovarian cancer are also at increased risk to develop ovarian cancer.[7] However, ovarian cancer screening

modalities such as transvaginal ultrasound and CA-125 bloodwork are unreliable at detecting the presence of ovarian cancer. [73,74] Surgical removal of the ovaries and fallopian tubes via bilateral risk-reducing salpingo-oophorectomy is the only intervention known to reduce ovarian cancer mortality. [30-35] Some women choose to pursue this surgery based on family history alone.

Another possible genetic test result is a "variant of uncertain significance," or VUS. The American College of Medical Genetics has issued statements indicating that VUS results should not be used to change medical management.[76] About 90% of the time, evidence is gathered about these results suggesting that they are truly benign. [48-49]

A positive result indicates that a pathogenic variant was identified in one of the genes analyzed. Individuals carrying this pathogenic variant are at increased cancer risk. The degree of the risk and type of cancer depend on the gene carrying the pathogenic variant. Research on the effectiveness of different preventative measures and interventions for pathogenic variants in specific genes is compiled into national guidelines issued by the National Comprehensive Cancer Network (NCCN).[30] Based on these guidelines, breast cancer risk associated with most high-risk breast cancer genes like *BRCA1/2*, *TP53*, and *PTEN* can be managed by surgical intervention or increased surveillance. The guidelines recommend consideration of prophylactic bilateral mastectomy, which is known to reduce the risk of an initial breast cancer diagnosis by up to 90%.[30] The alternative strategy is initiation of screening at a younger age, usually sometime between 20-30 years, and use of breast MRI screening in conjunction with mammograms. [34]

For some of the other high-risk breast genes and the moderate-risk breast genes, the NCCN recommends increased surveillance with annual breast MRIs along with mammograms (with consideration of tomosynthesis) starting between ages 30 and 40 depending on the gene.[30,48] For these genes, there is insufficient evidence to recommend prophylactic bilateral mastectomy, but

guidelines indicate that the procedure may be beneficial for individuals with a strong family history of breast cancer. [30]

For the class of more newly researched breast cancer genes, there is not currently sufficient evidence for a specific screening or interventional program. Individuals carrying pathogenic variants in the newly researched genes are typically managed on an individual basis in the context of other personal and family risk factors.

Because ovarian cancer screening is unreliable, the NCCN recommends consideration of risk-reducing salpingo-oophorectomy (RRSO) for all individuals carrying pathogenic variants in clinically actionable ovary cancer genes, including the *BRCA* genes, the Lynch syndrome genes, *RAD51C, RAD51D,* and *BRIP1*.[30] The age at which this procedure can be considered varies from 35-40 for *BRCA1*, 40-45 for *BRCA2*, and 45-50 for *RAD51C*, *RAD51D*, and *BRIP1*.[48] The guidelines indicate that there is insufficient evidence that ovarian screening via transvaginal ultrasound and CA-125 levels decreases ovarian cancer mortality, but high risk individuals who do not pursue surgery may consider screening. [48]

3.1.3 Ob-Gyn Involvement with Cancer Genetic Testing

Since *BRCA* genetic testing was first introduced, Ob-Gyn providers have been involved in making this testing clinically accessible. From 2009-2011, the estimated range of Ob-Gyn providers who had ordered *BRCA* testing varied from 43-61%.[2,3,83] The likelihood that an Ob-Gyn provider had previously ordered *BRCA* testing was more than double that of an internal medicine physician ($p<0.01$).[83] Further, a 2010 survey of 65 Ob-Gyn residents across Texas found that 67% of the providers had referred a patient for cancer genetic counseling over the last year.[81] Non-genetics

provider use of genetic testing has been shown to stray from current guidelines is several key ways. Major areas in which practice can differ include counseling techniques and results interpretation.[84]

Several aspects of the pre-test counseling process have been shown to differ significantly between genetics and non-genetics providers. In a 2015 study, 473 patients who had genetic testing were surveyed about their pre-test counseling experience. The study found that 97% of patients who had testing facilitated through a genetics professional remembered that they had pre-test counseling. For those who had testing organized through a non-genetics professional such as an Ob-Gyn, surgeon, oncologist, or nurse practioner, only 59% recalled having pre-test counseling.[89]

The American Society of Cancer Oncology and the American College of Medical Genetics issued guidelines outlining topics that should be covered in the informed consent process prior to cancer genetic testing.[94,95] These topics included possible medical implications, psychosocial effects, results implications for family members, and privacy/confidentiality concerns with testing.[87] A 2016 survey by Cragun et al asked patients about their pre-test genetic counseling experiences. Patients reported that they were significantly less likely to be counseled about employment and insurance discrimination when the counseling was performed by a non-genetics professional ($p<=0.01$).[87–89] Further, they were significantly less likely to receive a summary letter of what had been discussed ($p=0.02$).[89] Non-genetics providers also reported discussing psychosocial concerns and the possibility of a VUS result significantly less than genetics providers.[88,89] Amongst the Ob-Gyn providers, about 50% indicated that they sometimes or rarely covered all pre-test counseling topics issued by ASCO and ACMG.[96]

The interpretation of *BRCA* test results by non-genetics professionals can also sometimes be clinically problematic. First, there are concerns that *BRCA* positive individuals are not always being managed appropriately. One 2011 survey of non-genetics professionals found that 76% of

Ob-Gyn providers recommended that *BRCA* positive patients should consider RRSO. [3,4] National management guidelines recommend that this surgery should always be discussed, because there are no reliable screening alternatives.[30] Some women with positive *BRCA* test results do not pursue this surgery for various reasons, including possible side-effects. However, rates at which recommendations for RRSO were made by physicians completing this survey still appear lower than would be advised by these national guidelines.

In 2016, non-genetics professionals were surveyed regarding how to manage a patient with a family history of cancer and a negative *BRCA* result. Of this surveyed group, 19% wrongly indicated that this high risk patient should pursue general population screening recommendations.[87] This suggests that almost one-fifth of surveyed providers would have mis-managed this patient.

Non-genetics providers have been shown to have concerns related to managing patients with variant of uncertain significance (VUS) results. [5] About 60% of the 92 surveyed physicians working at Mayo Clinic in Florida in 2018 reported being uncomfortable interpreting this type of result. [5] This study also found discrepancies in how providers viewed VUS results, with 11.9% indicating that they did not believe the VUS explained their patient's condition, while another 32.1% thought it was very likely that the VUS was responsible for the condition. [5] Only 16% answered all theoretical management questions about VUS results correctly.[5]

Researchers have tried to determine what factors are contributing to these mismanagement trends. One potential contributing factor is that some of these providers do not feel comfortable managing these *BRCA* positive patients. In one 2010 study, 26-35% of the 289 surveyed Ob-Gyn ACOG fellows indicated that they did not feel at all qualified to manage breast and gynecologic risk for *BRCA* positive patients.[81] Furthermore, another 60% indicated that they felt only partially

qualified to manage each of these cancer risks.[81] Although high risk breast specialists or gynecologic oncologists are sometimes available to help manage these patients, in other cases this responsibility may fall upon Ob-Gyns despite their feelings of discomfort.

Studies also found that individuals who were more confident in their level of genetics knowledge were more likely to correctly interpret results and manage patients.[3,86] One way they gain knowledge is through clinical experience. Those providers who had ordered the most tests tended to manage patients more appropriately. For example, providers who had more experience ordering testing were significantly more likely to recommend RRSO for *BRCA* positive patients.[3]

Formal genetics training also affects knowledge, comfort level, and management. In a 2013 study, 44-55% of 91 responding Florida-based non-genetics providers who had ordered *BRCA* testing reported that they had some form of genetics training. [86,87] About 30-57% of those providers stated that they had been trained by educational materials issued by commercial labs.[86,87] In a 2010 study by Ready et al, 65 Ob-Gyn residents in Texas were surveyed and 76% indicated that they would value improvements in their genetics training.[98] This study echoed findings from a survey of Ob-Gyns conducted in 2000, which found that providers who reported that they had formal training in genetics were more likely to follow management guidelines for theoretical clinical scenarios.[99]

3.1.4 Multi-Gene Panel Testing

There has been little research about how these concerns with *BRCA* testing have been manifesting since non-genetics providers have started to use cancer panel testing. Based on the wide range of

risks associated with the genes included on some of these panels, it is reasonable to predict that non-genetic provider use of panel testing may present additional challenges.

Previous data has shown that providers are not comfortable interpreting and managing VUS results identified on *BRCA* testing. Because more genes are included on panels, the likelihood of receiving a VUS result is higher. Current estimates suggest that there is at least a 1% chance of finding a VUS per gene studied.[101] Therefore, providers ordering panels will likely have to interpret these types of results more often.

Further, many gene panels now include moderate penetrance genes and newly researched genes. Some guidelines have been issued indicating best practice for the management of moderate penetrance pathogenic variants.[48] However, experience with *BRCA* testing showed that providers do not always follow the management guidelines. One potential concern is that providers may not correctly assess the level of risk associated with each gene and may make inappropriate management recommendations. They may also lack knowledge about the types of cancer associated with each gene and therefore miss opportunities for intervention.

Additionally, for many of these newly researched genes, there is not enough information to establish guidelines. Without a standard of care for these patients, providers have to individualize management plans. This lends itself to management inconsistencies dependent on risk perception by the provider. As more is learned about these genes, recommendations may change, which puts the responsibility on the ordering provider to stay updated about genetics research.

Initial data from non-genetics providers' use of *BRCA* testing has identified some areas in need of improvement. Multi-gene panel testing presents some additional potential challenges. The

purpose of this study is to learn more about how local providers are using this cancer panel testing.

The **specific aims** of this study are as follows:

- To identify how often Ob-Gyn providers are using cancer gene panel testing
- To gather data about how providers would manage patients at varying genetic risk levels for breast and ovarian cancer
- To ascertain Ob-Gyn provider perspectives about their role in panel testing

3.2 METHODS

3.2.1.1 Study Population

The target population for survey distribution consisted of all Ob-Gyn providers working for two major healthcare systems that are centered in the Pittsburgh area. Qualifying providers included attending Ob-Gyn physicians, midwives, gynecologic oncologists, Ob-Gyn residents and fellows, and physician's assistants and nurse practitioners working in obstetrics/gynecology. The population was expanded to include providers outside of physicians, as it was recognized that these providers do sometimes order cancer genetic testing within these healthcare systems. The population included providers practicing in urban, suburban, and rural areas across Western and Central Pennsylvania through these healthcare systems. Both systems have access to cancer genetic counselors who are centered in Pittsburgh but also do outreach in suburban and rural clinics in Western Pennsylvania.

The email addresses for all practicing Ob-Gyn providers within these two healthcare systems were collected. For healthcare system A, a contact within the Ob-Gyn department

provided email addresses for all active providers. For healthcare system B, the study coordinator was granted access to a previously compiled distribution list for Ob-Gyn providers. This list was supplemented by additional provider email addresses listed on a public domain.

3.2.1.2 Survey Development

Prior to recruitment efforts and distribution, exempt IRB approval was obtained from the University of Pittsburgh and Allegheny Health Network (Appendix A).

The study survey was developed using the Qualtrics survey system, which was accessed through a University of Pittsburgh license. The survey included four major sections: a demographic section, a section about ordering and referral practices, a section of theoretical management scenarios and risk assessment questions, and a section about provider perspectives regarding cancer genetic testing. The demographic section included questions about current job title, level of experience, and type of community practice. The ordering practices section asked participants questions about prior use of genetic testing within their practices. The theoretical management scenarios were organized into matrix tables in which providers could indicate all relevant management options for individuals found to be at different breast and ovary cancer risk levels. For each management scenario, providers had to select at least one response. Risk assessment questions asked providers to indicate whether patients in different scenarios would be at average or increased cancer risk. The provider perspective section listed statements and asked providers to respond on a 5-point Likert scale (strongly agree, agree, neither agree nor disagree, disagree, strongly disagree). All questions were newly developed based on information gathered during the literature review and are listed in Appendix D.

3.2.1.3 Recruitment and Survey Distribution

An in-person meeting and emails were both used to recruit participants. For healthcare system A, the study coordinator met with practice managers to explain the major aims of the study. Physical copies of the survey were distributed as a reminder for managers to discuss the survey with employees. In-person recruitment was not performed at healthcare system B. For both healthcare systems, a recruitment email explaining the study aims and containing the survey link was distributed. The inclusion criteria listed within the email indicated that participants must be Ob-Gyn providers and that they must have prior experience or future intent to use multi-gene cancer panel testing. The email indicated that participants could request a cancer genetics referral guide from the study coordinator after the study ended.

Surveys were distributed to healthcare system A via the Qualtrics email distribution function. Weekly reminders were issued though individualized email links to try to improve response rate. Data collection from healthcare system A lasted three weeks. Surveys were distributed to healthcare system B via the Qualtrics email distribution function. Weekly reminders were also issued using this function. Data collection from healthcare system B lasted two weeks.

A statement listing study aims and potential benefits/harms was included before the survey questions. Survey completion was used as proof of informed consent. Five partial responses were not included in the data analysis process because these respondents left most questions unanswered.

3.2.1.4 Statistical Methods

Descriptive statistics were used to indicate how frequently each response was selected. Logistic regression was used to study the association between demographic categories and certain

management responses. Fisher's exact test was used to study the association between demographic factors and Likert scale responses. Chi-squared analysis was used instead if expected counts in the two-way tables were greater than 5. P-values under 0.05 were considered statistically significant. Stata statistical software was used for all statistical analyses.

3.3 RESULTS

3.3.1 Demographic Information

The survey was distributed to 424 Ob-Gyn providers and 67 completed it, giving a 16% response rate. Almost 60% of respondents were Ob-Gyn physicians, while 22.4% were residents or fellows, 6.0% were gynecologic oncologists, and the remaining 13.5% were PA-Cs, CRNPs, or midwives (Table 1). Almost half of all providers indicated that they were still in training (residents/fellows) or that they had been practicing independently for less than 5 years. The remaining two categories, which were 5-20 years' and over 20 years' experience, each had about one quarter of respondents. Providers were also asked whether they practiced in urban, suburban, or rural communities, with the majority (54.0%) indicating that they worked in an urban setting and only 9.2% indicating that they worked in a rural setting (Table 6, Appendix E).

Table 1. Respondent Demographic Information

What is your current professional role at your institution?	N=67 (%)
Ob-Gyn	39 (58.2%)
Gynecologic Oncologist	4 (6.0%)
Resident/Fellow	15 (22.4%)
PA-C, CRNP	6 (9.0%)
Other (Midwife)	3 (4.5%)
How many years have you been practicing independently?	
I am still in training	15 (22.4%)
Less than 5 years	18 (26.9%)
5-10 years	7 (10.5%)
11-20 years	10 (14.9%)
21-30 years	10 (14.9%)
Over 30 years	7 (10.5%)

3.3.2 Ordering Practices

Respondents were asked questions about their prior experience with cancer genetic testing. About 61% indicated that they had used multi-gene panel testing to guide patient management before, while about 39% had not. The providers who indicated that they had not used panel testing results before were not asked additional questions about ordering and referral practices, but were asked later questions related to theoretical management scenarios and provider perspectives on cancer genetic testing (Figure 1).

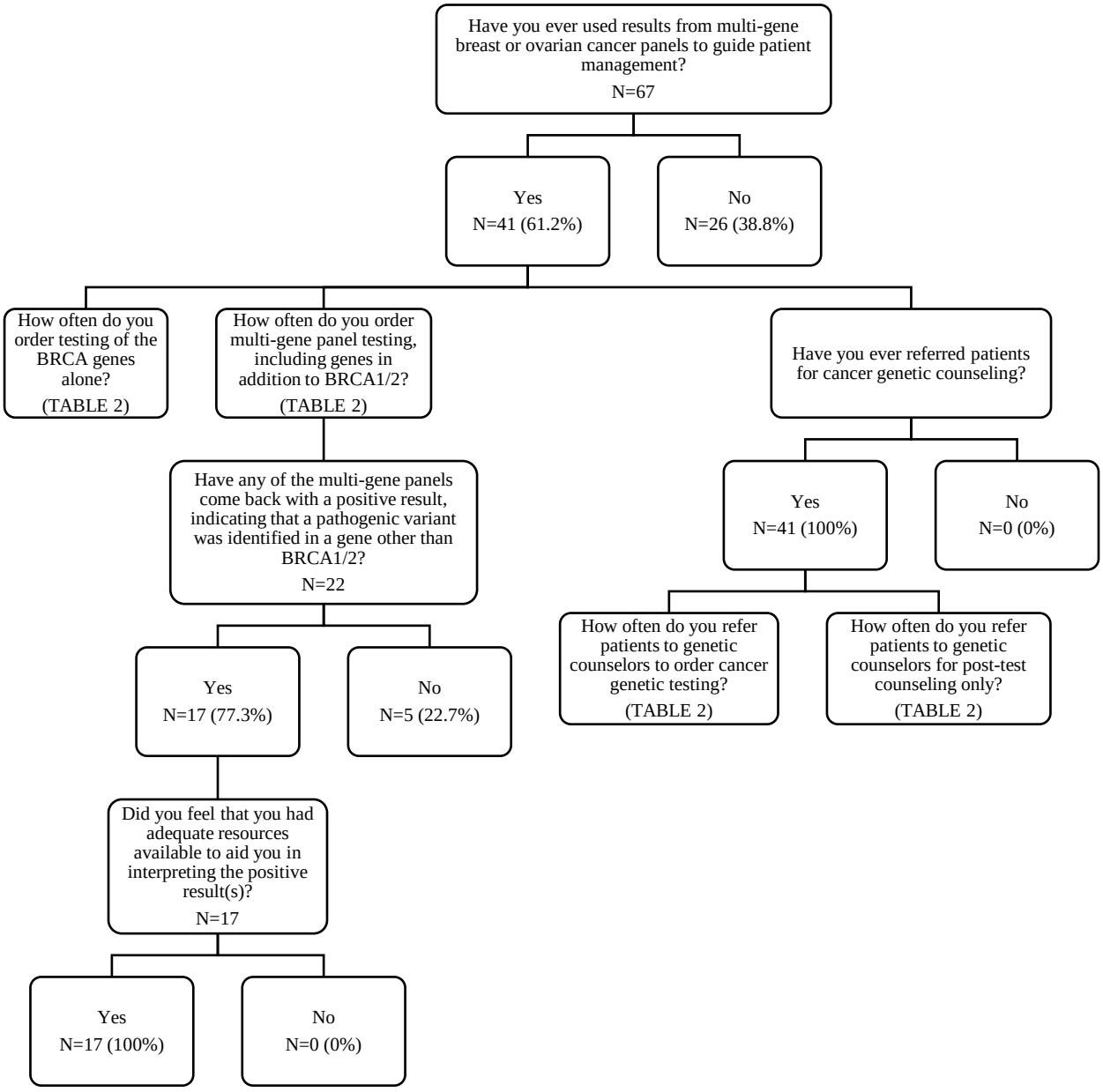

Figure 1. Ordering Practice Survey Flow

Of the 61% of providers who had used panel testing results in their practice, none indicated that they order *BRCA* testing at least once per week. About 10% of providers (N=4) indicated that they order multi-gene panel testing at least once per week. For both *BRCA* and panel testing, 40-45% of providers indicated that they order testing rarely, or about once per month. Similarly, about 45% of providers indicated that they never order testing on their own (Table 2).

About 50% of providers who had used multi-gene panel testing results indicated that they had some prior experience ordering either *BRCA* or panel testing. The majority of this cohort (77.3%) indicated that at least one of their patients was found to carry a pathogenic variant in a gene other than *BRCA1/2*, with all of these providers indicating that they had the necessary resources to help them manage these patients (Figure 1).

All of the providers with prior experience using panel testing indicated that they had referred patients for cancer genetic counseling. Over half of providers indicated that they used genetic counselors to facilitate ordering testing at least once per week. Only about 5% indicated that they had never used a genetic counselor to facilitate ordering testing. About 66% of providers indicated that they referred patients for post-test counseling at least once per month, with 34.2% indicating that they had never referred patients for post-test counseling only (Table 2).

Table 2. Ordering and Referral Practices

	Frequently (several times per week)	Often (at least once per week)	Sometimes (several times per month)	Rarely (about once per month)	Never
How often do you order the following testing? N=41 (%)					
BRCA1/2 Only	0 (0%)	0 (0%)	5 (12.2%)	18 (43.9%)	18 (43.9%)
Multi-Gene Panel Testing	0 (0%)	4 (9.8%)	2 (4.9%)	16 (39.0%)	19 (46.3%)
How often do you refer patients to genetic counselors for the following? N=41 (%)					
To order genetic testing	3 (7.3%)	19 (46.3%)	10 (24.4%)	7 (17.1%)	2 (4.9%)
For post-test counseling	0 (0%)	1 (2.4%)	7 (17.1%)	10 (46.3%)	14 (34.2%)

3.3.3 Management Results

All providers (N=67) were next asked to respond to several theoretical management scenarios. The first scenario asked providers to select which screening and management options they would choose for a patient with a family history of early onset breast cancer and a pathogenic variant in a gene associated with varying levels of breast cancer risk. Management options included initiating screening at a younger age, adding breast MRI, referral to a high-risk breast clinic, adding risk-reducing medications, and referral to discuss prophylactic mastectomy. Providers were able to select multiple appropriate management options for the patient. The varying lifetime risk levels included 15%, 20%, 40%, 60%, and undefined.

Figure 2 demonstrates the number of providers who chose each management option for a given risk level. Figure 3 indicates the percentage of providers selecting each option. Figure 2 clearly demonstrates that the total number of management options selected increased as the risk level increased from 15% to 60%. For the undefined risk category, the total number of options chosen was similar to the 15% risk category. However, for the undefined category, about 30% more providers chose to refer patients to a high-risk clinic and 5% more providers selected a referral to discuss prophylactic mastectomy (Figure 3).

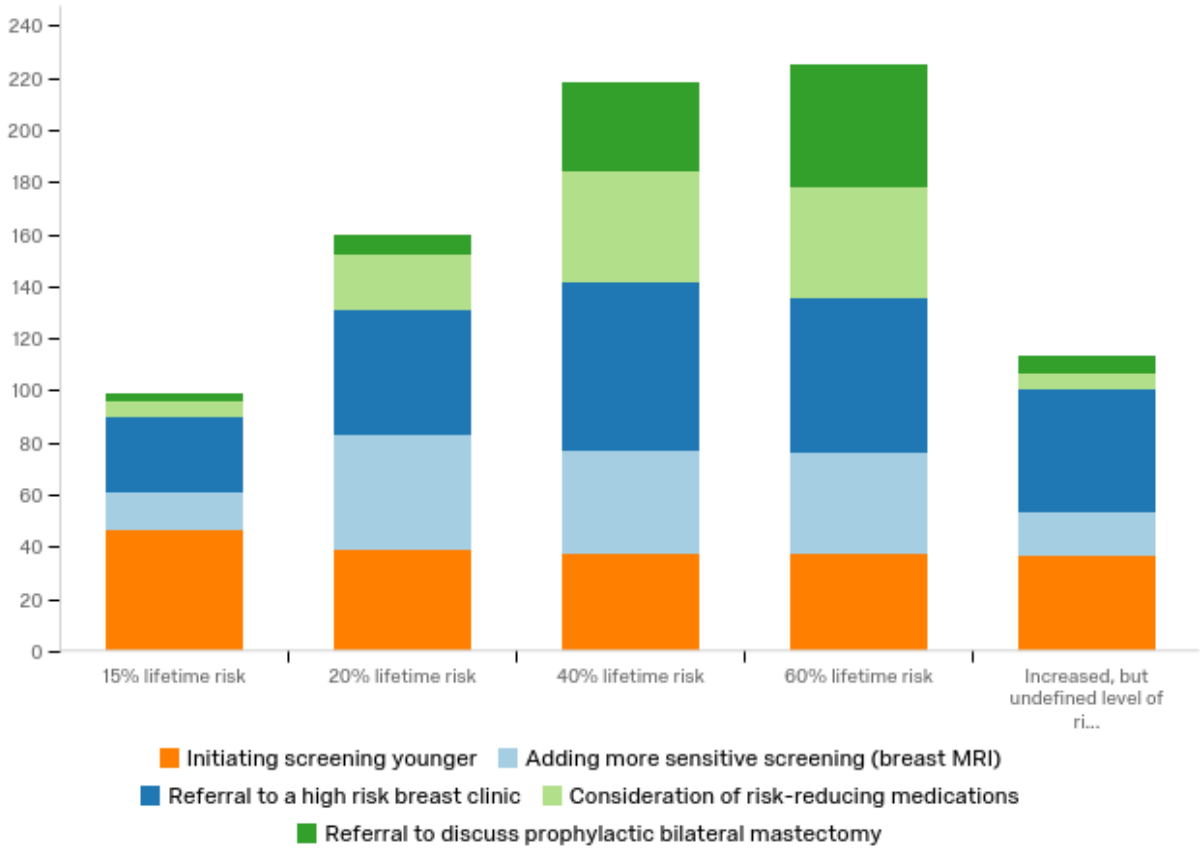

Figure 2. Breast Cancer: Count of Management Options by Risk Level

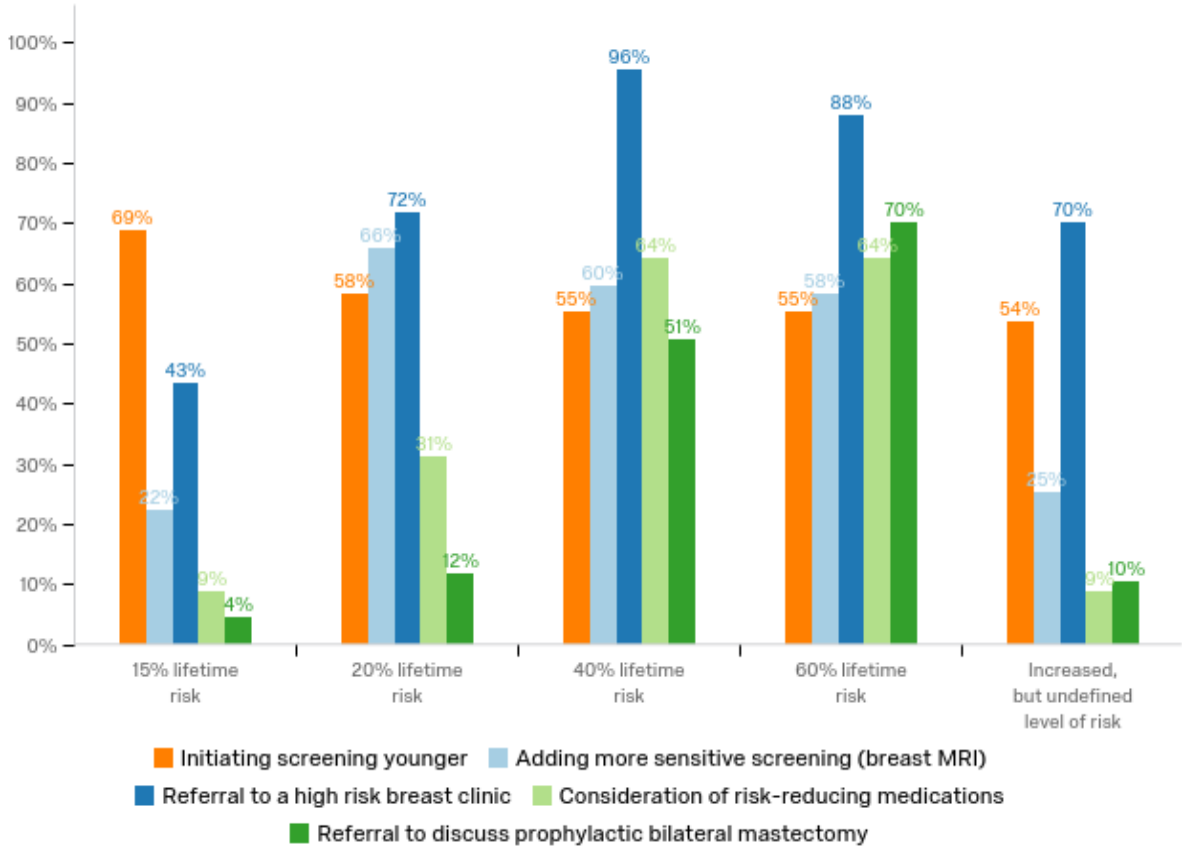

Figure 3. Breast Cancer: Percent of Respondents Selecting Each Management Option by Risk Level

Several trends appeared across the risk categories. The percent of providers recommending initiation of screening at a younger age was similar across the categories, with 54-69% of providers choosing this option. For the breast MRI option, the percent of recommending providers tripled from the 15% to the 20% risk categories. For both the high-risk referral and risk-reducing medication options, the percentage of providers selecting each option increased from the 15% category to the 40% category and then plateaued from 40% to 60%. The percent of providers choosing the referral to discuss prophylactic mastectomy continued to increase across categories.

The largest increase in mastectomy referral occurred between the 20% and 40% categories, with about a 40% increase in the percent of recommending providers.

Figure 4 represents the percentage of providers recommending bilateral risk-reducing salpingo-oophorectomy (RRSO) for various ovarian cancer risk levels (5%, 10%, 20%, and undefined level). The percentage of providers recommending RRSO increased across risk categories, with 94% of providers recommending this procedure at the 20% risk level. Similar to the breast cancer management question, the trends within the undefined risk category were nearly identical to the lowest, 5% risk category.

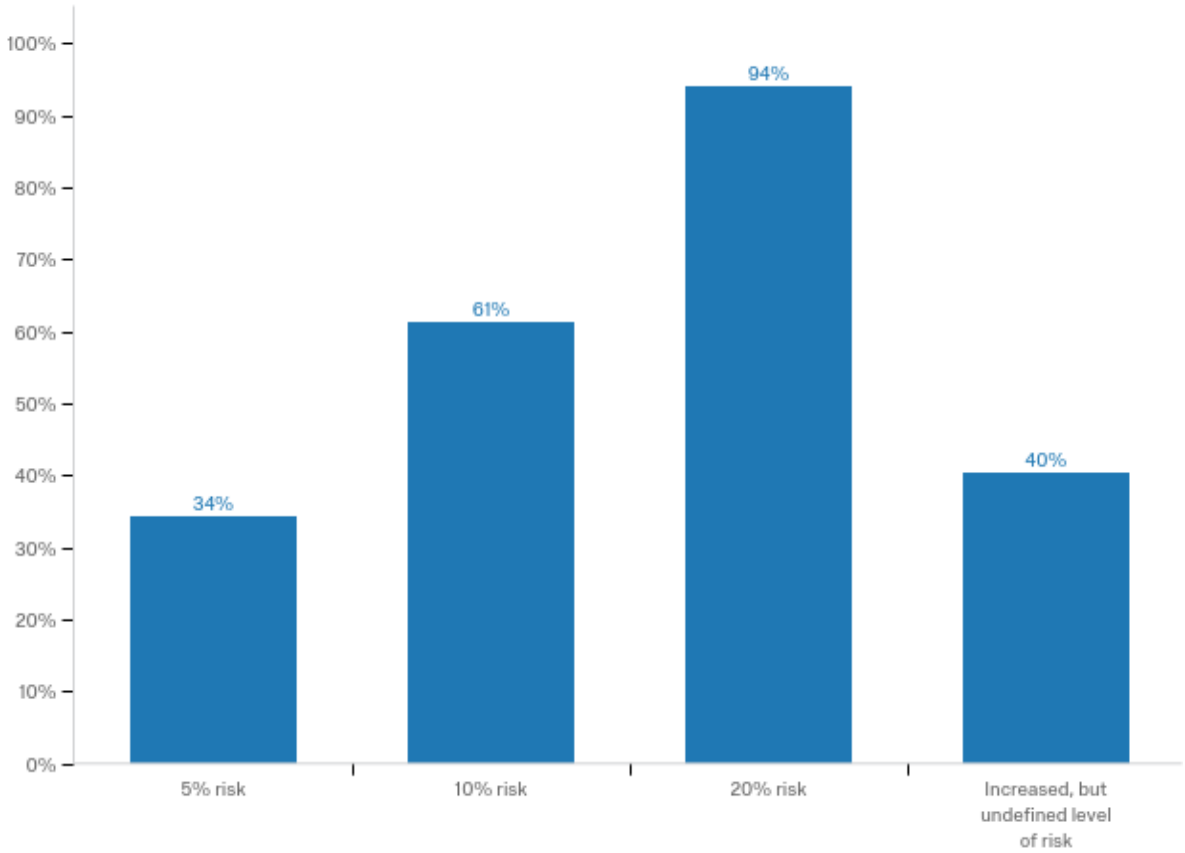

Figure 4. Ovary Cancer: Percent of Respondents Selecting RRSO by Risk Level

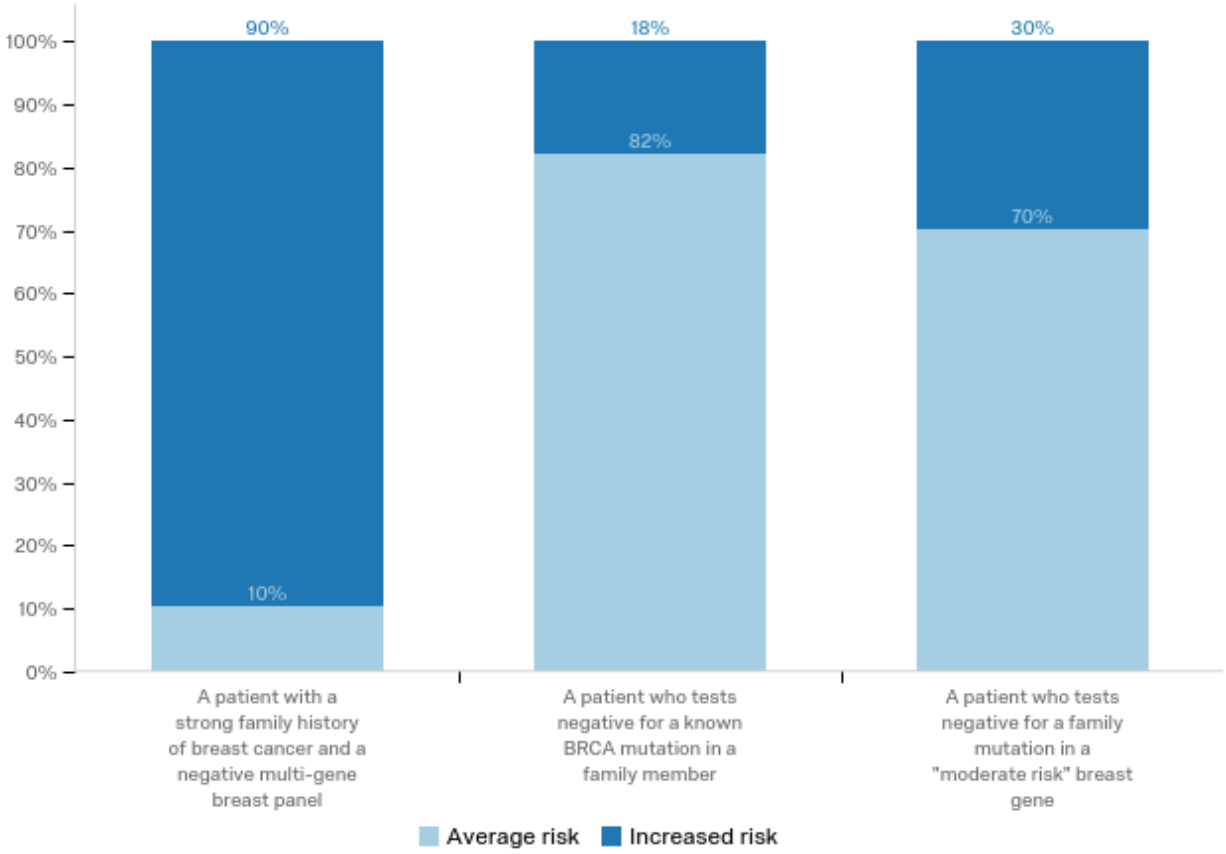

Figure 5. Percent of Respondents Indicating Risk Level for Different Clinical Scenarios

The final management-based question asked providers whether they would consider a patient to be at an average or increased cancer risk for a number of different clinical scenarios. Figure 5 indicates the number of providers choosing each option. About 90% of providers stated that an individual with a family history of cancer and a negative cancer panel would still be at increased cancer risk. About 82% indicated that an individual who tests negative for a known familial *BRCA* pathogenic variant would be at average risk. Similarly, 70% of providers indicated that an individual testing negative for a known familial pathogenic variant in a moderate-risk gene would be at average risk.

3.3.4 Provider Perspectives

Providers were then asked to give their perspectives regarding different aspects of cancer panel testing (Table 7, Appendix E). The responses were graded on a Likert scale. About 66% of providers indicated that they agreed or strongly agreed that Ob-Gyn providers are the most appropriate individuals to identify patients who need further cancer genetics workup. About 85% indicated some level of agreement that identifying these patients is a priority in their practice.

When asked about ordering and counseling practices, about half of providers indicated that they do not feel that they can adequately gather informed consent for panel testing. There did not appear to be a strong trend regarding whether providers are more or less likely to order testing since panels were introduced.

The next section asked providers about their comfort interpreting test results. About 42% indicated that they were familiar with national management guidelines for positive results, while another 42% indicated that they were not familiar with them. Figure 6 shows trends in reported comfort level interpreting different types of test results. Most providers indicated discomfort interpreting positive or VUS panel test results. In contrast, 70% felt comfortable interpreting negative test results. Providers were then asked questions regarding their genetics education. About half of providers indicated that their formal genetics education was not adequate. About 45% indicated that they had been provided with opportunities for genetics-based continuing education credits. About an equal number of providers disagreed and agreed with the statement regarding their ability to stay updated about genetics research (Table 7, Appendix E).

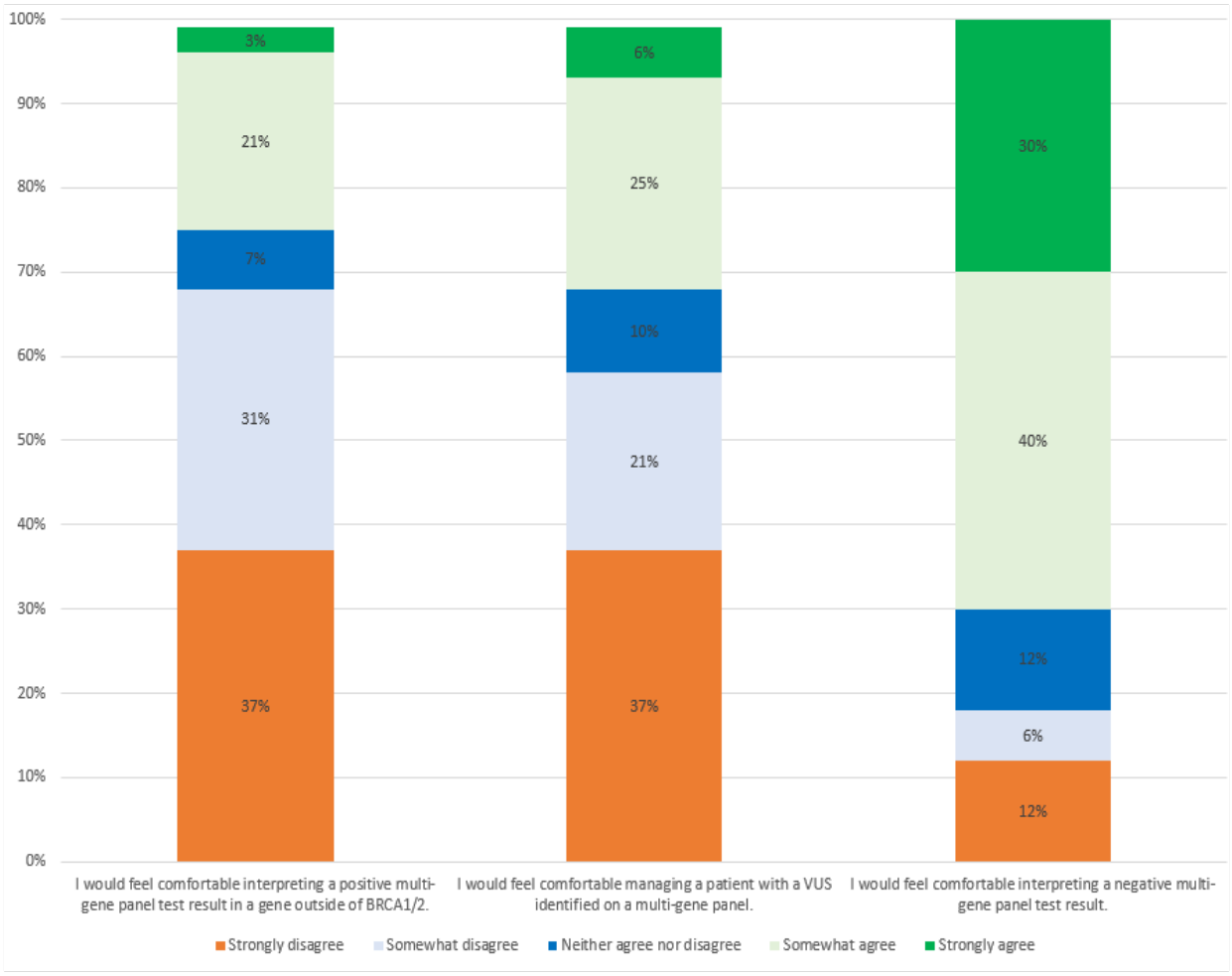

Figure 6. Provider Comfort Interpreting Test Results

3.3.5 Data Trends

Various analyses were used to describe the relationship between demographic factors such as provider type and experience level with different survey outcomes. Figures 7-10 depict trends in theoretical management recommendations based on these factors by using "surgical management sums." A management sum was calculated for each respondent. This sum calculated the number of times that a given provider recommended a particular intervention across increasing risk

categories. For example, in the breast cancer management scenario, the management sum counts the number of times that a provider recommended referral to discuss mastectomy across the 15%, 20%, 40%, and 60% lifetime risk categories. A score of 0 indicates that a given provider did not recommend mastectomy referral for any risk levels, while 4 indicates that the provider recommended mastectomy referral at all risk levels. For the ovarian cancer scenario, the management sum counts the number of times that a provider recommended RRSO across the 5%, 10%, and 20% risk categories. A score of 0 indicates that a given provider did not recommend RRSO for any risk levels, while 3 indicates that the provider recommended RRSO at all risk levels. These sums are not meant to score the appropriateness of management recommendations. Instead, they are used to indicate how frequently each provider considered surgical intervention across these risk categories.

Figures 7 and 8 show how often a particular management sum was indicated by Ob-Gyn provider type and experience level respectively for the breast cancer theoretical management scenario. Providers were grouped into four categories: Ob-Gyn physicians, gynecologic oncologists, PA-Cs/CRNPs/midwives, and residents/fellows. Experience level was grouped into three categories: less than 5 years, 5-20 years, and over 20 years. These two figures are used to depict any differences in likelihood to recommend mastectomy referral by provider type and experience. An underlying assumption is that respondents are more likely to consider surgical intervention for higher risk levels than for lower risk levels. For instance, a management sum of 1 indicates that a provider recommended mastectomy referral at the highest risk level (60%). A management sum of 2 indicates that the provider recommended referral for the 60% risk level and then next highest risk level (40%).

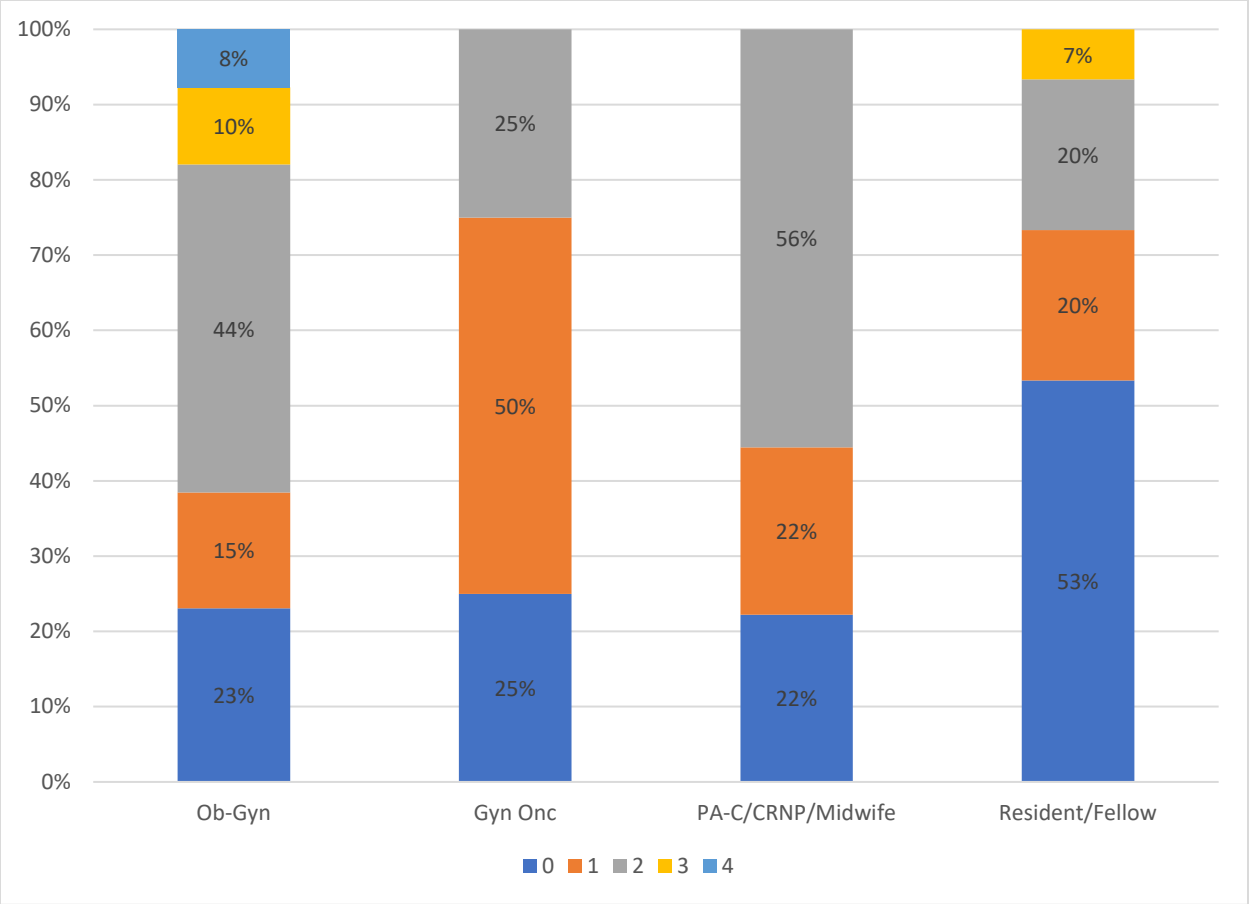

Figure 7. Provider Type and Mastectomy Referral Sum

Figure 7 depicts the management sum for mastectomy referral amongst provider types. One notable trend is that none of the gynecologic oncologists or PA-Cs/CRNPs/midwives recommended referral to discuss mastectomy across more than two categories. Assuming that these providers are more likely to consider surgical intervention for higher risk levels, none of these providers considered mastectomy for the 15% or 20% risk categories. In contrast, 7% of residents/fellows and 10% of Ob-Gyn physicians recommended referral to discuss mastectomy across three risk categories (20%, 40%, 60%). Another 8% of Ob-Gyn physicians considered mastectomy referral for all of the risk levels (15%, 20%, 40%, 60%). Also of note, about 20-25%

of Ob-Gyn physicians, gynecologic oncologists, and PA-Cs/CRNPs/midwives and about 50% of residents/fellows did not consider referral to discuss mastectomy at any of the risk levels (management sum of 0).

A management sum of 1 indicates referral at the 60% risk level, a sum of 2 indicates referral at 40% and 60% risk levels, and a sum of 3 indicates referral at the 20%, 40%, and 60% risk levels. Thus, a sum of 1 estimates the frequency of providers considering surgical referral for the "high penetrance" breast category while sums of 2 and 3 indicate referral for both "moderate penetrance" and "high penetrance levels." Based on this assumption, gynecologic oncologists were 2-3 times as likely as other providers to refer for the high penetrance level only. Only about one quarter of gynecologic oncologists and residents/fellows considered referral within the "moderate penetrance range," compared to at least 50% of Ob-Gyns physicians and PA-Cs/CRNPs/midwives.

Figure 8 depicts mastectomy referral sum across experience levels. The percent of providers with a management score of 0 decreased by one half across each interval between experience levels. Further, the percent of providers considering mastectomy referral in the "moderate penetrance range" continued to increase with increasing experience level.

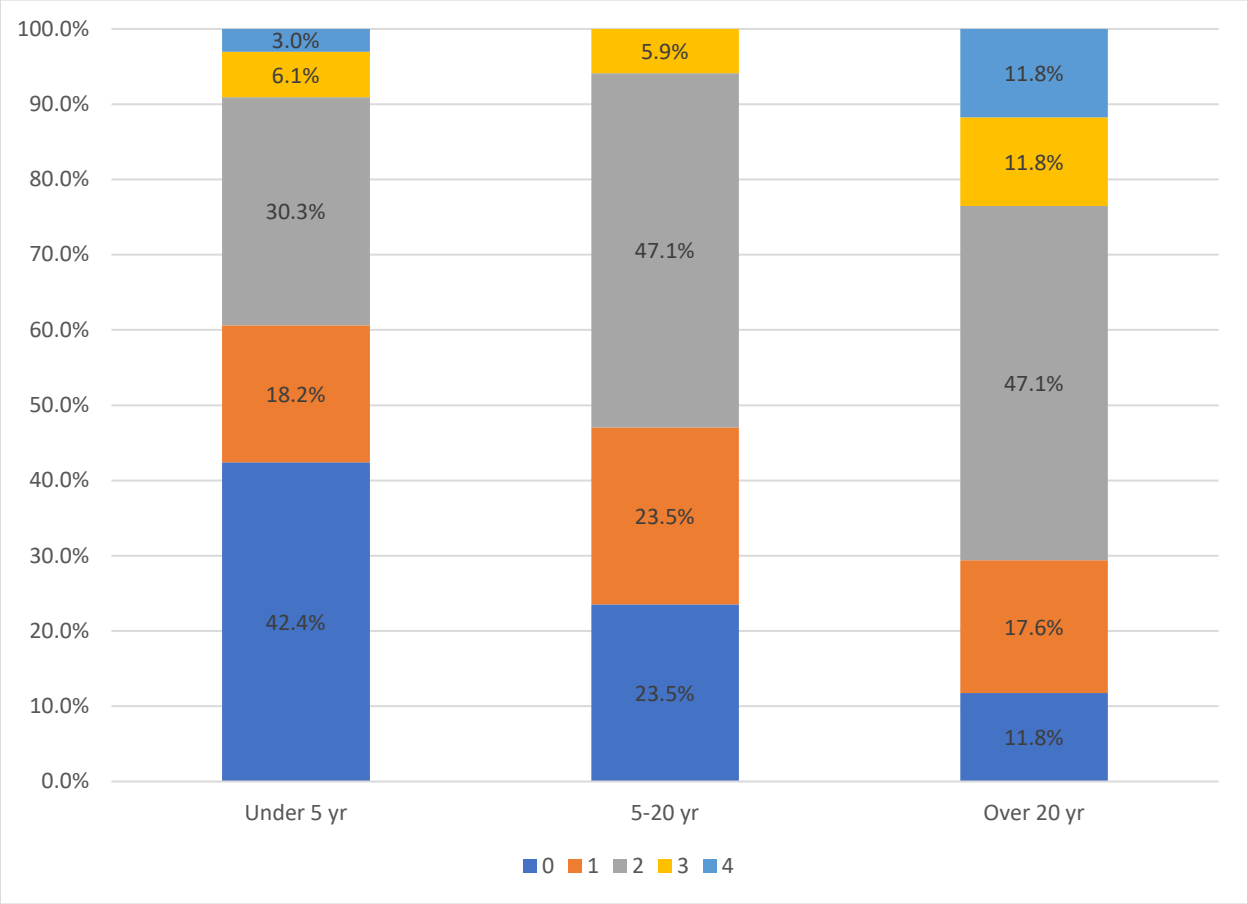

Figure 8. Experience Level and Mastectomy Referral Sum

Figures 9 and 10 examine similar trends in RRSO recommendations. A management sum of 1 assumes that an individual selected RRSO for the highest risk category (20%) only. A management sum of 2 assumes RRSO selection for 10% and 20%, and a sum of 3 assumes RRSO selection for 5%, 10%, and 20%. The 5% and 10% categories represent risk levels associated with ovarian cancer genes with moderate cancer risk, including *BRIP1 RAD51C,* and *RAD51D*. At least one fifth of each provider type selected RRSO across all three risk categories. Notably, gynecologic oncologists were 2-3 times more likely than other providers to recommend RRSO for all three risk categories. Overall, PA-Cs/CRNPs/midwives were the least likely to select RRSO

for any “moderate risk” ovary genes, followed by Ob-Gyn physicians, and then residents/fellows. All gynecologic oncologists selected RRSO within this moderate risk category.

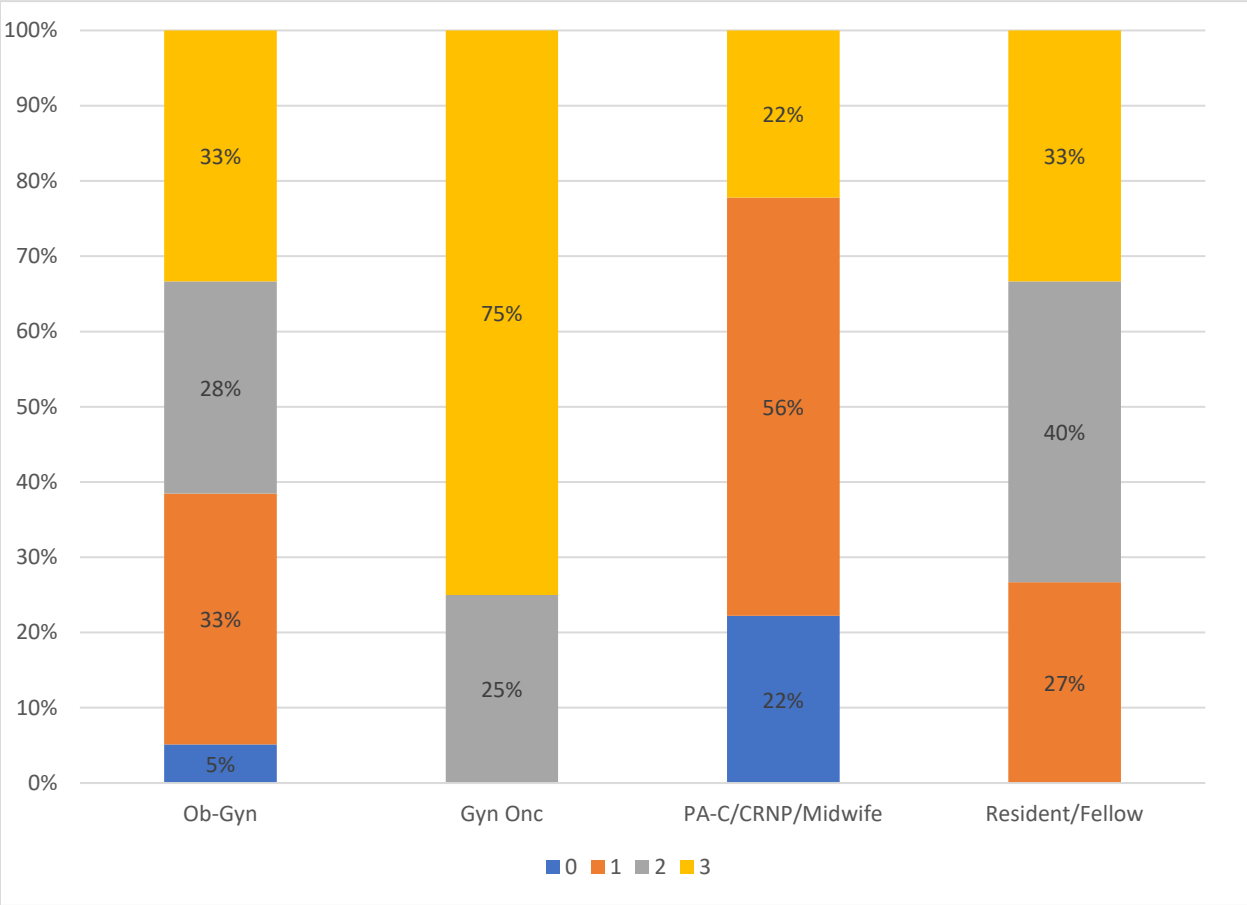

Figure 9. Provider Type and RRSO Recommendation Sum

Figure 10 focuses on RRSO referral sums based on experience level. Overall, the individuals with 5-20 years’ experience were more likely to recommend RRSO within the moderate risk range compared to other experience levels.

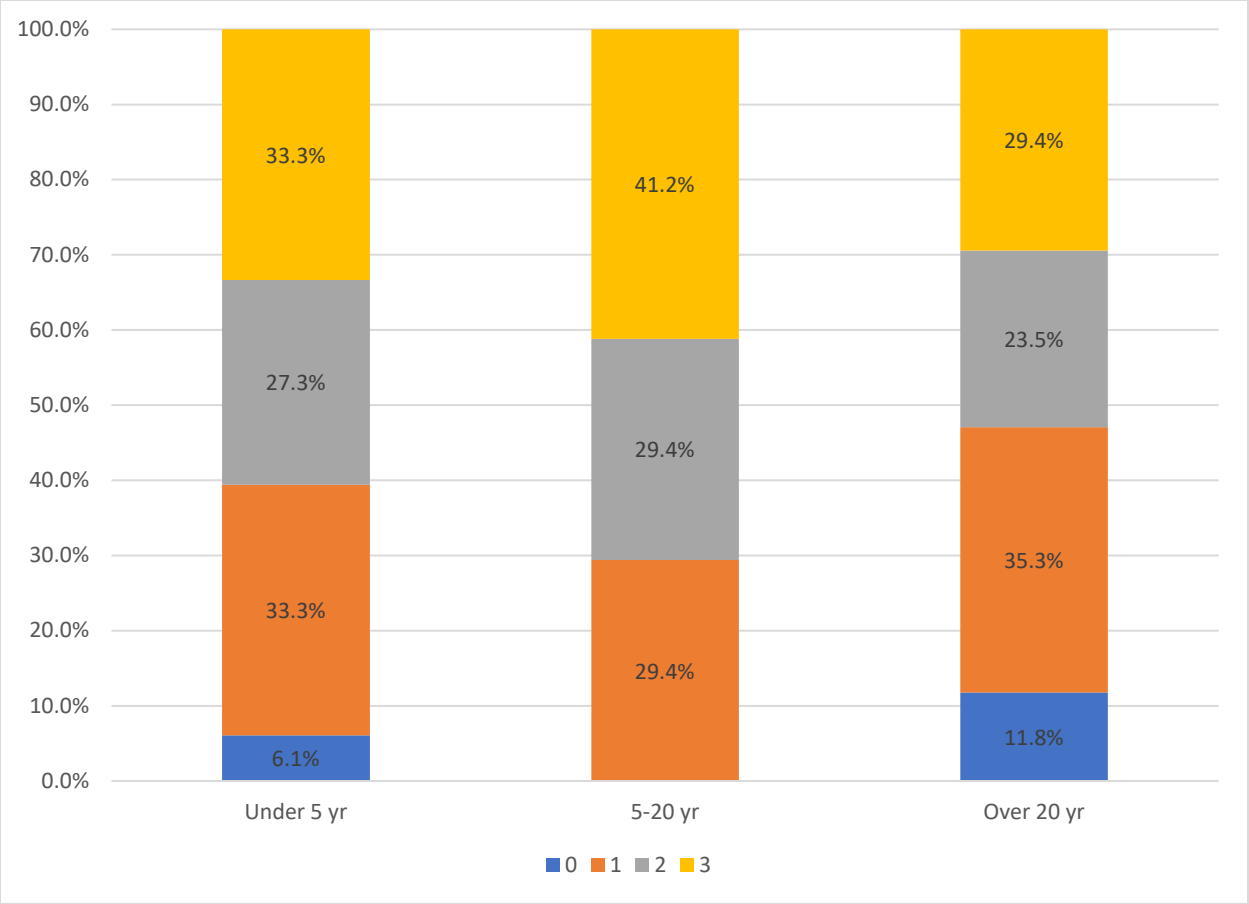

Figure 10. Experience Level and RRSO Recommendation Sum

Table 3 represents measures of association between provider type or experience level and risk category for breast and ovary surgical interventions. The moderate risk breast category included 20% and 40% risk levels while high risk was 60%. The moderate risk ovary category included the 5% and 10% risk levels, while high risk was 20%. A management sum was used to measure how often a given provider recommended either mastectomy or RRSO for each risk category. For example, for the moderate risk breast category, a provider would receive a score of 2 if he/she recommended mastectomy referral both the 20% and 40% risk category, a score of 1 if this referral was made for one of the two categories, and a score of 0 if mastectomy referral was

not indicated for either of these two categories For the high risk category (60%), possible scores included 1 if mastectomy referral was indicated and 0 if it was not. The same process was applied to the ovarian cancer genes. Next, these individual scores for different risk categories were summed across different provider types or experience levels. Chi-squared or Fisher's exact tests were performed on the tables to determine whether provider type or experience level significantly influenced a respondent's likelihood to recommend mastectomy referral or RRSO for the moderate risk category and the high risk category. None of the associations were statistically significant. The highest significance (p=0.07) arose from the relationship between experience level and likelihood to recommend mastectomy referral at the 60% risk category.

Table 3. Association Between Moderate and High Risk Surgical Management Sums and Provider Type or Experience Level

	Breast	**Ovary**
	P-Value	P-Value
Ob-Gyn Provider Type		
Moderate-Risk (20%+40%)	0.23	0.21
High-Risk (60%)	0.17	1.0
Experience Level		
Moderate-Risk (5%+10%)	0.20	0.86
High-Risk (20%)	0.07*	1.0
*indicates that Chi-squared analysis was performed instead of Fischer's exact test		

Table 4 documents the relationship between provider type and different outcomes compared to a reference group (Ob-Gyn physicians). For each provider type, logistic regression was performed to determine the odds of surgical consideration (either mastectomy referral or RRSO) by breast or ovary risk level compared to Ob-Gyn physicians. Of note, Ob-Gyn physicians had about four times the odds of recommending mastectomy referral at both the 40% and 60% risk levels compared to residents/fellows ($p<0.05$). None of the odds ratios for RRSO were statistically significant.

Table 4 also indicates that Ob-Gyn physicians had about six times the odds of having used panel test results previously compared to the PA-C/CRNP/midwife category and the resident/fellow category. Ob-Gyn physicians also had four times the odds of being in regular contact with a cancer genetics professional and over six times the odds of being contacted by a lab that offers panel testing when compared to residents/fellows.

Table 4. Association Between Provider Type, Management, and Other Demographic Factors

	Gynecologic Oncologists		**PA-Cs/CRNPs/Midwives**		**Residents/Fellows**	
Mastectomy Referral by Risk Levels						
	OR	P-value	OR	P-value	OR	P-value
15%	-	-	-	-	-	-
20%	-	-	-	-	0.33	0.32
40%	0.21	0.19	0.78	0.74	**0.23**	**0.03**
60%	0.90	0.93	1.05	0.96	**0.26**	**0.04**
Undefined	2.92	0.40	1.09	0.94	0.63	0.69
RRSO by Risk Levels						
	OR	P-value	OR	P-value	OR	P-value
5%	0.85	0.89	3.18	0.13	1.70	0.41
10%	0.21	0.19	0.78	0.74	1.72	0.42
20%	-	-	-	-	1.17	0.90
Undefined	0.53	0.60	1.28	0.30	1.40	0.42
Other Demographic Questions						
	OR	P-value	OR	P-value	OR	P-value
Have you ever used results from multi-gene breast or ovarian cancer panels to guide patient management?	-	-	**0.17**	**0.03**	**0.17**	**0.01**
Are you in regular contact with a cancer genetics professional?	*	*	0.27	0.13	**0.24**	**0.05**
Have you been contacted by at least one genetic testing laboratory that offers multi-gene panel testing?	0.63	0.66	0.50	0.35	**0.16**	**0.01**

*Empty categories indicate that statistical analysis could not be performed due to lack of variance. Bolded values are statistically significant.

Finally, Table 5 shows the relationship between Ob-Gyn provider type or experience level and response to Likert scale questions regarding perceived knowledge and education level. Likert scale responses were grouped into two categories: strongly agree/agree and strongly disagree/disagree. Chi-squared or Fisher's exact tests were performed to determine the relationship between these two Likert response categories and provider type or experience level. The analysis

revealed a statistically significant association between provider type and familiarity with management guidelines. The proportion of residents/fellows indicating that they lacked familiarity with these guidelines compared to those indicating familiarity was 7.5. All gynecologic oncologists indicated that they were familiar with these guidelines. It also found statistically significant associations between genetics CEU access and ability to stay updated about genetics research based on experience level. Individuals with more experience were more likely to indicate adequate CEU access and ability to stay informed about genetics research.

Table 5. Association Between Provider Perspectives and Provider Type or Experience Level.

	Provider Type	**Experience Level**
	P-Value	P-Value
I am familiar with national management guidelines for individuals with a positive multi-gene panel result.	**0.02**	0.17*
I have been able to stay informed about new cancer genetics research.	0.06	**0.01***
I feel that I received an adequate education in cancer genetics during my professional training.	0.07	0.22
I have been provided with continuing education opportunities related to cancer genetics.	0.10	**0.03***
* indicates that Chi-squared analysis was performed instead of Fischer's exact test. Bolded values are statistically significant.		

3.4 DISCUSSION

3.4.1 Ordering Practices

While many studies have focused on analyzing Ob-Gyn use of *BRCA* testing, there is limited data about how panel testing is being used. Initial reports from 2016 estimated that 42% of non-genetics providers had previously used cancer panel testing.[87] The first goal of this study was to gather additional data regarding how often and in what ways Ob-Gyn providers are currently using cancer panel testing.

Within this study population, 61% of providers indicated that they had used panel results to guide patient management, which is a 20% increase over previous estimates.[87] Over half of these providers had experience ordering this testing themselves. However, almost three-quarters of providers who had ordered testing indicated that they did so rarely (about once per month). In contrast, more than half of providers reported referring patients for genetic counseling often (at least once per week). The respondents' *BRCA* ordering patterns were very similar to these panel ordering patterns. The study results did not reveal a clear preference for *BRCA* or panel testing. All those who did order testing themselves reported having necessary support resources to interpret positive results in genes outside of *BRCA1/2*.

Within this population of respondents, it appears that much of the cancer genetic testing responsibility is managed by genetic counselors instead of Ob-Gyns. However, trends in other geographic areas are likely different. Both healthcare systems used in this study have well-established cancer genetics programs that serve as a resource for Ob-Gyn providers. Ordering and referral trends are likely different in areas without access to cancer genetics professionals.

3.4.2 Management and Risk Assessment

Breast Cancer Management Scenario

One of the primary aims of this study was to describe trends in how Ob-Gyn providers manage patients with different cancer risk levels. The risk categories used in the breast and ovary management scenarios were designed to simulate the range of cancer risks associated with different genes on panel tests.

Some of these responses can be compared to national management guidelines to assess how closely Ob-Gyn providers followed these guidelines. For instance, the American Cancer Society (ACS) recommends that individuals with a family history of early onset breast cancer consider initiating screening 5-10 years prior to the earliest diagnosis in the family.[35] The breast cancer management scenario indicated that the theoretical patient had a family history of early onset breast cancer. Based on this statement, providers would have been correct in considering early screening initiation for this patient across all risk categories. The majority of providers (53-69%) did select this management option across all risk categories. The percent of providers selecting this option did decrease slightly for higher risk categories, possibly because more providers began to select surgical interventions instead of screening options. Overall, most providers answered according to ACS guidelines, although optimally more providers would have considered this option.

The American Cancer Society also recommends that individuals with a lifetime breast cancer risk over 20% consider breast MRI screening in addition to mammograms. [18] Breast MRIs are not generally recommended for individuals with less than a 20% lifetime risk of breast cancer, unless the individual meets another ACS high risk criteria.[35] About 22.4% of providers did

recommend breast MRI screening for the 15% risk category, which does not align with the ACS guidelines. However, the jump from 22.4% at 15% risk to almost 66% for the 20% risk category suggests that many providers are knowledgeable about the 20% risk threshold for breast MRIs.

There are not specific risk cutoffs for when prophylactic mastectomy and bilateral salpingo-oophorectomy should be considered for a patient. Often, guidelines suggest that surgical intervention can be considered if research has shown that this procedure reduces morbidity or mortality for individuals with disease-causing pathogenic variants in a particular gene.[30] Generally, studies conducted on most high-risk breast genes have found that bilateral prophylactic mastectomy is an effective risk-reducing option. [30] Individuals with moderate risk breast cancer pathogenic variants are advised to pursue increased screening measures and to undergo individualized assessment to determine whether surgery may be appropriate based on family history.[48,103] Many outside factors also play a role in determining whether prophylactic mastectomy may be warranted for a patient, including the patient's psychosocial response to the implications of surgery.

The trends in mastectomy recommendations in this study appear to align with these general practices. The recommendation percentage continued to increase from 4.5% to about 70% across increasing risk categories. The largest jump in mastectomy consideration occurred between the 20% and 40% risk categories, with a 40% increase. One half of Ob-Gyn providers indicated a preference for surgical discussion at this 40% risk level.

Based on the calculated management sums for breast and ovarian cancer scenarios and some basic assumptions listed in the Results section, all provider types excluding residents/fellows were about equally likely to indicate referral to discuss mastectomy for one or more risk categories. About 20-25% of these providers did not indicate mastectomy referral for any risk categories,

including the 60% category representing high risk genes like *BRCA*. More than half of residents/fellows did not indicate mastectomy referral for any breast risk levels. These percentages are higher than appropriate based on current NCCN management guidelines, which recommend consideration of prophylactic bilateral mastectomy for all individuals in this high-risk category. [30] Although some women chose to pursue more intensive screening instead of surgery, more of these providers should be referring patients to high-risk breast specialists or surgeons to at least initiate an informed discussion about the pros and cons of surgery for high-risk breast genes.

Ob-Gyn physicians were the most likely to recommend referral for mastectomy for the moderate risk levels followed by PA-Cs/CRNPs/midwives. About 55-60% of these provider groups indicated that they would refer a patient to discuss mastectomy if they had a 20% or 40% breast cancer risk, which corresponds to risks associated with moderate penetrance genes. About 8% of Ob-Gyns recommended this referral for the 15% risk category, for which there are no guidelines for surgical consideration. In contrast, only 25-30% of gynecologic oncologists and residents/fellows indicated referral within this moderate penetrance category.

Ob-Gyn physicians and PA-Cs/CRNPs/midwives may be more likely to initiate discussion of mastectomy with lower risk patients because they have more experience with breast cancer prevention than gynecologic oncologists and residents/fellows. Gynecologic oncologists deal primarily with gynecologic cancers and residents/fellows have a lower total amount of clinical experience. Having more experience with high-risk breast cancer patients may make Ob-Gyn physicians and PA-Cs/CRNPs/midwives more aware that breast cancer risk reduction preference often depends on factors outside of associated risk level. Therefore, they may be more willing to send patients from a wider range of risk categories to specialists to engage in a discussion about these other contributing factors. The role of clinical experience is also supported by the fact that

individuals with more than 20 years' experience are more likely to consider mastectomy referral at moderate risk levels compared to those with less than 20 years' experience.

Ovarian Cancer Management Scenario

In each interval between the 5%, 10%, and 20% ovary risk categories, provider recommendations for RRSO increased by 30%. The 5% ovarian category and 20% breast category each approximately represented a two-fold risk over general population risk. Three times as many providers recommended RRSO compared to mastectomy at these two-fold risk categories. These findings suggest that providers more readily recommend surgery to reduce ovary cancer risk compared to breast cancer risk.

Ovarian cancer screening is unreliable and ovarian cancer is often diagnosed at an advanced stage, leading to increased mortality rates.[43,46,104] Surgical removal of the ovaries and fallopian tubes is the only reliable way to reduce ovarian cancer mortality.[43,46,104] NCCN guidelines recommend consideration of RSSO for individuals carrying pathogenic variants in the *BRCA* genes, Lynch syndrome genes, and for other ovarian cancer genes like *BRIP1, RAD51C,* and *RAD51D*, which have associated lifetime risks from 5-15%.[71]. Nearly all providers indicated that they would recommend RRSO for patients at 20% lifetime ovary risk, which aligns with current practice trends.

However, gynecologic oncologists were much more likely to recommend RRSO for the moderate-risk levels (5% and/or 10% risk) compared to other providers. All gynecologic oncologists recommended RRSO for a least the 10% risk category and 20% risk categories. About 30-40% of Ob-Gyn physicians and residents/fellows and over 70% of PA-Cs/CRNPs/midwives did not recommend RRSO for either of the moderate-risk categories. This percentage is much

higher than indicated based on the NCCN recommendations for RRSO for all individuals carrying pathogenic variants in genes falling within this moderate-risk range.

One reason that Ob-Gyn physicians, residents/fellows, and PA-Cs/CRNPs/midwives did not sufficiently recommend RRSO for moderate risk scenarios may be that this surgical decision making falls outside of their scope of practice. These providers, especially PA-Cs/CRNPs/midwives, may typically refer patients to gynecologic oncologists to make these surgical decisions.[30] However, a remaining concern is that these providers are not aware that they should recommend RRSO for these moderate risk levels based on NCCN guidelines.[30] Knowledge of these guidelines is important for all of these providers to ensure that they are either appropriately referring patients to surgical specialists or to be able to make appropriate surgical decisions themselves. Prior literature suggests that some non-genetics providers do not always follow these guidelines, as in the 2011 survey of non-genetics professionals which found that only 76% of Ob-Gyn providers recommended RRSO consideration for *BRCA* positive patients.[3,4]

Trends in RRSO recommendations did not vary much across different experience levels. However, about 10% of providers with over 20 years' experience and 6% of providers with less than 5 years' experience did not recommend RRSO at any risk level. This trend suggests that a proportion of these providers lacks knowledge about high-risk ovarian cancer management guidelines.

Although some variability in surgical recommendations between different providers may be expected, these larger trends based on job role and experience levels are concerning and suggest that a patient may receive different care based on factors other than their individualized risk assessment. Some of these differences may be due to differing knowledge of management guidelines. For genes without strict management guidelines, recommendations may vary by a

provider's ability to stay updated about new genetics research. Additional studies examining why these differences occur between these groups of providers would be a helpful first step in attempting to provide more consistent care to patients receiving cancer genetic testing.

Risk Assessment

Risk assessment questions were used to identify trends in how providers interpret specific test results. One scenario involved a patient with a strong family history of breast cancer and a negative panel test. Individuals within this familial category have been shown to be at increased risk despite negative genetic testing.[8] A 2016 study posed this same question for negative *BRCA* testing, with about 20% of providers answering incorrectly. [87] In this study, about 10% of providers answered incorrectly. It is reassuring that the strong majority of providers answered this question correctly. However, even the small percentage of providers answering incorrectly could have a negative clinical impact in real-world practice because high risk patients would not be receiving the appropriate surveillance.

The final two questions were scenarios in which a patient tested negative for a known pathogenic variant in a family member. In one case, the pathogenic variant was in a *BRCA* gene while the other was in a moderate risk breast gene. For the *BRCA* gene, current protocol would be to consider the patient to be at average risk, since she does not carry this large risk factor. For moderate risk genes current data suggests that other risk factors are often involved in determining cancer risk within a family. An individual testing negative for a moderate risk familial pathogenic variant should still be considered to be at elevated risk. About 80% of providers answered the *BRCA* question correctly, while 70% answered the moderate risk question incorrectly.[54] The

difference in accuracy between the *BRCA* and moderate-penetrance gene risk assessment scenarios suggests that providers may have difficulty staying informed about new genetics research.

3.4.3 Provider Perspectives

Many of the results regarding provider perspectives on panel testing mirrored those from previous *BRCA* studies. In prior studies, non-genetics providers reported feeling unqualified providing pre-test counseling and interpreting positive and VUS test results. A 2010 study of Ob-Gyn providers found that 28% felt completely unqualified performing pre-test *BRCA* counseling, and another 64% felt only partially qualified.[81] Other studies found that 60% of Ob-Gyn physicians reported discomfort interpreting VUS results and around 90% of providers felt unqualified or only partially qualified managing *BRCA* positive individuals.[5,81] This study found similar results. Only 30% of providers felt that they could adequately perform pre-test counseling for panel testing. Further, only 20-30% of providers indicated that they felt comfortable interpreting positive and VUS panel results.

In this study, about 70% of providers indicated that they were comfortable managing negative panel test results. However, the majority of providers were not able to accurately answer the risk assessment question for an individual who tested negative for a known familial pathogenic variant in a moderate penetrance gene. This suggests that providers may not recognize some of the knowledge deficits that they have. This lack of recognition introduces an additional complication to addressing this knowledge deficit.

Less than half of providers reported having adequate genetics education during their professional training. This sentiment mirrors that from a 2010 *BRCA* study, which found that 76%

of Ob-Gyn providers would value improvements in their genetics education. [98] Also, less than half of providers reported familiarity with national management guidelines for positive results and an ability to stay updated about genetics research. Familiarity with national management guidelines was significantly associated with provider type. In contrast to other providers, most gynecologic oncologists reported having adequate genetics education in professional school, being familiar with management guidelines, and being able to keep updated about genetics research.

Gynecologic oncologists may be expected to have better knowledge of ovary-based genetics management guidelines because they have more extensive clinical and training experience related to ovarian cancer prevention and treatment. Current guidelines indicate that all patients diagnosed with epithelial ovarian cancer should pursue cancer genetic testing for the *BRCA* genes.[29,45] This is in part due to the availability of targeted medications (PARP inhibitors) for BRCA-related ovarian cancers.[105] Therefore, a gynecologic oncologist's management of an individual with ovarian cancer often involves the use of genetic testing. Unaffected patients found to carry an ovarian-cancer related pathogenic variant are also often referred to gynecologic oncologists. [30] However, other Ob-Gyn providers are highly involved in breast cancer prevention, identifying patients to refer to gynecologic oncologists, and occasionally making preventative ovarian cancer surgical decisions themselves. Therefore, it is important that these providers are knowledgeable about new genetics research and the most updated breast and ovarian genetics management guidelines.

In accordance with previous studies, this study suggests that clinical experience plays an important role in the appropriateness of breast cancer management decisions.[3] Although this clinical expertise can only be achieved over time, formal changes to genetics training programs can be modified to try to improve cancer genetics knowledge and management decision-making.

The training programs for gynecologic oncologists may serve as models for effective cancer genetics education.

3.4.4 Study Limitations

Although this study provided some new information about how Ob-Gyn providers use panel testing, several limitations can be noted. One limitation of this study is that it is unlikely to represent cancer genetic testing culture across the United States. Both major healthcare systems in this Western Pennsylvania region have practicing cancer genetics professionals who offer services close to Pittsburgh and in outreach clinics in more rural communities. These professionals serve as formal and informal resources to their colleagues through attendance at tumor boards, continuing education lectures, and the distribution of detailed consultation notes. Many other geographic areas in the United States are likely to have different ordering/referral patterns because they have lesser access and exposure to cancer genetic counselors. The study responses were also likely influenced by selection bias. Providers with a stronger interest in or more experience with cancer genetic testing may have been more likely to respond. Further, the sample size was small and lacked diversity. The respondent population was dominated by Ob-Gyn physicians, particularly newly practicing physicians, and was lacking in gynecologic oncologists and providers practicing in rural environments.

Further, this study used various breast and ovarian risk levels to estimate provider management of different categories of breast and ovarian cancer genes. In reality, genetic management decisions depend on many factors outside of the absolute risk associated with a

particular gene. Some of these additional factors include the clinical utility of different interventions and an individual's assessment of the pros and cons of a given intervention.

The data regarding RRSO recommendation may not have been an accurate representation of differences in knowledge of management guidelines by provider type. This question is complicated by the fact that providers outside of gynecologic oncologists often do not make surgical decisions for RRSO on their own. In future studies, this question could be clarified by asking providers more directly about their knowledge level instead of their clinical recommendations.

This study was also limited in that it was primarily descriptive in nature. It identified trends in management, risk assessment, and perceptions based on provider type and experience level. However, this study did not examine reasons for the underlying causes of these trends. Additional studies would be needed to investigate these reasons.

3.4.5 Future Directions

One area of future research is to conduct similar studies regarding Ob-Gyn use of panel testing on a larger scale and over a broader geographic area. This would provide a more representative and less biased view of current ordering and referral practices, management decisions, educational experiences, and other trends identified in this study.

Another area for future research could be focused on understanding more about the differences in management trends based on provider type and experience level. For instance, studies could investigate the reasons why providers with more clinical experience tend to refer patients to discuss mastectomy at lower risk levels and why most provider types are missing

appropriate opportunities for RRSO recommendations. After these trends are understood more clearly, efforts could be focused on informing providers about these differences and developing more consistent practices across provider types.

The need to provide further education on moderate risk genes will grow as panels continue to be used more frequently. Although most providers indicated comfort interpreting negative test results, this study found some inaccuracies in negative interpretation for moderate risk genes. Future research is needed to validate these results in a larger population and to investigate effective interventions for improving awareness of these knowledge deficits.

Additional studies are needed to learn more about how Ob-Gyn providers currently learn about cancer genetics and how current methods may be improved upon. Further insight into training programs and CEU credits offered to gynecologic oncologists may be helpful in learning more about effective genetic education strategies for all providers.

3.5 CONCLUSION

This study serves as one of the initial efforts in classifying how Ob-Gyn providers are using and interpreting results from multi-gene breast and ovarian cancer panels. Prior studies of non-genetics provider use of *BRCA* testing identified several areas for improvement related to ordering practices, counseling skills, and results interpretation. While many of these initial concerns with *BRCA* testing remain unresolved, multi-gene cancer panels have gained popularity and further complicate these issues. One of the primary aims of this study was to learn more about how often Ob-Gyn providers use breast and ovarian cancer panel testing. About 61% of surveyed providers had used panels to help manage patients, highlighting the growing popularity of this testing. However, this rate is likely higher compared to other geographic areas due to local access to genetics professionals.

Another major aim was to document how these providers would manage patients at varying cancer risk levels meant to simulate risks associated with different panel genes. Overall, most providers seemed to follow current management trends. However, some providers are missing appropriate management recommendations. For instance, about one third of providers failed to recommend breast MRI at the 20% breast cancer risk level. Further, the majority of providers incorrectly indicated that an individual testing negative for a known familial pathogenic variant in a moderate risk gene would be at average cancer risk. These deviations in practice suggest that a significant proportion of providers lack knowledge of these management and risk assessment trends and reinforce the need for improvements in genetics education.

Further, surgical recommendations varied significantly by provider type. Ob-Gyn physicians and providers with more than 20 years' experience were more likely than other provider

types to refer patients with moderate breast cancer risk to discuss mastectomy. About 30-70% of different providers outside of gynecologic oncologists failed to recommend RRSO at the 5% and 10% risk categories although NCCN recommends this intervention for genes associated with similar levels of risk. Further studies investigating why these trends occur may lead to more consistent, evidence-based practices.

This study also found that most providers are not comfortable interpreting positive and VUS panel results or obtaining informed consent for panel testing. Similar to prior *BRCA* studies, this study found that most providers excluding gynecologic oncologists do not feel that they received adequate genetics training. Additional studies investigating ways to improve and maintain cancer genetics knowledge may be warranted.

4.0 PUBLIC HEALTH AND GENETIC COUNSELING SIGNIFICANCE

Understanding how Ob-Gyn providers are implementing breast and ovarian panel testing into their practice is the first step in recognizing and repairing any clinical problems with this testing. New genetic technologies are being rapidly developed and introduced to the clinical setting, and non-genetics providers are not often trained on how to accurately use these tests to benefit patient care. Addressing this issue could have an immense public health impact. The combination of increasingly complex genetic test results and the systematic deficits in provider genetics education and training opportunities across institutions has the potential to create widespread negative health outcomes.

One of the core functions of public health is assessment, which involves the service of "monitor(ing) environmental and health status to identify and solve community environmental health problems."[106] In the context of this survey, the community of Ob-Gyn providers are being surveilled to identify problems with cancer panel testing implementation or interpretation that may negatively impact patient health outcomes. For instance, if patients are not counseled about the increased possibility to receive a VUS result on panel testing, they may choose to pursue this testing without being provided the opportunity to consider how the uncertainty of this result may impact them psychologically. Only about one third of providers in this study indicated that they felt adequately able to obtain informed consent for panel testing. This raises concerns that patients might not be receiving adequate informed consent if these providers are ordering panel testing.

Another area of concern with non-genetic use of cancer panel testing is results interpretation. Inaccurate interpretation of cancer panel tests could cause patients to receive

suboptimal cancer screening. One example demonstrated in this survey involves inaccurate assessment of a negative panel test result. Most providers incorrectly indicated that an individual testing negative for a familial pathogenic variant in a moderate risk breast cancer gene would be at average instead of increased breast cancer risk. If this interpretation was made in a real clinical setting, it could result in this patient missing the opportunity to pursue increased breast cancer surveillance. Theoretically, if an individual is not enrolled in a screening plan proportionate to their level of risk, it could increase the chance that a cancer diagnosis is missed or caught at a later stage.

An additional service involved in the assessment function of public health is "diagnos(ing) and investigating environmental health problems and health hazards in the community."[106] This study as well as previous surveys on provider use of *BRCA* testing help to fulfill this function of public health. In this study, trends between different management choices and demographic factors like provider type were examined. For instance, Ob-Gyn providers and those with more than 20 years' experience were more likely to recommend mastectomy across more risk categories compared to other providers. The identification of these trends can be used to initiate investigations into their causes in future studies. Understanding the reasons for these differences in practice type can be used to initiate conversations between providers regarding their unique clinical experiences. These conversations can be used to identify any areas of need, such as improvements in provider genetics education. It can also be used to establish consistent management practices and policies incorporating input from a board range of providers. The development of policies to ensure consistent and evidence-based care is another major function of public health practice. [106]

As more is understood about these management concerns, genetic counselors and other genetics professionals will likely become integral players in addressing this issue. This and other

preliminary studies repeatedly suggest that non-genetics providers are looking for ways to improve their professional training in genetics and to stay updated with new research. This creates the opportunity for cancer genetic counselors to expand their role as professional researchers and educators. Further, it calls upon cancer genetics professionals to extend their services to areas currently lacking in cancer genetics resources. One way that cancer genetics professionals have tried to extend their services is through phone or video-chat counseling for communities that cannot be accessed in person.[107] Learning more about gaps in non-genetic provider knowledge and developing new ways to help improve their education and access to genetics resources lies firmly within the genetic counselor's primary duty to ensure optimal clinical translation of new genetics technology for the benefit of the patient.

APPENDIX A: IRB APPOVAL

AHN Research Institute
320 East North Avenue
Pittsburgh, PA 15212-4722

Certification of Exemption

April 11, 2018

Jaclyn Amurgis
Department of Cancer Genetics

RE: **2018-092 "Exploring Ob/Gyn Providers' Experience with and Knowledge of Multi-Gene Panels for Hereditary Breast and Ovarian Cancer"**

Dear Ms. Amurgis:

The Institutional Review Board (IRB) of Allegheny General Hospital is in receipt of the above-referenced protocol.

The IRB has reviewed this information and finds it qualifies for exempt status according to the following category in the Code of Regulations: 45 CFR 46.101 (b) Category (Exempt Category 2).

Please retain this letter as evidence of IRB review and determination of exempt status for this research.

Annual review of this research is not required provided the research is conducted as proposed. If there are modifications or changes to this study, the Investigator must have the IRB review the study prior to initiating the changes.

If you have any questions, please contact the IRB office.

Sincerely,

Signed Wednesday, April 11, 2018 9:48:45 AM ET by Colonias, Athanasios MD

Athanasios Colonias, MD
Vice-Chairman
Institutional Review Board

Pitt Seal

University of Pittsburgh
Institutional Review Board

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

Memorandum

To: Jaclyn Amurgis
From: IRB Office
Date: 11/10/2017
IRB#: PRO17080582
Subject: Exploring Ob/Gyn Providers' Experience with and Knowledge of Multi-Gene Panels for Hereditary Breast and Ovarian Cancer

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

45 CFR 46.101(b)(2)

Please note the following information:

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

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

APPENDIX B: INFORMED CONSENT STATEMENT

Consent for survey participation:

The following survey is a research study that will be used to assess the current role of local Ob-Gyns in the ordering and interpretation of multi-gene panels for breast and/or ovarian cancer.

The survey will be conducted through the Qualtrics survey system. Data collection will proceed for 3 weeks, with weekly reminders to those who have not yet completed the survey. There will be no direct benefits to the study participants, but the study has the potential to provide information that could inform future practice. IP and email addresses will be securely collected through the system to track completion status.

The risks include the possibility of a confidentiality breach involving the collected IP and email addresses in association with survey responses. Use of the Qualtrics system helps to minimize this risk, as the system has been approved by the University of Pittsburgh for secure collection and storage of survey information. Further, the survey primarily involves responses to theoretical scenarios and opinion-based questions and is therefore unlikely to contain sensitive information. The raw data will only be accessed by the PI. Several AHN study personnel and University of Pittsburgh staff members will have immediate access to final data analysis. Final data analysis and any published works will not involve any of these personal identifying factors and analyses will not be segregated by health system.

Participation is voluntary and there will be no penalties for non-completion. Participants will be able to withdraw their responses until the end of the study collection period by contacting the PI. **Initiation of the survey will be used as proof of consent to the above statements.**

If you have any additional questions or concerns, the study PI Jaclyn Amurgis can be reached at Jaclyn.Amurgis@ahn.org or at 412-359-8267. This research has been reviewed and approved by the AHN and University of Pittsburgh Institutional Review Boards. You may talk to them by calling this toll free number, 1-844-577-4621 for questions, concerns, or complaints regarding this study.

APPENDIX C: RECRUITMENT EMAILS

Hello, my name is Jaclyn Amurgis and I am a current student pursing my Master's degree in genetic counseling at the University of Pittsburgh. I have been working to create a survey to assess the current role of local Ob-Gyns in the ordering and interpretation of multi-gene panels for breast and/or ovarian cancer. For years, Ob-Gyn providers have been highly involved in the ordering of BRCA1/2 testing for patients with a personal or family history of breast/ovarian cancer. More recently, multi-gene cancer panels have become available and allow providers to look for pathogenic variants in breast or ovarian genes in addition to BRCA. Cancer panels are useful because they examine many genes simultaneously, but interpreting panel test results is complicated by the fact that each gene is associated with different types of cancer and lifetime risk levels.

Few studies have been conducted examining if and how Ob-Gyn providers have transitioned from ordering *BRCA* testing alone to these larger multi gene panels. **This survey serves to gain more information about how often breast/ovary cancer panel testing is being ordered by local Ob-Gyn providers, trends in how gene risk level affects management, and provider perspectives on their involvement with this newer type of genetic testing.**

The survey is a research study that will be conducted through the Qualtrics survey system via the link provided below. Data collection will proceed for 3-4 weeks, with weekly reminders to those who have not yet completed the survey. **Eligible participants include any providers within the Ob-Gyn field who have in the past or may in the future use multi-gene cancer panel testing to inform patient care. The survey is estimated to take 5 minutes to complete.**

This research has been reviewed and approved the University of Pittsburgh Institutional Review Board. If you have any additional questions or concerns, the study PI Jaclyn Amurgis can be reached at jka16@pitt.edu. The University IRB may be reached at 412-383-1480 with any concerns.

Hello, my name is Jaclyn Amurgis and I am a current AHN employee and student pursing my Master's degree in genetic counseling. Dr. Gaulin and I have been working to create a survey to assess the current role of local Ob-Gyns in the ordering and interpretation of multi-gene panels for breast and/or ovarian cancer. For years, Ob-Gyn providers have been highly involved in the ordering of BRCA1/2 testing for patients with a personal or family history of breast/ovarian cancer. More recently, multi-gene cancer panels have become available and allow providers to look for pathogenic variants in breast or ovarian genes in addition to BRCA. Cancer panels are useful because they examine many genes simultaneously, but interpreting panel test results is complicated by the fact that each gene is associated with different types of cancer and lifetime risk levels.

Few studies have been conducted examining if and how Ob-Gyn providers have transitioned from ordering *BRCA* testing alone to these larger multi gene panels. **This survey serves to gain more information about how often breast/ovary cancer panel testing is being ordered by local Ob-Gyn providers, trends in how gene risk level affects management, and provider perspectives on their involvement with this newer type of genetic testing.**

The survey is a research study that will be conducted through the Qualtrics survey system via the link provided below. Data collection will proceed for 3-4 weeks, with weekly reminders to those who have not yet completed the survey. **Eligible participants include any providers within the Ob-Gyn field who have in the past or may in the future use multi-gene cancer panel testing to inform patient care. The survey is estimated to take 5 minutes to complete.**

This research has been reviewed and approved by AHN and University of Pittsburgh Institutional Review Boards. If you have any additional questions or concerns, the study PI Jaclyn Amurgis can be reached at Jaclyn.Amurgis@ahn.org or at 412-359-8267. You may talk to them by calling this toll free number, 1-844-577-4621 for questions, concerns, or complaints regarding this study.

APPENDIX D: SURVEY CONTENT

Multi-gene cancer panels can be used to analyze a group of genes in addition to *BRCA1/2* that are associated with an increased risk of breast and/or ovarian cancer.
Genetic panel testing can have three possible results:

-**Positive**: A disease-causing pathogenic variant was identified in a gene
-**Negative**: No pathogenic variants were identified in any of the examined gene
-**Variant of uncertain significance or VUS**: A variant was identified, but the laboratory needs to gather more data on the variant to determine whether it is benign or harmful.

Have you ever used results from multi-gene breast or ovarian cancer panels to guide patient medical management?

O Yes

O No

How often do **you order** testing of the *BRCA* genes **alone**?

O Frequently (several times per week)

O Often (several times per month)

O Sometimes (about once per month)

O Rarely (a few times per year)

O Never

How often do **you order** multi-gene panel testing, including genes in addition to *BRCA1/2*?

- O Frequently (several times per week)
- O Often (several times per month)
- O Sometimes (about once per month)
- O Rarely (a few times per year)
- O Never

Have any of the multi-gene panels come back with a **positive result**, indicating that a pathogenic variant was identified **in a gene other than *BRCA1/2***?

- O Yes
- O No

Did you feel that you had adequate resources available to aid you in interpreting the positive result(s)?

- O Yes
- O No

Have you ever referred patients for cancer genetic counseling?

- O Yes
- O No

How often do you refer patients to genetic counselors to **order** cancer genetic testing?

- O Frequently (several times per week)
- O Often (several times per month)
- O Occasionally (about once per month)
- O Rarely (a few times per year)
- O Never

How often do you refer patients to genetic counselors for **post-test counseling** only?

- O Frequently (several times per week)
- O Often (several times per month)
- O Occasionally (about once per month)
- O Rarely (a few times per year)
- O Never

The genes on panels can confer different lifetime cancer risks. Some genes are similar to the *BRCA* genes and cause a high lifetime risk of breast and/or ovarian cancer. Other genes increase breast or ovarian cancer risk to a smaller, or "**moderate**" degree or have **undefined** risk levels.

The following theoretical scenarios aim to gather consensus about how varying risk level may impact screening/management recommendations.

A patient with a strong family history of early onset (<50 years) breast cancer is found to carry a pathogenic variant in a hereditary breast cancer gene other than *BRCA1/2*. **In each scenario, the gene is associated with a different level of lifetime breast cancer risk. Which screening or management recommendation(s) would you consider in the following situations?** Average lifetime breast cancer risk for women is 12.5%.

	Initiating screening younger	Adding more sensitive screening (breast MRI)	Referral to a high risk breast clinic	Consideration of risk-reducing medications	Referral to discuss prophylactic bilateral mastectomy
15% lifetime risk	☐	☐	☐	☐	☐
20% lifetime risk	☐	☐	☐	☐	☐
40% lifetime risk	☐	☐	☐	☐	☐
60% lifetime risk	☐	☐	☐	☐	☐
Increased, but undefined level of risk	☐	☐	☐	☐	☐

A patient is found to carry a pathogenic variant in a hereditary ovarian cancer gene other than *BRCA1/2*. In each scenario, the gene is associated with a different level of lifetime ovarian cancer risk. **Which screening or management recommendation(s) would you consider in the following situations?** Average lifetime ovarian cancer risk is 1-2%.

	Regular Ca-125 levels	Regular transvaginal US	Consideration of risk-reducing BSO
5% risk	☐	☐	☐
10% risk	☐	☐	☐
20% risk	☐	☐	☐
Increased, but undefined level of risk	☐	☐	☐

For the each of the following clinical situations, would you consider the patient to be at average or increased lifetime breast cancer risk?

A patient with a variant of uncertain significance identified on a multi-gene breast panel	Average risk/Increased risk
A patient with a strong family history of breast cancer and a negative multi-gene breast panel	Average risk/Increased risk
A patient who tests negative for a known BRCA pathogenic variant in a family member	Average risk/Increased risk
A patient who tests negative for a family pathogenic variant in a "moderate risk" breast gene	Average risk/Increased risk

Choose to what degree you agree or disagree with the following statements.
For patients with a strong family history of breast or ovarian cancer, Ob-Gyns should be the primary providers responsible for initiating genetic testing efforts.

- O Strongly agree
- O Somewhat agree
- O Neither agree nor disagree
- O Somewhat disagree
- O Strongly disagree

Identifying patients who might benefit from cancer genetic testing is a priority in my practice.

- O Strongly agree
- O Somewhat agree
- O Neither agree nor disagree
- O Somewhat disagree
- O Strongly disagree

I am more likely to order cancer genetic testing since the introduction of multi-gene panels.

- O Strongly agree
- O Somewhat agree
- O Neither agree nor disagree
- O Somewhat disagree
- O Strongly disagree

I feel that I am able to adequately obtain informed consent for multi-gene panel testing.

- O Strongly agree
- O Somewhat agree
- O Neither agree nor disagree
- O Somewhat disagree
- O Strongly disagree
- O N/A

I would feel comfortable interpreting a positive multi-gene panel test result in a gene outside of *BRCA1/2*.

- O Strongly agree
- O Somewhat agree
- O Neither agree nor disagree
- O Somewhat disagree
- O Strongly disagree

I would feel comfortable managing a patient with a variant of uncertain significance identified on a multi-gene panel.

- O Strongly agree
- O Somewhat agree
- O Neither agree nor disagree
- O Somewhat disagree
- O Strongly disagree

I would feel comfortable managing a patient with a negative multi-gene panel result.

- O Strongly agree
- O Somewhat agree
- O *N*either agree nor disagree
- O Somewhat disagree
- O Strongly disagree

I have found that it is easy to refer patients to cancer genetics professionals.

- O Strongly agree
- O Somewhat agree
- O Neither agree nor disagree
- O Somewhat disagree
- O Strongly disagree
- O N/A

I am familiar with national management guidelines for individuals with a positive multi-gene panel result.

- O Strongly agree
- O Somewhat agree
- O Neither agree nor disagree
- O Somewhat disagree
- O Strongly disagree

I feel that I received an adequate education in cancer genetics during my professional training.

- O Strongly agree
- O Somewhat agree
- O Neither agree nor disagree
- O Somewhat disagree
- O Strongly disagree

I have been provided with continuing education opportunities related to cancer genetics.

- O Strongly agree
- O Somewhat agree
- O Neither agree nor disagree
- O Somewhat disagree
- O Strongly disagree

I have been able to stay informed about new cancer genetics research.

- O Strongly agree
- O Somewhat agree
- O Neither agree nor disagree
- O Somewhat disagree
- O Strongly disagree

I attend a regular multi-disciplinary tumor board meeting that includes a genetics professional.

- O Strongly agree
- O Somewhat agree
- O Neither agree nor disagree
- O Somewhat disagree
- O Strongly disagree

Please complete the following demographic questions.

What is your current professional role at your institution?

- O Ob-Gyn
- O Gynecologic oncologist
- O PA-C
- O CRNP
- O Resident
- O Fellow
- O Other

How many years have you been practicing independently?

- O I am still in training
- O Less than 5 years
- O 5- 10 years
- O 11-20 years
- O 21-30 years
- O Over 30 years

What type of community do you practice within? (Can select multiple responses)

- ☐ Urban
- ☐ Suburban
- ☐ Rural

Are you in regular contact with a cancer genetics professional?

- O Yes
- O No

Have you been contacted by at least one genetic testing laboratory that offers multi-gene panel testing?

- O Yes
- O No

APPENDIX E: SUPPLEMENTAL DATA

Table 6. Supplemental Demographic Information

What type of community do you practices within?	N=67
Urban	47 (54.0%)
Suburban	32 (36.8%)
Rural	8 (9.2%)
Are you in regular contact with a cancer genetics professional?	N=67
Yes	29 (43.3%)
No	38 (56.7%)
Have you been contacted by at least one genetic testing laboratory that offers multi-gene panel testing?	N=67
Yes	33 (49.3%)
No	34 (50.8%)

Table 7. Provider Perspectives on Cancer Genetic Testing

	Strongly Agree	Somewhat Agree	Neither agree nor disagree	Somewhat Disagree	Strongly disagree	N/A
For patients with a strong family history of breast or ovarian cancer, Ob-Gyns should be the primary providers responsible for initiating genetic testing efforts.	23 (34.3%)	23 (34.3%)	10 (14.9%)	6 (9.0%)	5 (7.5%)	
Identifying patients who might benefit from cancer genetic testing is a priority in my practice.	38 (56.7%)	19 (28.4%)	7 (10.5%)	2 (4.5%)	0 (0%)	
I am more likely to order cancer genetic testing since the introduction of multi-gene panels.	5 (7.5%)	12 (17.9%)	32 (47.8%)	8 (11.9%)	10 (14.9%)	
I feel that I am able to adequately obtain informed consent for multi-gene panel testing.	6 (9.0%)	16 (23.9%)	12 (17.9%)	14 (20.9%)	18 (26.9%)	1 (1.5%)
I have found that it is easy to refer patients to cancer genetics professionals.	43 (64.2%)	10 (14.9%)	4 (6.0%)	5 (7.5%)	1 (1.5%)	4 (6.0%)
I am familiar with national management guidelines for individuals with a positive multi-gene panel result.	6 (9.0%)	22 (32.8%)	11 (16.4%)	15 (22.4%)	13 (19.4%)	
I feel that I received an adequate education in cancer genetics during my professional training.	0 (0.0%)	20 (29.9%)	13 (19.4%)	25 (37.3%)	9 (13.4%)	
I have been provided with continuing education opportunities related to cancer genetics.	5 (7.5%)	25 (37.3%)	20 (29.9%)	15 (22.4%)	2 (3.0%)	
I have been able to stay informed about new cancer genetics research.	1 (1.5%)	28 (41.8%)	11 (16.4%)	21 (31.3%)	6 (9.0%)	
I attend a regular multi-disciplinary tumor board meeting that includes a genetics professional.	7 (10.5%)	8 (11.9%)	8 (11.9%)	11 (16.4%)	33 (49.3%)	

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