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Knowledge, Attitudes, and Utilization of BRCA Testing Among Obstetricians and Gynecologists

Salma Nassef

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KNOWLEDGE, ATTITUDES, AND UTILIZATION OF BRCA TESTING AMONG
OBSTETRICIANS AND GYNECOLOGISTS

by

Salma A. Nassef, BS

APPROVED:

Cathy M. Sullivan, MS, CGC
Supervisory Professor

Kate L. Wilson, MS, CGC

Karen M. Schneider, MD
PhD

Syed Shahrukh Hashmi, MD, MPH,

Karen Lu, MD

Manju Monga, MD

Jon Gogola, MD
Ad Hoc Member

APPROVED:

Dean, The University of Texas
Health Science Center at Houston
Graduate School of Biomedical Sciences

KNOWLEDGE, ATTITUDES, AND UTILIZATION OF BRCA TESTING AMONG
OBSTETRICIANS AND GYNECOLOGISTS

A THESIS

Presented to the Faculty of
The University of Texas Health Science Center at Houston and
The University of Texas M.D. Anderson Cancer Center
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in Partial Fulfillment of the Requirements

For the Degree of

MASTER OF SCIENCE

by

Salma A. Nassef, BS

Houston, Texas

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KNOWLEDGE, ATTITUDES, AND UTILIZATION OF BRCA TESTING AMONG OBSTETRICIANS AND GYNECOLOGISTS

Publication No. _____

Salma A. Nassef, BS

Supervisory Professor: Cathy Sullivan, MS, CGC

Hereditary breast and ovarian cancer (HBOC) is an inherited cancer syndrome that is associated with mutations in the *BRCA1* and *BRCA2* genes. Carriers of *BRCA* mutations, both men and women, are at an increased risk for developing certain cancers. Carriers are most notably at an increased risk to develop breast and ovarian cancers; however an increased risk for prostate cancer, melanoma, and pancreatic cancers has also been associated with these mutations. In 2009 the American Congress of Obstetricians and Gynecologists (ACOG) released a practice bulletin stating that evaluating a patient's risk for HBOC should be a routine part of obstetric and gynecologic practice.

A survey was created and completed by 83 obstetricians and gynecologists in the greater Houston, TX area. The survey consisted of four sections designed to capture demographic information, attitudes towards HBOC and *BRCA* testing, utilization of *BRCA* testing, and the overall knowledge of respondents with regards to HBOC and *BRCA* testing. This study found that the majority of participants indicated that they felt that obstetricians and gynecologists should have the primary responsibility of identifying patients who may be at increased risk of carrying a *BRCA* mutation. Moreover, this study found that the majority of participants indicated that they felt comfortable or very comfortable in identifying patients at an increased risk of carrying a *BRCA* mutation. However, only about a quarter of participants indicated that they order *BRCA* genetic testing one to two times per month or more. Lastly, this study demonstrates that the overall knowledge of HBOC and *BRCA* testing among this population of obstetricians and gynecologists is poor.

The results of this study stress the need for more education regarding HBOC, genetic testing, and strategies for identifying patients that may be at risk for having a mutation in a *BRCA* gene. Furthermore, it reiterates the importance of raising awareness to current practice guidelines and recommendations that can assist obstetricians and gynecologist to better identify and manage patients that may be at an increased risk of having HBOC.

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BACKGROUND

Introduction

Hereditary breast and ovarian cancer (HBOC) is an inherited cancer syndrome that is associated with mutations in the *BRCA1* and *BRCA2* genes [1,2]. Mutations in either *BRCA1* or *BRCA2* are inherited in an autosomal dominant manner, and these mutations cause carriers, both men and women, to be at an increased risk for developing certain cancers. Carriers are most notably at an increased risk to develop breast and ovarian cancers; however an increased risk for prostate cancer, melanoma, and pancreatic cancers have also been associated with these mutations [3,4].

Prevalence

Originally, it was estimated that 1/5000-1/10000 individuals in the general population carried a mutation in either the *BRCA1* or *BRCA2* gene [5]. However, with recent advancements in research and testing, the accepted prevalence of *BRCA* mutation carriers is now thought to be between 1/400 and 1/800 individuals in the general population [6,7]. This number becomes even more significant in select populations, such as Ashkenazi Jewish individuals, where founder mutations in *BRCA1* and *BRCA2* have been identified. Three specific mutations have been identified in the Ashkenazi Jewish population and include the 185delAG and

5382insC mutations in the *BRCA1* gene and the 6174delT mutation in the *BRCA2* gene [8]. The prevalence of a *BRCA* mutation in the Ashkenazi Jewish population is 1/40 [9]. Other specific founder mutations have been described in individuals from Iceland, Norway, Finland, Sweden, France, the Netherlands, Italy, Mexico, and Pakistan [10].

BRCA1

The *BRCA1* gene, located on chromosome 17q21, was first mapped in 1990 [11,12]. The *BRCA1* gene consists of 22 coding exons, spanning 80 kb of DNA [13]. Since that time it was thought to have many regulatory functions within the cell. One such function of the *BRCA1* gene is to act as a negative regulator of tumor growth or as a tumor suppressor gene [1]. Moreover, the *BRCA1* gene is thought to play a part in the repair and regulation of cell-cycle checkpoints in response to DNA lesions with indications of damage [14]. The exact molecular mechanisms and role of the *BRCA1* gene are still under investigation today. To date, there have been more than 1600 mutations identified in the *BRCA1* gene, the majority of which are frameshift mutations resulting in non-functional protein products [15].

BRCA2

The *BRCA2* gene, located on chromosome 13q12-q13, was identified shortly after the *BRCA1* gene in 1994 [2]. This gene consists of 26 coding exons and spans 70

kb of DNA [13]. Like *BRCA1*, the *BRCA2* gene is a tumor suppressor gene and its primary role is to maintain genomic integrity in DNA. Studies have indicated that cells with a non-functional *BRCA2* gene have been shown to be hypersensitive to ionizing radiation resulting in permanent DNA damage [16,17]. To date, there have been approximately 1800 mutations identified in the *BRCA2* gene, which include frameshift deletions, insertions, and nonsense mutations [15]. As both *BRCA* genes act as tumor suppressor genes, individuals identified with a mutation in either their *BRCA1* or *BRCA2* gene are at an increased risk to develop breast, ovarian, and other associated cancers.

Breast and Ovarian Cancer Risk

In the general population, a woman has an approximate 12% risk of developing breast cancer and a 1.4% risk of developing ovarian cancer during her lifetime [18]. These risk estimates greatly increase if a mutation in either the *BRCA1* or *BRCA2* genes is identified. Hereditary forms of both breast and ovarian cancer make up about 5-10% of all breast and ovarian cancers seen in the population [19]. Both the *BRCA1* and *BRCA2* genes have variable penetrance. That is to say, a mutation in *BRCA1* or *BRCA2* will significantly increase the likelihood to developing breast and ovarian cancer; however, all carriers do not develop cancer during their lifetime. Differences in penetrance can be seen between individuals

with *BRCA1* or *BRCA2* mutations and even between family members who carry the same identified mutation [20,21]. While generally referenced as a pair, both the *BRCA1* and *BRCA2* genes carry their own risk estimates with regards to developing breast and ovarian cancer. Several studies have examined the risk for developing breast and ovarian cancer in both the *BRCA1* and *BRCA2* genes individually. In 2003, a meta-analysis of 22 studies looking at over 8,000 index cases found that individuals that carried a *BRCA1* mutation had a 65% risk of developing breast cancer and a 39% risk of developing ovarian cancer by the age of 70 [22]. Analysis of this same study population also indicated that individuals that carried a *BRCA2* mutation had a 45% risk of developing breast cancer and an 11% risk of developing ovarian cancer before the age of seventy [22]. Following this analysis, in 2006, a separate group again tried to quantify the breast and ovarian cancer risks associated with *BRCA1* and *BRCA2* through population based studies. The first study looked at risks before the age of 80 years and found that individuals that carried a *BRCA1* mutation had a 90% risk of developing breast cancer and 24% risk of developing ovarian cancer [7]. The same group found that individuals with a mutation in the *BRCA2* gene had a 41% risk to develop breast cancer and an 8.4% risk for developing ovarian cancer [7]. These two studies represent the variability seen in the literature with regards to associated risk. Based on the most up to date surveillance epidemiology and end results (SEER) cancer statistics, women that

carry a *BRCA1* or *BRCA2* mutation have a 60% lifetime risk to develop breast cancer and a 15-40% risk to develop ovarian cancer [18].

Other studies have looked particularly at the risk to develop a second primary breast cancer in the same (ipsilateral) or opposite breast (contralateral). Most studies have found that younger age at the primary diagnosis is strongly correlated to increased risk for developing a contralateral breast cancer [23]. A woman without a *BRCA* mutation has a lifetime risk of 10% to develop contralateral breast cancer. For individuals with a mutation in either the *BRCA1* or the *BRCA2* gene this risk is increased to 13-30% [24,25]. One population based study, looking at women with a breast cancer detected before the age of 55 years, found that individuals with a *BRCA1* mutation had a 4.5 fold increased risk while those that carried a mutation in the *BRCA2* gene had a 3.4 fold increased risk for developing contralateral breast cancer [24]. In 2011, a UK cancer research team confirmed these results. They found that age of the primary breast cancer did in fact influence the risk estimates for developing contralateral breast cancer. Moreover, they quantified their findings showing that individuals with a *BRCA1* mutation had an approximate 36% risk estimate for developing contralateral breast cancer within 15 years from the primary diagnosis. Those with *BRCA2* mutations were found to have 28.5% risk estimate for the same period [26]. Studies have shown however, that the risk for recurrence of breast cancer after surgery in

known *BRCA* carriers is not at an increased risk as compared to the general population [27]. Risk assessments for breast (both ipsilateral and contralateral) and ovarian cancers are constantly being investigated and updated, as more is understood.

Other Associated Cancers

The association between mutations in the *BRCA* genes and breast and ovarian cancer has been well established in the literature over the past twenty years. However, breast and ovarian cancers are not the only cancers associated with the *BRCA1* and *BRCA2* genes. Fallopian tube carcinoma, rare in the general population, has been associated with both *BRCA1* and *BRCA2* mutations [18,28,29]. For individuals with a known *BRCA* mutation the risk for fallopian tube carcinoma increases to 0.6%, about 120-fold increase compared to the general population [30]. Studies have also found up to an 11% lifetime risk for *BRCA* carriers to develop primary papillary serous carcinoma of the peritoneum, as compared to the general population risk of 0.07-0.24%.

Individuals with *BRCA2* mutations also have an increased risk of developing pancreatic cancer, male breast cancer, and prostate cancer. While the general population risk of male breast cancer is less than 1%, the National Cancer Institute (NCI) evaluated 97 males with breast cancer and found that those with a *BRCA2*

mutation had a 6.8% risk to develop breast cancer and men with a *BRCA1* mutation had a 1.2% risk for breast cancer [32,33]. In the general population a man has about a 16% chance of developing prostate cancer in his lifetime [34]. Men with *BRCA2* mutations have a 4.6 fold risk over the general population of developing prostate cancer [4]. Similarly, there is a slightly increased 1.07 fold risk for individuals with a *BRCA1* mutation to develop prostate cancer before the age of 70 years [35]. *BRCA2* mutations have also been shown to increase the risk for pancreatic cancer. One study found that individuals with a *BRCA2* mutation have a 7.3% risk to develop pancreatic cancer in comparison to the 1.45% lifetime risk in the general population [18,36].

Other cancers such as gallbladder, bile duct, and melanoma have also been associated with *BRCA2* mutations [4]. In the general population the lifetime risks for developing both gallbladder and bile duct cancers are less than one percent while the lifetime risk to develop melanoma is 2% [18]. For *BRCA2* mutation carriers the relative risk of developing gallbladder and bile duct cancers becomes 4.97, while the relative risk for developing melanoma is 2.58 [4]. Identifying individuals that carry mutations in *BRCA1* and *BRCA2* is clinically important in order to provide accurate cancer risk assessment and in order to create personalized management plans.

Molecular Testing

Testing for mutations in *BRCA1* and *BRCA2* became commercially available in the United States in 1996 through Myriad Genetics laboratory. While Myriad Genetics is currently the only laboratory offering full sequencing of the *BRCA* genes, other laboratories are offering both multisite and single site testing. Through Myriad, there are currently four testing types offered with regards to the *BRCA* genes [37]. These four mutational analyses are comprehensive analysis, single site analysis, multisite analysis, and rearrangement analysis. Comprehensive BRACAnalysis®, includes full sequencing of the *BRCA1* and *BRCA2* genes as well as analysis of five specific large rearrangements in the *BRCA1* gene. *BRCA1* full sequencing includes both forward and reverse directions of 22 coding exons and about 750 base pairs in the adjacent non-coding introns. Similarly, *BRCA2* full sequencing includes both forward and reverse directions of 26 coding exons and approximately 900 base pairs in the adjacent non-coding introns. The five specific large rearrangements of *BRCA1* included in comprehensive BRACAnalysis® include founder mutations found in individuals of Dutch and European ancestry [38]. Single site BRACAnalysis® is for individuals where a known familial deleterious mutation has been identified. This testing type evaluates an individual for a specific mutation that has previously been identified in their family. Multisite BRACAnalysis® is designed to look for the three founder mutations that have been

identified in the Ashkenazi Jewish population. Ashkenazi Jewish individuals have been found to have a 1/40 risk to be a carrier of a *BRCA* mutation [39]. One study evaluating a group of unselected Ashkenazi Jewish patients with breast cancer found that 12% had a mutation in one of these three founder mutation sites [40]. Similarly another study identified that 35% of unselected Ashkenazi Jewish patients with ovarian cancer carried one of the three founder mutations [41]. If a woman of Ashkenazi Jewish descent were to carry a *BRCA* mutation, 90% of the time it would be one of these three founder mutations. Therefore, recommendations for multisite testing for individuals of Ashkenazi Jewish ancestry regardless of a known familial mutation is indicated because of the high incidence in this population. Finally, BRACAnalysis® Rearrangement testing (BART) evaluates all coding exons of both the *BRCA1* and *BRCA2* genes for deletions and duplications [37]. Less than 2% of individuals with a strong family history suggestive of carrying a *BRCA* mutation with no deleterious mutation identified via comprehensive testing will have a positive BART testing result [42]. While BART testing is typically not covered by most insurance plans, utilization of this testing may be beneficial in individuals with previously negative comprehensive BRACAnalysis®. For patients evaluated for having a high risk of *BRCA* mutation and ROA October 2011

Testing Results

There are three types of *BRCA* test results: positive, negative, and variant of uncertain significance (VUS). Individuals undergoing comprehensive BRACAnalysis® may receive one of the three aforementioned results. A negative test would indicate that no mutation was present or that a known non-deleterious change, which is found in the general population, was present and classified as a “favor polymorphism”. A positive test result indicates a mutation was found and may be classified as a deleterious mutation or suspected deleterious depending on the level of clinical certainty backed by literature. This would indicate that the patient would benefit from added screening. Finally a VUS would indicate that a mutation was found but the exact nature of the mutation (deleterious or not) is still not known at this time. A VUS will continue to be studied by Myriad in an attempt to reclassify it as deleterious or a favor polymorphism. For single site BRACAnalysis®, multisite BRACAnalysis®, and BRACAnalysis® Rearrangement testing (BART) the possible results are either negative or positive.

Identifying at risk individuals

Many professional guidelines have been implemented in regards to identifying individuals who may be at increased risk of having a mutation in either *BRCA1* or *BRCA2* gene. The American Congress of Medical Genetics (1999), The American Society of Clinical Oncology (2003), The American Congress of Obstetrics

and Gynecology (2009), and the United States Preventive Services Task Force (2005) have all published guidelines regarding the identification of patients at a high risk to carry a *BRCA* mutation. The National Comprehensive Cancer Network developed a set of clinical practice guidelines for identifying individuals at increased risks to have a mutation in either of the *BRCA* genes [57]. Those individuals identified may benefit from genetic testing and increased surveillance. Criteria for further risk evaluation, according to the NCCN guidelines, include individuals with one or more of the following:

For those individuals with cancer:

1. Early onset of breast cancer (Clinically using age <50 years old)
2. Triple negative breast cancer (estrogen receptor negative, progesterone receptor negative, and Human Epidermal Growth Factor Receptor 2 negative)
3. Two breast cancer primaries in an individual
4. Breast cancer at any age, with
 - i. 1 close relative with breast cancer \leq 50 years old
 - ii. 1 close relative with epithelial ovarian/fallopian tube/primary peritoneal cancer at any age
 - iii. 2 close relatives with breast cancer and/or

pancreatic cancer

5. A combination of breast cancer with one or more of the following: thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, pancreatic cancer, brain tumors, diffuse gastric cancer, dermatologic manifestations, or leukemia/lymphoma on the same side of family
6. Ovarian/fallopian tube/primary peritoneal cancer
7. Male breast cancer

Unaffected individuals, with a family history of one or more of the following:

1. ≥ 2 breast primaries from the same side of family (maternal or paternal)
2. ≥ 1 ovarian primary from the same side of family (maternal or paternal)
3. A combination of breast cancer with one or more of the following: thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, pancreatic cancer, brain tumors, diffuse gastric cancer, dermatologic manifestations, or leukemia/lymphoma on the same side of family
4. A known mutation in a breast cancer susceptibility gene

5. From a population at risk (Ex. Ashkenazi Jewish ancestry)
6. Male breast cancer [57]

Following the clinical availability of testing the U.S. Preventive Services Task Force (USPSTF) released a statement recommending that “women whose family history is associated with an increased risk for deleterious mutations in *BRCA1* or *BRCA2* genes be referred for genetic counseling and evaluation for *BRCA* testing” [58].

Screening and Management

Ordering *BRCA* testing and accurately interpreting the results is an important aspect to assist in formulating appropriate screening, risk reduction options, and medical management plans. Clinical management recommendations have been published, by the National Comprehensive Cancer Network (NCCN), for individuals identified with a mutation in either of the *BRCA* genes. These recommendations include both increased and more frequent screening as well as prophylactic surgical options. The NCCN breast guidelines indicate monthly self breast examination beginning at 18 years old, semiannual clinical breast examinations beginning by age 25 years and annual mammograms and breast MRI screening at age 25 years or 10 years before the earliest age of onset in the individuals family [43,44]. Surgical options such as prophylactic bilateral mastectomy in individuals with *BRCA* mutations has been shown to reduce breast

cancer risk by up to 90% [45,46]. While screening guidelines for breast cancer risks have been established, ovarian cancer screening has been shown to be ineffective [47]. Transvaginal ultrasound and CA-125 levels every six months starting at 35 years old or 5-10 years before the earliest age of onset in the individuals family is still the recommendation despite its lack of clinical utility [48]. Prophylactic bilateral salpingo-oophorectomy (BSO), once a woman has completed childbearing, is the most effective risk reduction strategy for ovarian cancer for individuals with a *BRCA* mutation [49]. Studies have shown that a prophylactic BSO reduces a woman's risk of developing ovarian, peritoneal, and fallopian tube cancer by up to 90%. Furthermore, prophylactic BSO reduces the risk of breast cancer by almost 50% by eliminating hormone production that may contribute to development of cancer [49,50,51].

A recent study showed that with no intervention the survival rate of *BRCA* carriers was between 53-71%. They also found that prophylactic oophorectomy by age 40 paired with either screening (MRI and mammography) or prophylactic mastectomy at age 40 increased survival by 24% for *BRCA1* carriers and by 11% for *BRCA2* carriers [52].

Chemoprevention, the use of agents to delay or reduce the risk of cancer or recurrence, is another management tool that has been used for risk reduction in individuals with *BRCA* mutations. Studies have reported that individuals with a

BRCA2 mutation may have up to a 62% reduced risk for breast cancer following a five-year tamoxifen course [53]. Individuals with *BRCA1* mutations generally have ER/PR negative tumors and would therefore not benefit from chemoprevention. Alternatively, aromatase inhibitors, anti-estrogenic agents are also being investigated to determine the effects despite a woman's estrogen receptor status. However, studies have reported that aromatase inhibitors may have associated risks such as hot flashes and increased incidence in bone fractures. The same study found that these aromatase inhibitors also reduce the risk of developing contralateral breast cancer [54]. Similarly oral contraceptive use has been associated with risk reduction for ovarian cancer in both *BRCA1* and *BRCA2* carriers. Small studies have shown that ovarian cancer risks in *BRCA1* mutation carriers may be reduced by up to 50% with the use of an oral contraceptive. Similarly, ovarian cancer risks for *BRCA2* carriers were shown to be reduced by up to 60% in this study population [55,56]. Through the understanding of the inheritance of the *BRCA* mutations, associated cancer risks, different testing options, and screening and management guidelines, one can begin to appreciate the importance of adequately individuals at risk of carrying *BRCA* mutations.

In 2009, the American Congress of Obstetricians and Gynecologists (ACOG) and the Society of Gynecologic Oncologists (SGO) partnered to release a practice

bulletin regarding clinical management guidelines for Obstetricians and Gynecologists with regards to HBOC. This bulletin, based off the 2008 version of the NCCN guidelines, first outlined how to identify individuals who should be offered a hereditary risk assessment. The bulletin states that “evaluating a patient’s risk for hereditary breast and ovarian cancer syndrome should be a routine part of obstetric and gynecologic practice” [59].

The ACOG Practice bulletin also discusses the best testing strategies for individuals at risk of carrying a *BRCA* mutation. They recommend that when possible, genetic testing should begin with the “affected individual”. For this, full sequencing of the *BRCA1* and *BRCA2* genes is advised. Once a specific mutation is identified or if the specific mutation is known in the family then single-site testing is recommended. Furthermore, ACOG states that for specific populations where founder mutations are known (Ashkenazi Jewish, French Canadian, Icelandic, Netherlandic, and Swedish) common mutation testing versus full sequencing should be offered [59]. While the aforementioned guidelines are representative of the general consensus with regards to identifying at risk individuals, the question still remains as to who should be identifying these individuals.

Previous Studies

Several studies have looked at the utilization of *BRCA* testing among physicians in the United States and abroad [60 ,62]. In a study of 1500 primary care physicians, 87% of respondents were aware of the availability of *BRCA* testing while only 25% reported to having ordered it in the past year. Furthermore, obstetricians and gynecologist, which made 16.7% of the surveyed population, were in fact the most likely of all physician specialties to order the *BRCA* testing as compared to other specialties [62]. Another study, which surveyed non-academic physicians who have ordered *BRCA* testing, found that a third of obstetricians and gynecologists counsel the patient without the assistance of genetic counselor [60].

Other studies have specifically focused on the knowledge and attitudes of gynecologists with regards to HBOC. In a study of 172 gynecologists in Germany, 62% indicated that they would feel comfortable performing basic genetic counseling for a high risk patient but a majority, 94%, indicated the desire for more information on *BRCA* genetics [63]. Another study in the United States specifically looking at obstetricians and/or gynecologists residents and their knowledge of both HBOC and Lynch Syndrome, a hereditary condition caused by a mutations in the mismatch repair genes which increase the risks for colon and endometrial cancers, elucidated some areas of deficiency in knowledge with regards to how HBOC is inherited in families and what other cancer risks are associated with mutations in the *BRCA1* and *BRCA2* genes. Of 157 study participants, 51% incorrectly indicated

that colon cancer was associated with HBOC and only 62% correctly identified that a mutation could be inherited from paternal relatives. In one recent study, a group of 1,878 physicians from across the United States were surveyed and asked to identify individuals who should be referred for genetic testing and counseling based on the information provided in a vignette. Of those physicians that participated 18.1% identified themselves as obstetrician and/or gynecologists. This study found that among obstetricians and/or gynecologists only 57.3% were able to accurately identify a woman at a high risk for carrying a *BRCA* mutation [64].

Significance of this study

Hereditary breast and ovarian cancer syndrome is a well-defined and studied genetic condition. With the availability and documented benefits of cancer screening, early assessment of cancer risks and evaluation for hereditary cancer syndromes such as HBOC, it is important for implementing personalized screening and prevention guidelines for those found to have a *BRCA* mutation. These early interventions can ultimately reduce morbidity and mortality for both breast and ovarian cancer patients and can also assist in identifying other family members who may be at risk and could benefit from such information. While many women do not follow up with a primary care physician on a regular basis, some studies have shown an increase in the number of visits to their obstetricians and/or gynecologists

[65]. Therefore, obstetricians and/or gynecologists are in a position to identify patients who may benefit from *BRCA* testing. This study is designed to assess knowledge of HBOC and *BRCA* testing, attitude towards *BRCA* testing, and utilization of *BRCA* testing among obstetricians and/or gynecologists in the greater Houston area. With the information attained from this study, we hope to be able to begin to address areas where educational modules and clinical protocols may benefit patient care.

MATERIALS AND METHODS

Study Design

This study was conducted via questionnaire to determine the current knowledge, attitudes, and utilization of the Houston area obstetricians and/or gynecologists (Ob/Gyns) with regards to HBOC and *BRCA* testing. Specifically the aims of this study were to:

1. Determine the knowledge of Ob/Gyns with regards to hereditary breast and ovarian cancer syndrome and *BRCA* testing.
2. Assess how Ob/Gyns are utilizing *BRCA* testing.
3. Determine what Ob/Gyns feel their role is with regards to *BRCA* testing.

Database

All the data obtained from the surveys was entered into a Microsoft Excel 2010 spreadsheet. Each survey was assigned a unique identification number to ensure that the responses were anonymous. All of the information was then coded in order to be entered into the statistical software package for higher-level analysis. An overall knowledge score was calculated for each participant that answered the knowledge based questions and this information was also used for multivariate analysis.

Study Approval

The survey was approved by the Institutional Review Board at the University of Texas Health Science Center at Houston Graduate School of Biomedical Sciences (IRB# HSC-GSBS-11-0328). Additionally, a separate IRB approval was obtained from Woman's Hospital of Texas (264839-1); which was also accepted at Kelsey-Seybold Clinic for survey distribution. Approval to begin survey collection was received by the Memorial Hermann Clinical Innovation & Research Institute in order to administer the surveys at the affiliated Memorial Hermann Hospital System's institutions. Two institutions, Methodist Hospital and St. Joseph's Hospital, accepted the aforementioned UT IRB for survey distribution.

Study Population

The study was distributed to 268 physicians across institutions which included: Memorial Hermann Texas Medical Center, Memorial Hermann Katy, Memorial Hermann Memorial City, Memorial Hermann Southwest, Woman's Hospital, Kelsey-Seybold Clinic, Methodist Hospital Texas Medical Center, and St. Joseph's Hospital. The inclusion criteria for this study was board certified or board eligible Ob/Gyns in the Houston area; which excluded all other physicians practicing in other specialties and Ob/Gyns still in residency. The survey was only available in English and there was no opportunity for translation.

Survey/ Questionnaire

A questionnaire (Appendix A) was created in order to assess a sample of Ob/Gyns in the greater Houston area. A review of the literature did not identify a validated questionnaire specifically evaluating Ob/Gyn's knowledge, attitudes, or utilization of BRCA testing, therefore, an instrument was created. The survey was revised by committee members through several phases to determine whether it was clearly worded and appropriately structured to gather the desired information. Experts within the fields relevant to the questionnaire reviewed the survey in order to assess content and validity.

A cover letter explaining the nature of the survey and serving as the consent document was included with each survey (See Appendix B). Participation in the survey served as consent.

The questionnaire consisted of 40 questions and took about 15 minutes to complete. The questionnaire was divided into four main sections: (1) demographics, (2) attitude toward BRCA testing, (3) utilization of BRCA testing and (4) knowledge of BRCA testing.

1. Demographics: This section consisted of seven questions to gather gender, since the completing their residency, area of practice, practice setting, and number of patients typically seen per week. Questions in this section were

multiple choice and free response where applicable.

2. Attitudes toward BRCA testing: This section consisted of 5 questions regarding the overall comfort of identifying patients at risk of carrying a *BRCA* mutation, assessing participants' views on whether identifying at risk patients was one of their practice responsibilities, and determining barriers which could potentially prevent participants from ordering testing. Questions in this section were yes/no questions, multiple choice (some limited to one response while others were open to several responses), a five point likert scale to assess comfort (very uncomfortable, uncomfortable, uncertain, comfortable, and very comfortable), and free response where applicable.
3. Utilization of BRCA testing: This section consisted of seven questions designed to assess how often participants identified, initiated a conversation, ordered testing, or received questions related to hereditary breast and ovarian cancer and BRCA testing. Furthermore, this section served to gather information about participants' referral patterns once an individual with a suspected BRCA mutation was identified. Answers in this section were gathered via a five point likert scale to assess how often each of the aforementioned scenarios arose. The likert scale assessed the average number of times per month each scenario arose with the following choices: never, rarely (<1 time/mo), sometimes (1-2 times/month), often (3-4 times/month), and on a regular basis (≥ 5 times/mo).

A multiple choice question was used to assess the participants' referral patterns.

4. Knowledge of BRCA testing: This section consisted of twenty questions to assess the overall knowledge of each participant with regards to hereditary breast and ovarian cancer and BRCA testing. The questions in this section were yes/no choices with simple example patients to determine if the survey participant could correctly identify those at risk of having a BRCA mutation. Similarly, yes/no questions were used to determine knowledge of cancers associated with hereditary breast and ovarian cancer syndrome. Finally a series of multiple choice questions were used to assess the knowledge about the lifetime risks associated with hereditary breast and ovarian cancer syndrome and the type of testing that would be appropriate given a particular patient's personal and family background.

At the conclusion of the survey, there was a free response box designed for any comments regarding the survey or hereditary breast and ovarian cancer and BRCA testing in general.

Survey/ Data Collection

Two different methods of distribution were used in order to attempt to maximize the response rate. The first method was an online survey, with direct

contact information gathered from the respective hospital system email databases. A direct link to the survey, embedded in the body of the message, was sent out to all obtained email addresses. A follow up reminder email was sent out to all individuals for participation about one week after the initial distribution. The electronic version of the survey was created in such a way that individuals that participated in this format were allowed to skip over questions, but could not go back to change answers once the question had been submitted or skipped. IP addresses were tracked so that the survey could theoretically only be submitted once from a given computer. While individuals could theoretically use different computers to submit several responses, this would be highly unlikely.

The second distribution method was via a hard copy of the survey with in person contact. This contact was made through the attendance of various monthly hospital meetings. Individuals that had previously completed the online version of the survey were asked not to take part at these visits, but there was no way to ensure that an individual did not complete both formats of the survey.

Both hard copy and digital delivery methods were distributed between October 2011 and February 2012. The institutions, in which one or both methods of delivery were utilized, included: Memorial Hermann Texas Medical Center (both online and in person distribution), Memorial Hermann Katy (in person distribution), Memorial Hermann Memorial City (both online and in person

distribution), Memorial Hermann Southwest (in person distribution), Woman's Hospital (online and in person distribution), Kelsey-Seybold Clinic (online distribution), Methodist Hospital Texas Medical Center (online distribution), and St. Joseph's Hospital (in person distribution).

Statistical Analysis

Both univariate and multivariate analyses were performed on all applicable variables using the statistical software package STATA (v. 11, College Station, TX). Descriptive charts and graphs were created using Microsoft Excel. A comparison between groups was performed using contingency test (χ^2 or Fisher exact tests), Mann-Whitney sign-rank or Kruskal-Wallis tests where appropriate. Comparisons between paired groups were performed using Wilcoxon signed ranks test. Linear and logistic regression models were used to assess any linear trends over a series of ordinal categories. Spearman's correlation tests were utilized to assess the degree of correlation between two continuous variables. Tests were considered statistically significant at $p < 0.05$.

RESULTS

Survey Response

The total number of physicians present at meetings and/or providing an email address for access for survey distribution was 232. Of the surveys distributed online, 18 (6.7%) were invalid emails and were returned immediately. There were ninety-two surveys that were returned as completed. Fifty nine of these were hard copies of the survey distributed at various departmental meeting. The rest, thirty three, were online versions of the survey distributed through the online Survey Monkey database. Of the thirty three surveys completed online, two were opened online but no questions were attempted. An additional seven surveys (2.6%) were excluded. Of these seven, one was filled in by an RN, four were filled by physicians in residency, one was filled by a visiting foreign medical physician, and one participant only filled out the demographics section leaving the rest of the survey blank. Of the 92 surveys returned, 83 were used in statistical analysis, which resulted in a (30.97%) response rate overall. In both formats of the survey respondents were selective in which questions they answered, which resulted in varying numbers of total responses for some questions.

Part I: Demographics

Fifty three percent (n=44) of respondents were female, and forty seven percent (n=39) were male (Figure 1).

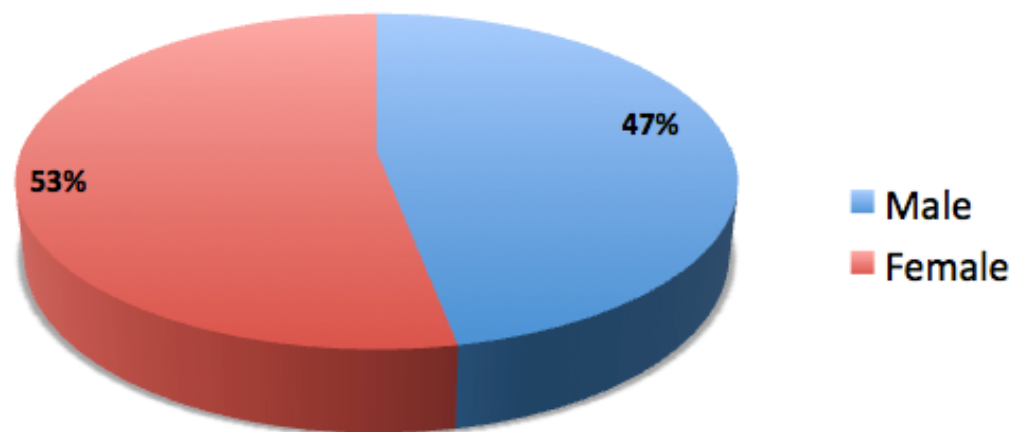


Figure 1: Gender, n=83.

Of the eighty three participants, seventy six (92%) were board certified in obstetrics and gynecology, while the remaining seven (8%) were not. The participants were asked to indicate the years since the completion of their primary residency. The average years reported was 17.89 years with a range from 0-47 years. This was consistent with the median of the group, which was found to be eighteen years.

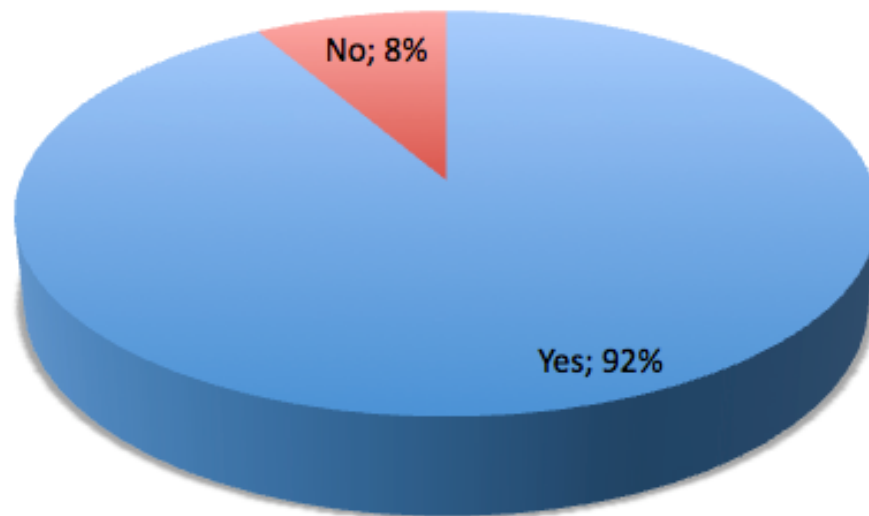


Figure 2: Percent certification in obstetrics and gynecology.

Seventy four (89.2%) participants indicated that they were not boarded in any other specialty, while nine (10.8%) indicated that they were. Of those, three (33.3%) were board certified in gynecologic oncology only, one (11.1%) was board certified in obstetrics only, two (22.2%) were boarded in gynecologic oncology, one (11.1%) was boarded in maternal fetal medicine, one (11.1%) was boarded in

reproductive endocrinology, and one chose no to indicate an additional sub-specialty.



Figure 3: Number certified in a sub-specialty other than obstetrics and gynecology .

Sixty nine (83%) participants identified their primary practice area as general obstetrics and/or gynecology, four (5%) were gynecology only, three (4%) as

gynecologic oncology, two (2%) as maternal fetal medicine, two (2%) as reproductive endocrinology, and three (4%) as urogynecology.

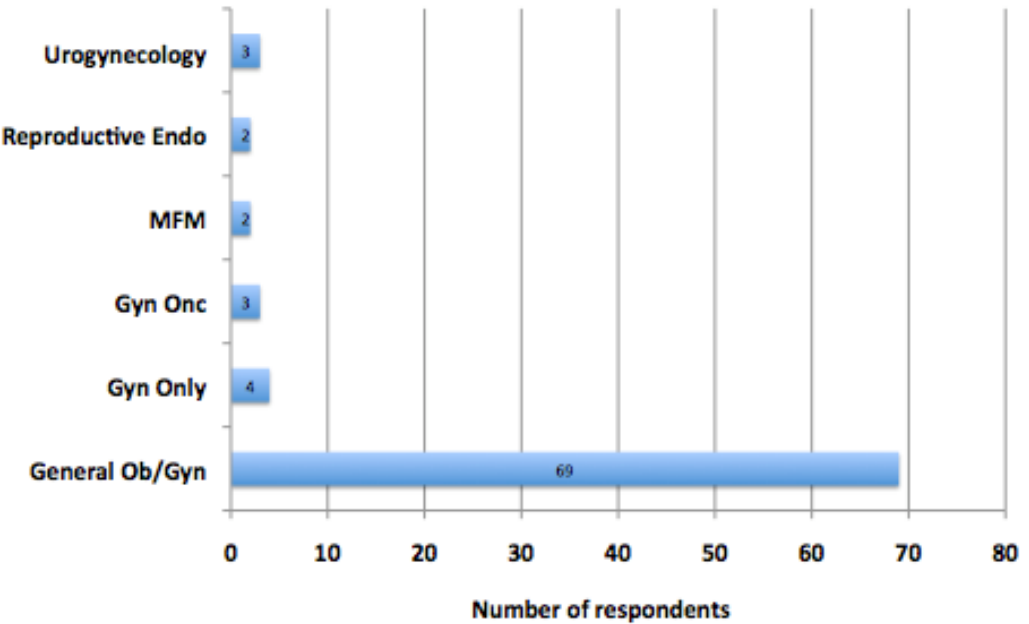


Figure 4: Area of practice.

The majority of participants, fifty six (67.5%), reported that they work in a private practice setting. Those that indicated private practice were then asked to indicate the average number of Ob/Gyns in their group. The average number of Ob/Gyns reported was 9.36 (SD 10.59). There were twenty seven (32.5%) participants who reported to work in an academic institution.

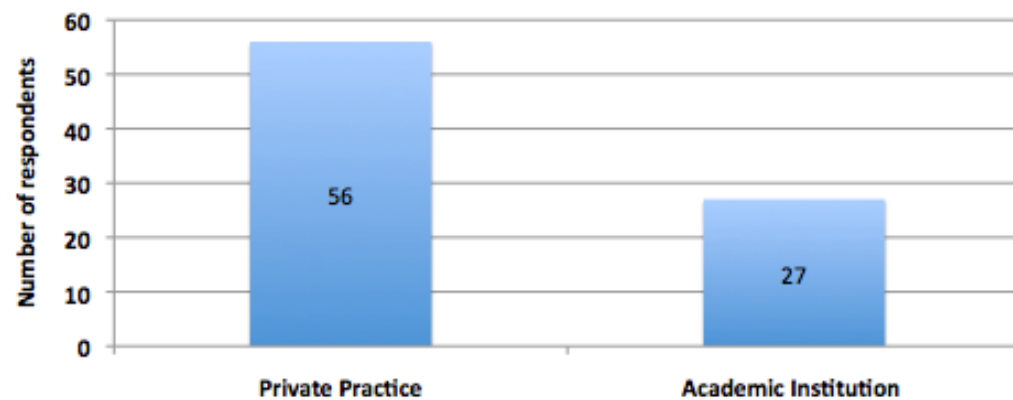


Figure 5: Primary practice setting.

The respondents were asked to identify the number of patients they see in the outpatient setting during an average week. They were given five ranges and about half (46%) stated that they see between 51-100 patients per week. A quarter of respondents reported to see between 101-150 patients per week, while 19% stated they saw less than 50 per week. Only 6% and 4% of respondents reported to seeing 151-200 and greater than 200 patients per week, respectively.

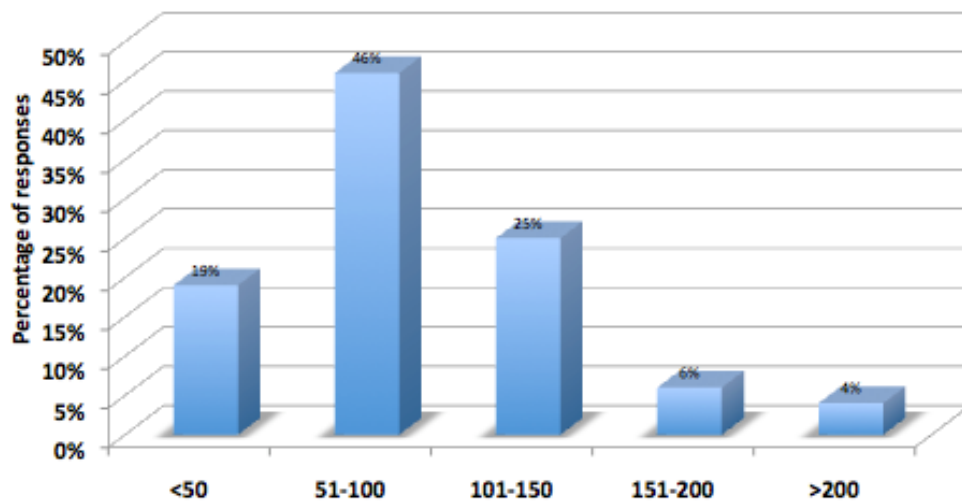


Figure 6: Number of patients seen in the outpatient setting during an average week.

Part II: Attitude toward HBOC and *BRCA* testing

The majority (57%) of respondents felt comfortable in identifying patients who are at an increased risk of carrying a *BRCA* mutation. An additional 20% of respondents indicated that they felt very comfortable with this task. The remaining 10%, 4%, and 8% of respondents were very uncomfortable, uncomfortable, or uncertain, respectively, with regards to identifying patients at an increased risk to

carry a BRCA mutation.

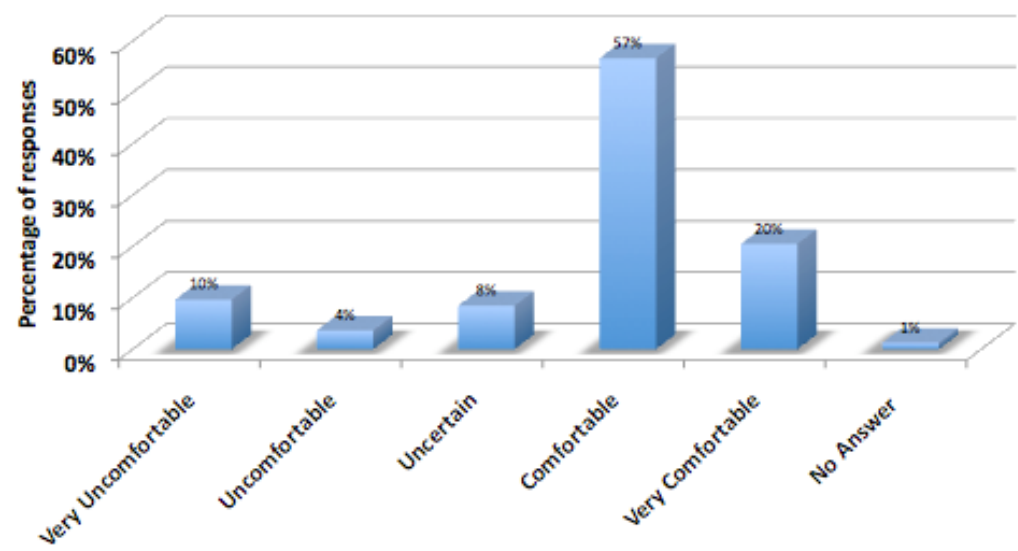


Figure 7: Comfort in identifying patients who are at an increased risk of carrying a *BRCA1/BRCA2* mutation.

Each participant was asked to evaluate a set of two statements. The first statement asked if he/she felt that it was one of their practice responsibilities to identify patients at risk of having a *BRCA* mutation. The majority (92.7%, n=77) of respondents indicated yes, 6% (n=5) indicated no, and 1.2 % (n=1) chose to not answer. The second statement asked if he/she felt that patient management would change if the patient was found to be a carrier of a *BRCA* mutation. Here 87.9%

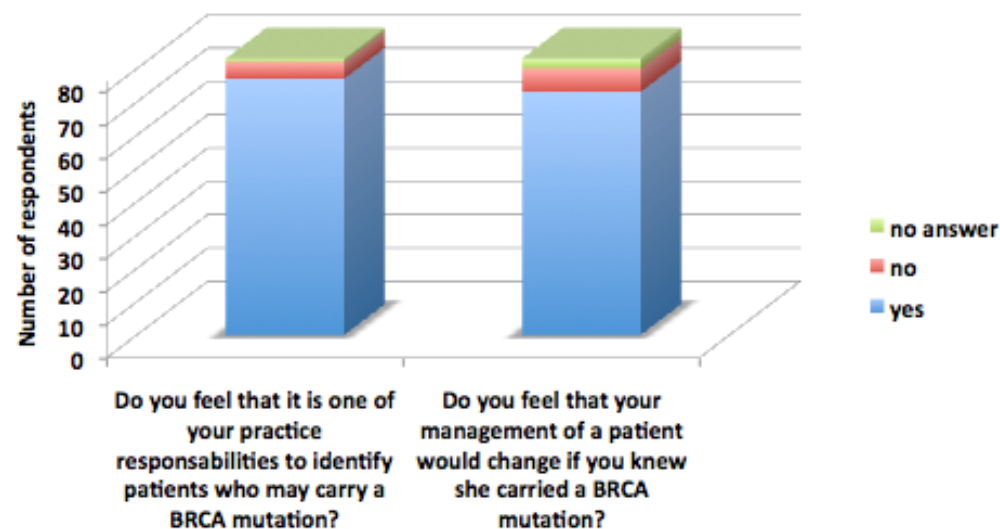


Figure 8: Physicians' attitude towards their responsibility to identifying *BRCA* mutation carriers and towards changes of management if a patient was found to be a *BRCA* carrier.

(n=73) indicated yes, 8.4% (n=7) indicated no, and 3.6% (n=3) chose not to answer.

There were seven respondents that indicated that identifying patients who may carry a BRCA mutation was one of their practice responsibilities and in a subsequent question indicated that their management of a patient would not change if the patient carried a BRCA mutation. Conversely, five respondents that indicated that identifying patients who may carry a BRCA mutation was not one of their practice responsibilities subsequently indicated that their management of a patient would change if the patient carried a BRCA mutation. A wilcoxon signed-rank test indicated that there was no significant difference between these two groups ($z=0.5637$). Additionally two respondents that indicated that identifying

patients who may carry a BRCA mutation was one of their practice responsibilities chose not to respond to the subsequent question. There was one respondent that chose not to answer either of the aforementioned questions.

The next question asked respondents to identify who they feel has the primary responsibility of identifying patients that are at risk of carrying a mutation in either the BRCA1/2 gene. Respondents taking the survey online were limited to only one answer choice, but it was not possible to prevent those taking the paper version of the survey from indicating more than one response. Each of the following responses was not mutually exclusive. The majority of respondents (84.3%, n=70) indicated that Ob/Gyns should have the primary responsibility of identifying these patients. Primary care physicians were identified by 26.5% (n=22) as the second highest group believed to be responsible for identifying these patients. This was followed by 10.8% (n=9) of respondents choosing oncologists, 3.6% (n=3) choosing radiologists, and 1.2% (n=1) chose other, with a written comment indicating that family members should have the primary role of identifying individuals at risk of having a *BRCA* mutation.

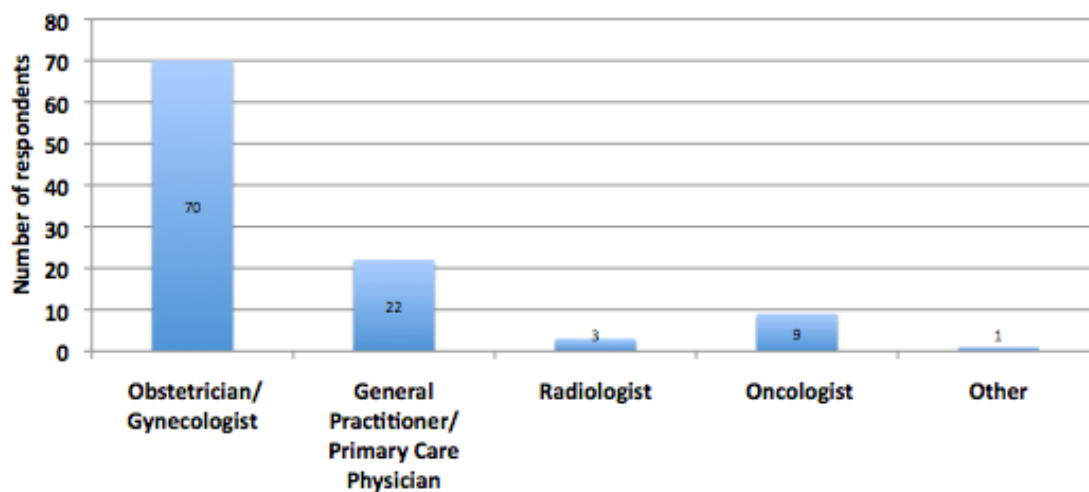


Figure 9: Physicians' attitude in who they feel has the primary responsibility of identifying patients that are at risk of carrying a *BRCA* mutation.

The final question in this section asked respondents to identify barriers they feel prevent the ordering of *BRCA* genetic testing. Multiple answers were accepted on both versions of the survey, indicating that the answer choices were not mutually exclusive. Most (80.7%, n=67) respondents indicated that the cost of testing was a barrier in genetic testing. Possibility of insurance discrimination was the second most chosen barrier by 37 respondents (44.6%). Additionally, time constraints in clinic (31.3%, n=26), lack of patient interest/uptake (22.9%, n=19), lack of knowledge regarding which patients are eligible for testing (8.4%, n=7), and feeling that *BRCA* testing is not an important aspect for their patient care (1.2%, n=1) were all indicated by the respondents as perceived barriers. Eight respondents (9.6%) also stated "other" as a potential barrier for ordering *BRCA* testing, and wrote in:

1. Physician asking questions
2. Usually refer to genetic counseling
3. I refer back to the PCP
4. Insurance denial
5. Refer to our high risk clinic for counseling rather than ordering the testing alone
6. There are often other greater priorities at the visit
7. Uncertain indications, understanding and interpretation of the test
8. I have a great go to person in my multi disciplinary practice, so if risk or inquiry I send the patient to him

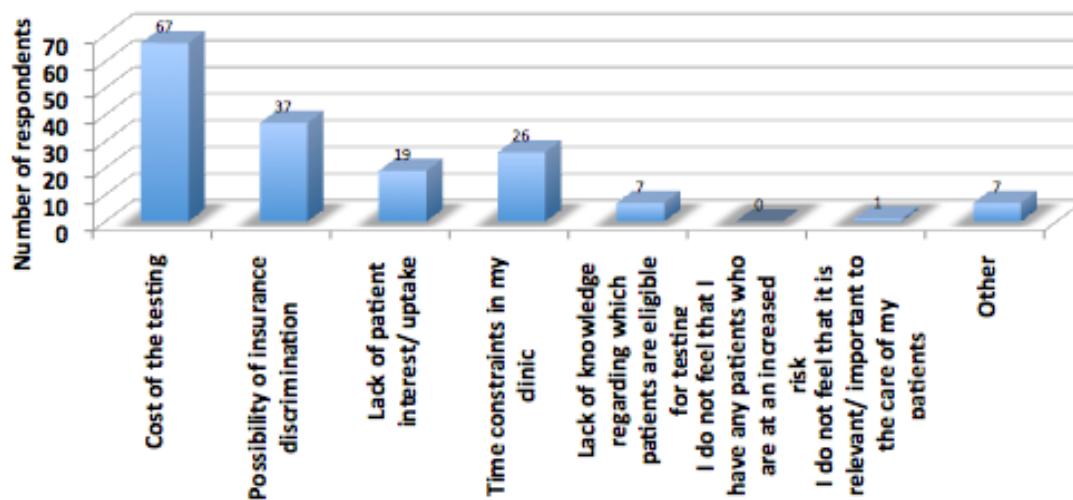


Figure 10: Physicians' perception of barriers which prevent the ordering of genetic testing for *BRCA* genes. Multiple responses were accepted, columns are not mutually exclusive.

Part III: Utilization of BRCA testing

All respondents answered the following series of questions by indicating their answer choice on a likert scale for the frequency of each situation per month. The answer choices were “never”, “rarely” (<1 time/month), “sometimes” (1-2 times/month), “often” (3-4 times/month), and “on a regular basis” (≥ 5 times/month). The first question asked how often the respondent saw a patient at an increased risk for HBOC. The majority (32.5%, n=27) indicated rarely, 30.1% (n=25) indicated sometimes, 22.9% (n=19) indicated often, 8.4% (n=7) indicated on a regular basis, 1.2% (n=1) indicated never, and 4.8% (n=4) chose not to respond. The frequency of seeing patients at an increased risk as reported in these responses and the number of patients seen by that physician in a typical week was not correlated ($r=0.16$). The second question asked how often the respondent received questions from patients about the heredity of breast cancer. The majority (39.8%, n=33) indicated rarely, 24.1% (n=20) indicated sometimes, 15.7% (n=13) indicated often, 9.6% (n=8) indicated on a regular basis, 6% (n=5) indicated never, and 4.8% (n=4) chose not to respond. The correlation between the responses given and the number of patients seen in a typical week was poor ($r=0.12$). The third question asked how often the respondent received questions from patients about BRCA1/2 testing. The

majority (43.4%, n=36) indicated rarely, 27.7% (n=23) indicated sometimes, 9.6% (n=8) indicated often, 3.6% (n=3) indicated on a regular basis, 10.8% (n=9) indicated never, and 4.8% (n=4) chose not to respond. The fourth question asked how often the respondent initiated a conversation regarding genetic testing for *BRCA1/2* with a patient. The majority (30.1%, n=25) indicated sometimes, 19.3% (n=16) indicated rarely, 21.7% (n=18) indicated often, 19.3% (n=16) indicated on a regular basis, 3.6% (n=3) indicated never, and 4.8% (n=4) chose not to respond. The fifth question asked how often the respondent ordered genetic testing for *BRCA1/2*. The majority (43.4%, n=36) indicated rarely, 14.4% (n=12) indicated sometimes, 6% (n=5) indicated often, 6% (n=5) indicated on a regular basis, 22.9% (n=19) indicated never, and 7.2% (n=6) chose not to respond. The final question in this series asked how often the respondent referred a patient to a genetic counselor or other specialist in order to discuss genetic testing for *BRCA1/2*. The majority (39.8%, n=33) indicated rarely, 21.7% (n=18) indicated sometimes, 9.6% (n=8) indicated often, 7.2% (n=6) indicated on a regular basis, 14.4% (n=12) indicated never, and 7.2% (n=6) chose not to respond.

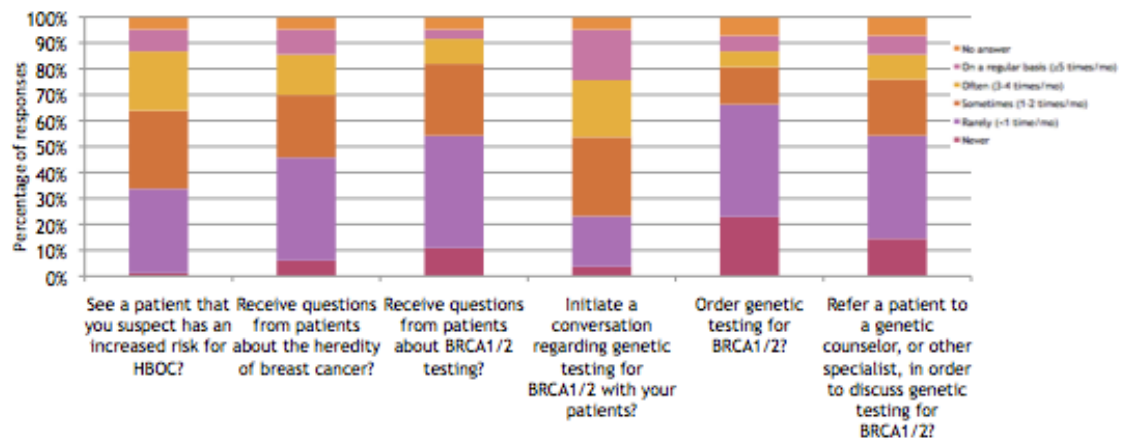


Figure 11: Physician reported frequencies of various practice scenarios.

Next we asked respondents to indicate what they would do after identifying patients at risk of carrying a *BRCA1/2* mutation. Respondents could choose multiple answers, indicating that the answer choices were not mutually exclusive. The majority (53%, n=44) indicated that they would discuss HBOC and order *BRCA* testing themselves. 48.2% (n=40) of respondents indicated that they would refer the patient to a genetic counselor for risk assessment and possible *BRCA* testing. 9.6% (n=8) of respondents indicated that they would refer a patient to another specialist, including: oncologist (n=2), hematology and oncology (n=1), breast center (n=1), and specifically a MDAnderson Cancer Center genetic counselor (n=1). Three respondents did not indicate to which specialist they would refer. Additionally, one respondent (1.2%) indicated that they would refer the patient back to their PCP and another respondent (1.2%) indicated that they would do nothing, because he/she

did not feel that knowing whether or not a patient carries a mutation in BRCA would change the management of the patient.

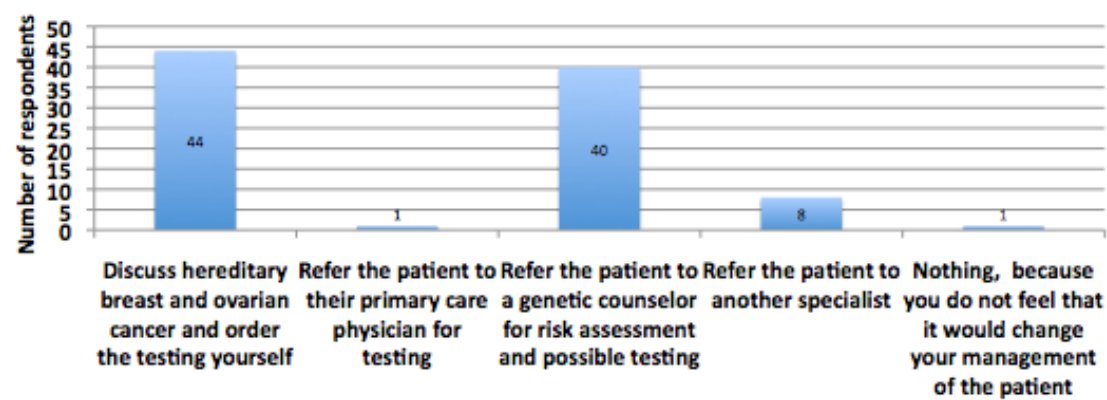


Figure 12: Physician-reported practice patterns after identifying patients who may be at risk of carrying a *BRCA1/BRCA2* gene mutation. Multiple responses were accepted, columns are not mutually exclusive.

Part IV: Knowledge

The first group of questions consisted of patient scenarios and respondents were asked whether each patient would be at an increased risk for having a mutation in the *BRCA1* or *BRCA2* gene. The first patient scenario was a patient who was diagnosed with breast cancer at 45 years but has no other family history of breast cancer. The majority of respondents, 62.7% (n= 52), correctly indicated that this patient would be at an increased risk, while 27.7% (n=23) indicated that this patient would not be at an increased risk and 9.6% (n=8) chose not to respond. The second patient scenario was a patient who was diagnosed with ovarian cancer at the age of 55 years. The majority of respondents, 53% (n= 44), correctly indicated

that this patient would be at an increased risk, while 36.1% (n=30) indicated that this patient would not be at an increased risk and 10.8% (n=9) chose not to respond. The third patient scenario was a patient who is Ashkenazi Jewish and was diagnosed with breast cancer at the age of 60 years. The majority of respondents, 69.9% (n= 58), correctly indicated that this patient would be at an increased risk, while 20.5% (n=17) indicated that this patient would not be at an increased risk and 9.6% (n=8) chose not to respond. The fourth patient scenario was a patient whose brother was diagnosed with breast cancer. The majority of respondents, 81.9% (n= 68), correctly indicated that this patient would be at an increased risk, while 7.2% (n=6) indicated that this patient would not be at an increased risk and 10.8% (n=9) chose not to respond. The fifth patient scenario was a patient whose paternal grandmother was diagnosed with breast cancer at the age of 50 and whose paternal aunt was diagnosed with breast cancer at 49 years old. The majority of respondents, 69.9% (n= 58), correctly indicated that this patient would be at an increased risk, while 18.1% (n=15) indicated that this patient would not be at an increased risk and 12% (n=10) chose not to respond. The sixth patient scenario was a patient whose paternal cousin was diagnosed with endometrial cancer at 45 and whose paternal aunt was diagnosed with colon cancer at 51 years. The majority of respondents, 48.2% (n= 40), correctly indicated that this patient would not be at an increased risk, while 42.2% (n=35) indicated that this patient would be at an increased risk and

9.6% (n=8) chose not to respond. The seventh patient scenario was a patient who has a family member with breast cancer, regardless of age. The majority of respondents, 77.1% (n=64), correctly indicated that this patient would not be at an increased risk, while 10.8% (n=9) indicated that this patient would be at an increased risk and 12% (n=10) chose not to respond. The final patient scenario was a patient whose mother was diagnosed with breast cancer at 60 years and whose maternal grandmother was diagnosed with breast cancer at the age of 70 years. The majority of respondents, 45.8% (n= 38), incorrectly indicated that this patient would be at an increased risk, while 44.6% (n=37) correctly indicated that this patient would not be at an increased risk and 9.6% (n=8) chose not to respond.

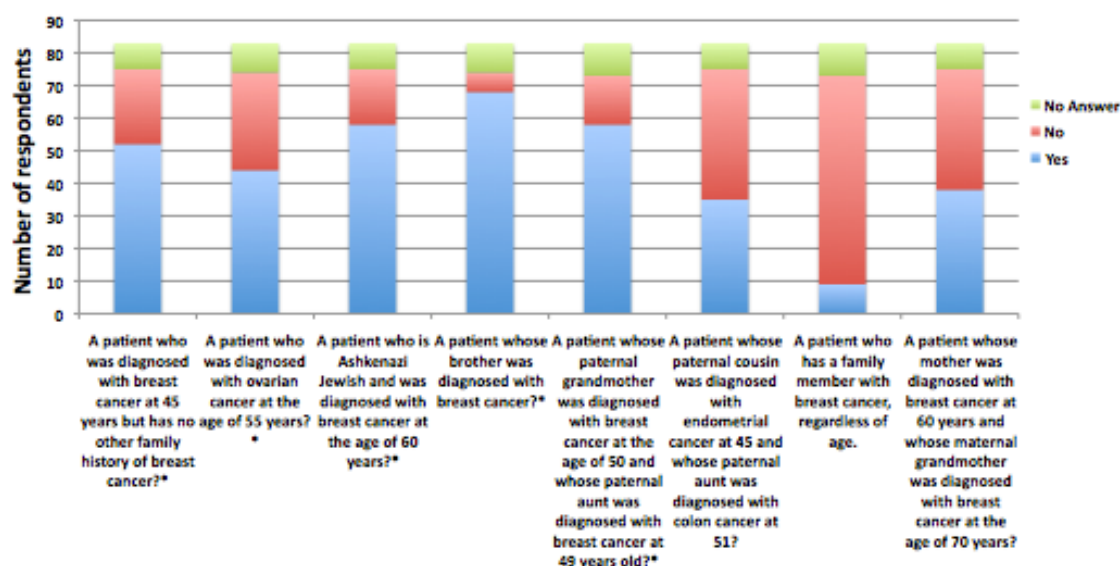


Figure 13: Physician perceptions of patients at risk of carrying a *BRCA* mutation.

The second group of knowledge questions consisted of a list of cancers and the respondents were asked to identify whether each particular cancer was associated with HBOC. The first cancer listed was breast cancer, which is associated with HBOC. The majority of respondents, 95.2% (n=79), indicated correctly that breast cancer is associated with HBOC while 4.8% (n=4) chose not to answer. The second cancer listed was colon cancer, which is not associated with HBOC. The majority of respondents, 53% (n=44), incorrectly indicated that colon cancer is associated with HBOC while 31.3% (n=26) indicated correctly that it is not associated and 15.7% (n=13) chose not to answer. The third cancer, which is associated with HBOC, was high grade serous or endometrioid ovarian cancer. The majority of respondents, 78.3% (n=65), correctly indicated that that high grade serous or endometrioid ovarian cancer is associated with HBOC while 10.8% (n=9) incorrectly indicated that it is not associated, and 10.8% (n=9) chose not to answer. Next, participants were asked to evaluate mucinous ovarian cancer, which is not associated with HBOC. The majority, 42.2% (n=35), correctly indicated that mucinous ovarian cancer is not associated with HBOC, while 38.6% (n=32) indicated that this cancer is associated with HBOC, and 19.3% (n=16) chose not to answer. The next cancer listed was prostate cancer, which is associated with HBOC. The majority, 50.6% (n=42), of participants incorrectly chose that prostate cancer is not associated with HBOC. Only 24.1% (n=20) correctly identified prostate cancer as

being associated with HBOC, and 25.3% (n=21) chose not to answer. The next cancer listed was uterine cancer, which is not associated with HBOC. The majority, 55.4% (n=46), of participants correctly indicated that uterine cancer was not associated with HBOC, while 25.3% (n=21) of respondents incorrectly indicated that uterine cancer is associated with HBOC, and 25.3% (n=16) chose not to answer. The final cancer listed was fallopian tube cancer, which is associated with HBOC. The majority of respondents, 59% (n= 49), correctly identified that fallopian tube cancer is associated with HBOC, while 24.2% (n=20) indicated that it was not, and 7.2% (n=14) chose not to respond.

The majority (86.6, n=58) of respondents that indicated that they would change their management of a patient if the patient carried a BRCA mutation were able to accurately identify ovarian cancer as being an HBOC associated cancer. However, nine respondents (13.4%) did not identify ovarian cancer as being an HBOC associated cancer. Similarly the majority (69.4%, n=43) of respondents that indicated that they would change their management of a patient if the patient carried a BRCA

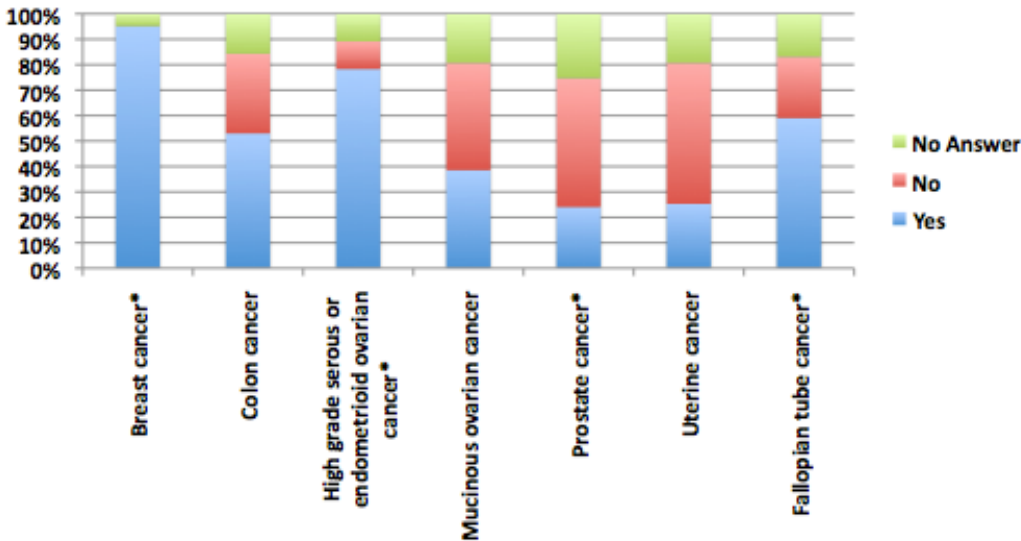


Figure 14: Physician perceptions of cancers associated with HBOC.

mutation were able to accurately identify fallopian tube cancer as being an HBOC associated cancer, while 30.6% (n=19) were not.

Respondents were asked what the lifetime risk for developing breast cancer is for a woman with a known *BRCA* mutation. Less than half (44.6%, n=37) correctly identified that the lifetime risk is up to 88%. About one third of respondents (30.1%, n=25) indicated that the risk is up to 44%, 9.6% (n=8) indicated that the risk is up to 22%, 1.6% (n=1) indicated that the risk is virtually 100%, 6% (n=5) indicated that they did not know, and 8.4% (n=7) chose not to answer.

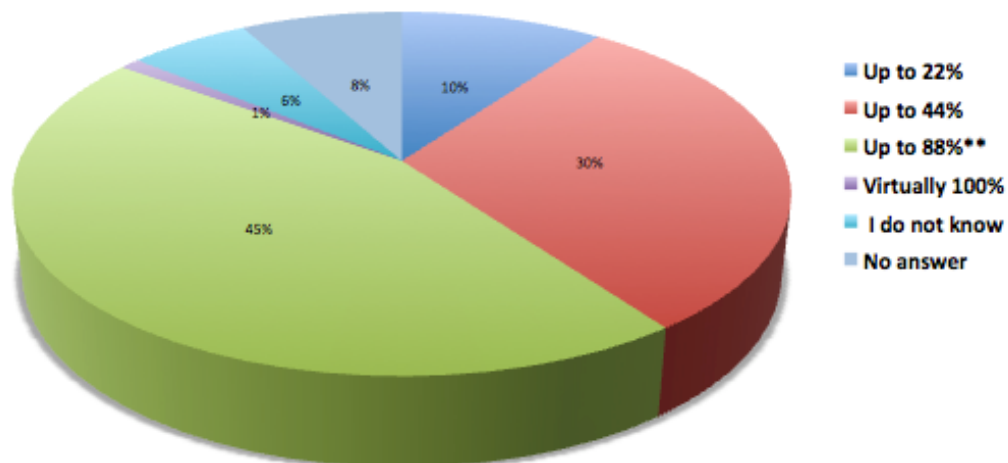


Figure 15: Physician perceptions of the lifetime risk of developing breast cancer with a known *BRCA* mutation.

Respondents were asked what the lifetime risk for developing ovarian cancer is for a woman with a known *BRCA* mutation. About half (54.2%, n=45) correctly identified that the lifetime risk is up to 44%. About one fifth of respondents (19.3%, n=16) indicated that the risk is up to 22%, 12% (n=10) indicated that the risk is up to 88%, 9.6% (n=8) indicated that they did not know, and 4.8% (n=4) chose not to answer.

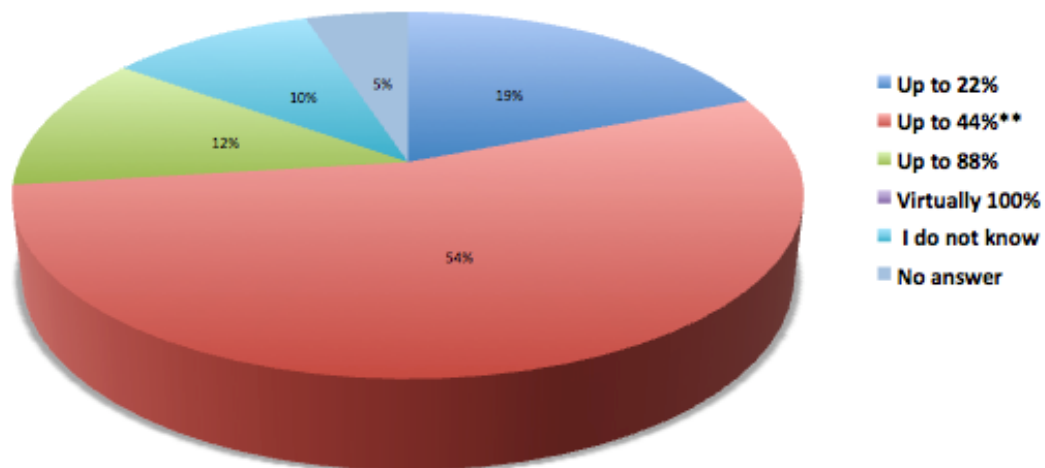


Figure 16: Physician perceptions of the lifetime risk of developing ovarian cancer with a known *BRCA* mutation.

Respondents were asked to identify the risk of inheritance for *BRCA* mutations if a known first-degree relative had an identified mutation. About half (48.2%, n=40) correctly identified the risk as 50%. About one third of respondents (28.9%, n=24) indicated the risk as 25%, and 1.6% (n=1) indicated the risk as 100%. There were two respondents (2.4%) that indicated that the risk level was dependent upon whether the maternal or paternal relative was the relative with the known mutation. Additionally, 14.5% (n=12) indicated that they did not know and 4.8% (n=4) chose not to answer.

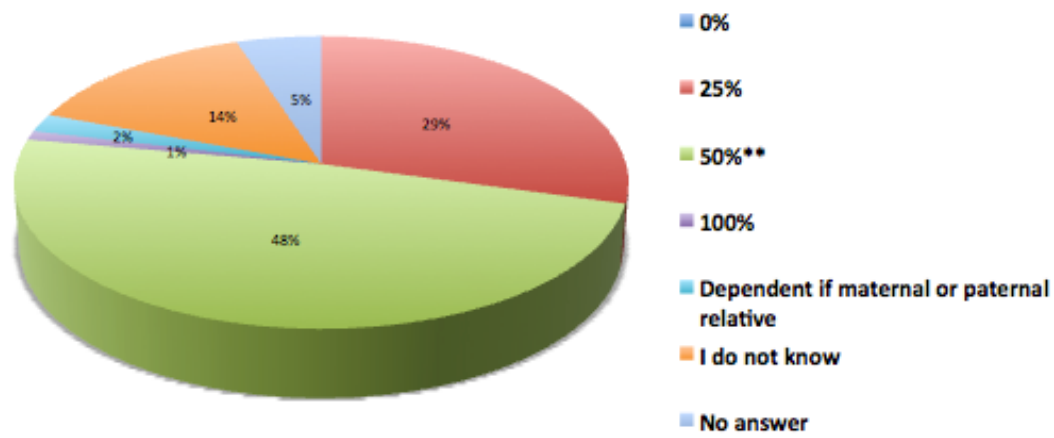


Figure 17: Physician perceptions of the risk of inheriting a *BRCA* from a first degree relative with known *BRCA* mutation.

Respondents were asked to identify the pattern of inheritance for *BRCA* mutations. The overwhelming majority (83.1%, n=69) correctly identified that mutations could be inherited from either the patients mother or father. Only 4.8% (n=4) indicated that a mutation could only be inherited from the patient's mother. Another 6% (n=5) stated they did not know, while an additional 6% (n=5) chose not to respond.

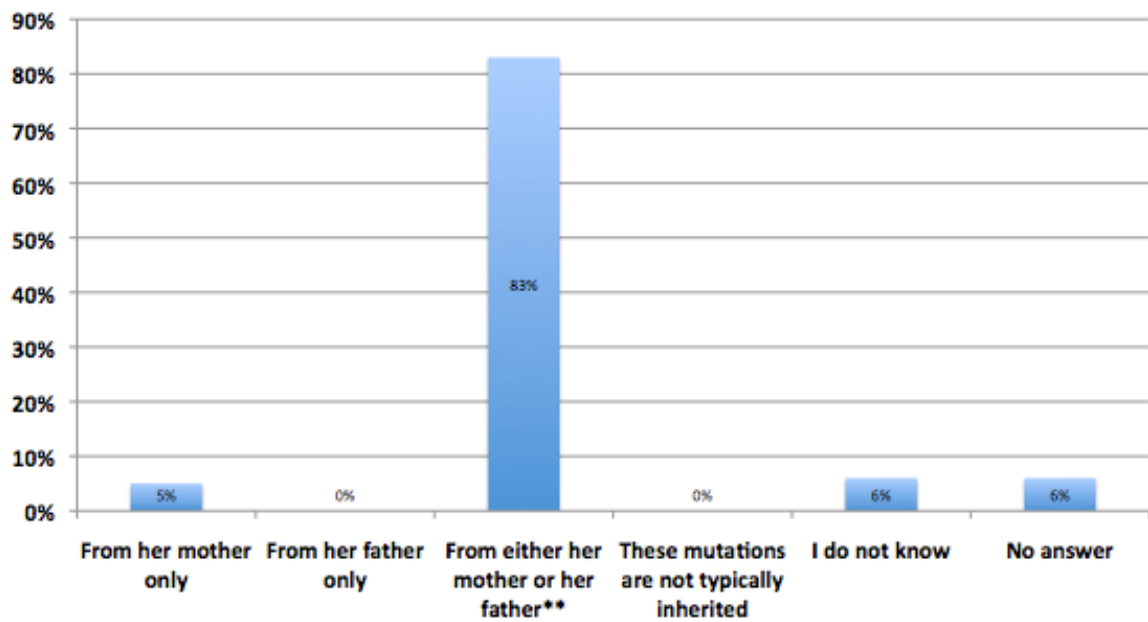


Figure 18: Physician perception of who a woman can inherit a BRCA mutation from.

The final knowledge question asked the respondents to identify the type of testing most appropriate for an Ashkenazi Jewish patient with a known familial mutation. Only 6% (n=5) correctly identified that multisite *BRCAAnalysis*® would be the most appropriate. The majority of participants, 42.2% (n=35), stated that they

did not know, while 20.5% (n=17) indicated that single site *BRACAnalysis*® would be the most appropriate. Another 19.3% (n=16) indicated that comprehensive *BRACAnalysis*® would be most appropriate and 6% (n=5) stated that BART testing was the most appropriate for the given patient. Additionally, 6% (n=5) chose not to respond.

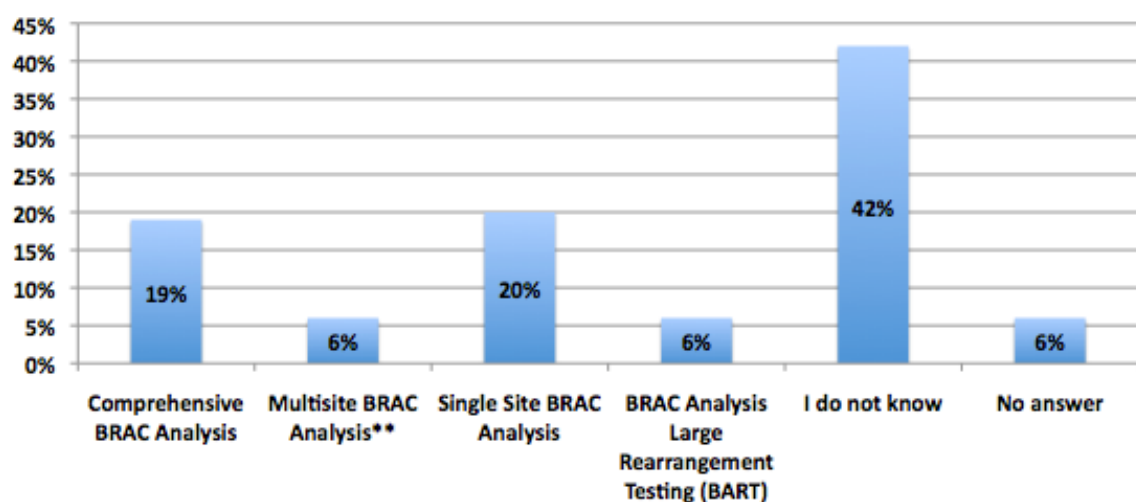


Figure 19: Physician perceptions of the most appropriate genetic testing for an Ashkenazi Jewish patient whose family has a known mutation in a BRCA gene.

Respondents were allowed to provide any comments with regards to this survey, identifying patients at risk for HBOC or BRCA testing. There were several respondents that opted to provide feedback, which included:

1. "Points out need to clarify type of BRCA analysis available and which one to use"
2. "It borders on the criminal that Myriad Lab was able to patent this gene and to be able to charge the exorbitant amount of money they are able to get for this testing"
3. "Insurance coverage is still lousy"
4. "Should probably cover colaris testing as well"
5. "Can we receive the answers and/or source to read"
6. "I obviously don't know as much as I thought I did"

Knowledge Score:

An overall knowledge score was calculated for each participant. Each correct answer received one point value, with a maximum of 20 total points. The average score attained by all respondents was 11.28 (56.4%), with a range of 0-18 total points. The median knowledge score was calculated for each of the practice settings. Gynecologic oncology (n=3) was the highest scoring group with a median score of 17(85%). Reproductive endocrinology was the next highest group (n=2) with a median score of 14.5(72.5%). Urogynecology (n=3) had a median of 12 (60%), Ob/Gyns (n=69) had a median of 11 (55%), gynecologist only (n=3) had a median score of 10 (50%), and MFM (n=2) had the lowest median score of 9(45%).

An arbitrary cut off was set at 70% for knowledge score and respondents were subsequently grouped into “high scorers” (above 70%) and “low scorers” (below 70%). The majority (69.6%, n=48) of Ob/Gyns were “low scorers”. Again the high and low scorers were stratified by practice. All of the gynecology only, MFMs, and urogynecologists surveyed were in the “low scorers” category. All of the gynecologic oncologists and reproductive endocrinologists surveyed were in the “high scorers” category.

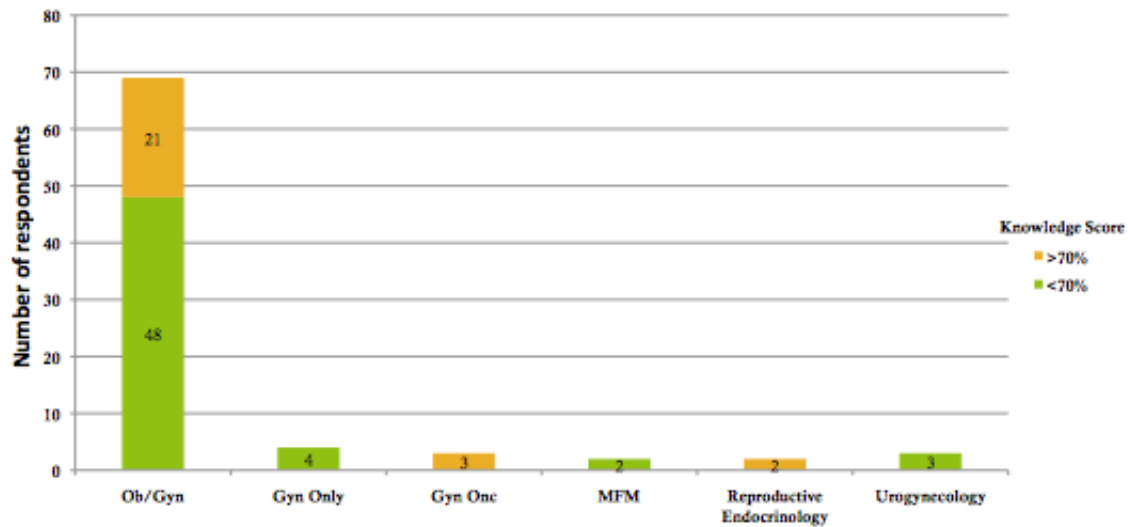


Figure 20: “High scorers” (>70%) and “low scorers” (<70%) by practice.

Stratification between “high and low scorers” and practice setting showed that 67.9% (n=38) of those in the private practice were “low scorers”. Similarly,

70.4% (n=19) of respondents in the academic institution practice setting were found to be “low scorers”. These distributions were not statistically significant ($p=0.82$).

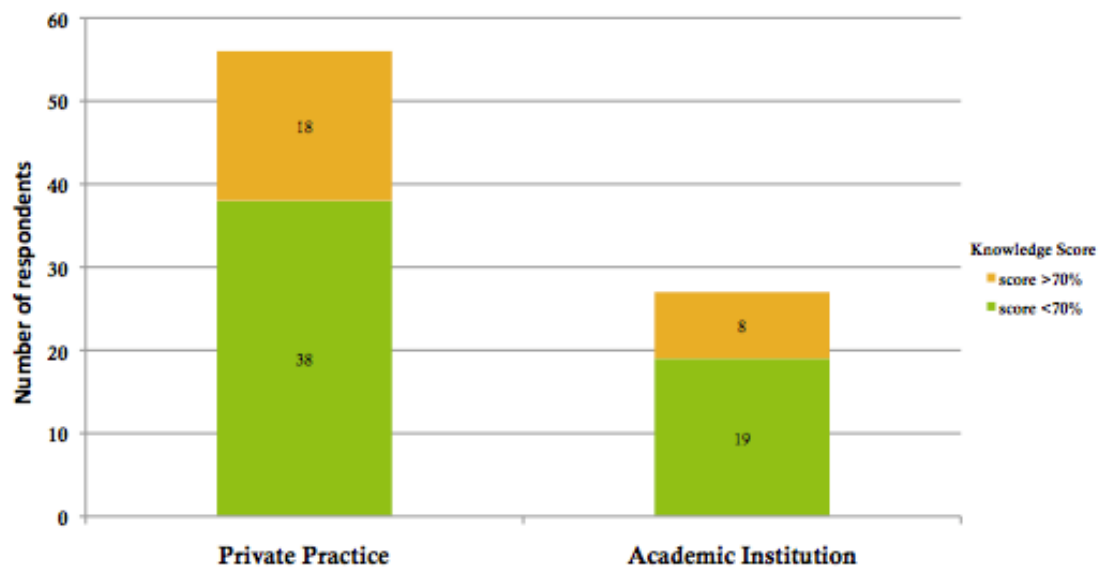


Figure 21: “High scorers” (>70%) and “low scorers” (<70%) by practice setting.

Both knowledge score and “high scorers” were evaluated with comparison to years since the completion of the respondents’ primary residency. A linear regression between overall knowledge score and years since completion of residency demonstrated a significant decrease in knowledge over time (β coefficient = -0.082, $p=0.032$). Despite the significant trend, there was considerable variability in knowledge score over time since residency and these two variables were poorly correlated ($r=-0.24$). Furthermore, a logistic regression performed between “high scorers” and the years since respondents’ completion of primary residency, found a 0.95 odds ratio (95% CI: -0.156 to -0.007), i.e. for every unit increase in years since primary residency, the odds of being a “high scorer” decrease by 5%.

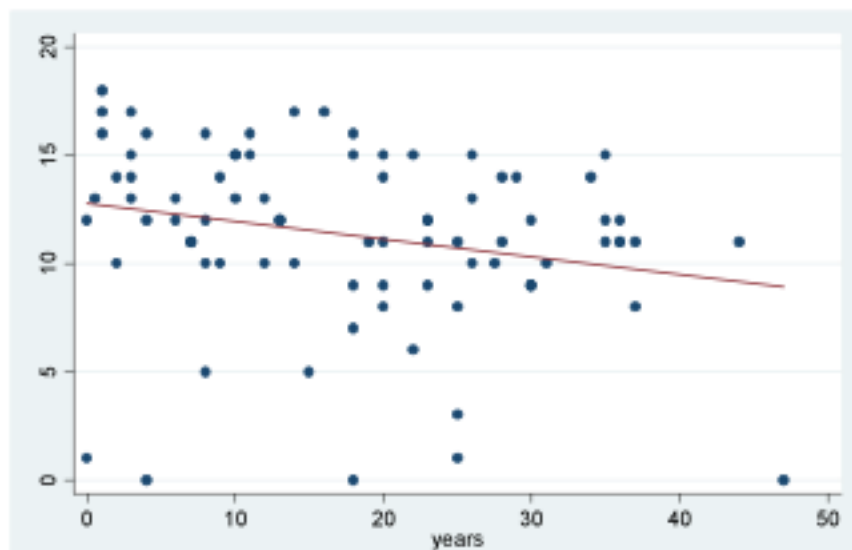


Figure 22: Years since the completion of residency (x-axis) vs. Knowledge score (y-axis)

A regression between “high scorers” and the number of patients seen was not statistically significant ($p=0.273$). About two-thirds of respondents (68.8%, $n=11$) that indicated they saw fewer than fifty patients in a typical week were found to be “low scorers”. 65.8% ($n=23$) of respondents that indicated they saw between 51-100 patients were found to be “low scorers”. The majority (81%, $n=17$) of respondents that indicated they saw between 101-150 patients were found to be “low scorers”. Sixty percent ($n=3$) of respondents that indicated they saw between 151-200 patients were found to be “low scorers”, while all (100%, $n=3$) respondents that indicated they saw over two hundred patients were found to be “low scores”.

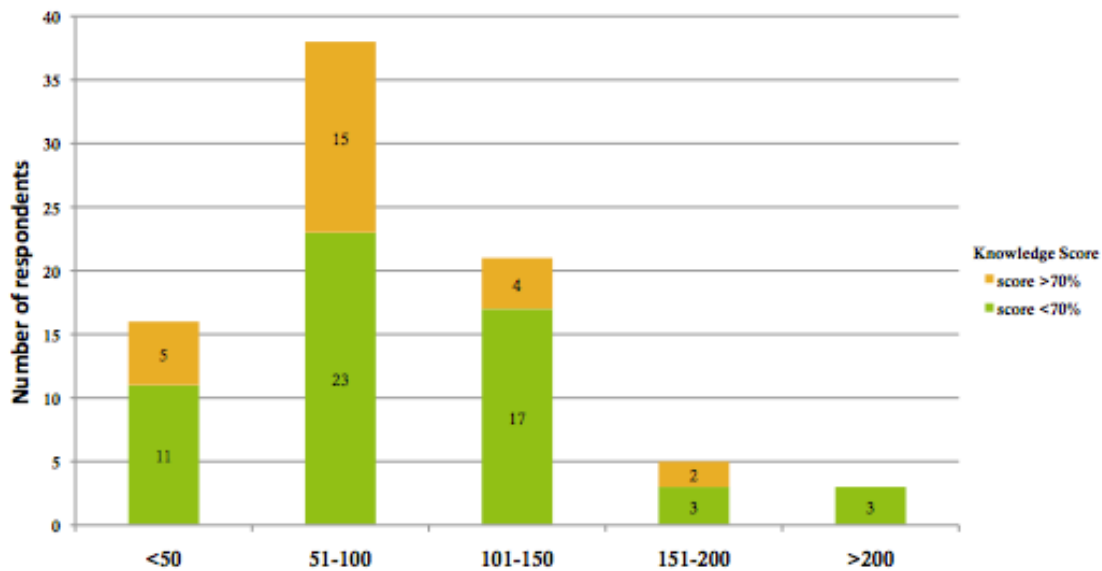


Figure 23: “High scorers” (>70%) and “low scorers” (<70%) by the number of patients seen in the outpatient setting in an average week.

A linear regression between knowledge score and comfort in identifying patients demonstrated a non-significant decrease of 0.2% for every unit increase in comfort level (β coefficient = -0.20, $p=0.617$). High scorers and low scorers were also stratified by comfort. Three quarters (75%, $n=6$) stated they were very uncomfortable and were found to be “low scorers”. Similarly 66.67% ($n=2$) of respondents that stated they were uncomfortable and 71.4% ($n=5$) of respondents that stated they were uncertain with regards to comfort were found to be “low scorers”. About three quarters (70.2%, $n= 33$) of respondents that indicated they

were comfortable and 58.8% (n=10) of respondents that indicated they were very comfortable were found to be “low scorers”, answering less than 70% of knowledge based questions correctly on the survey.

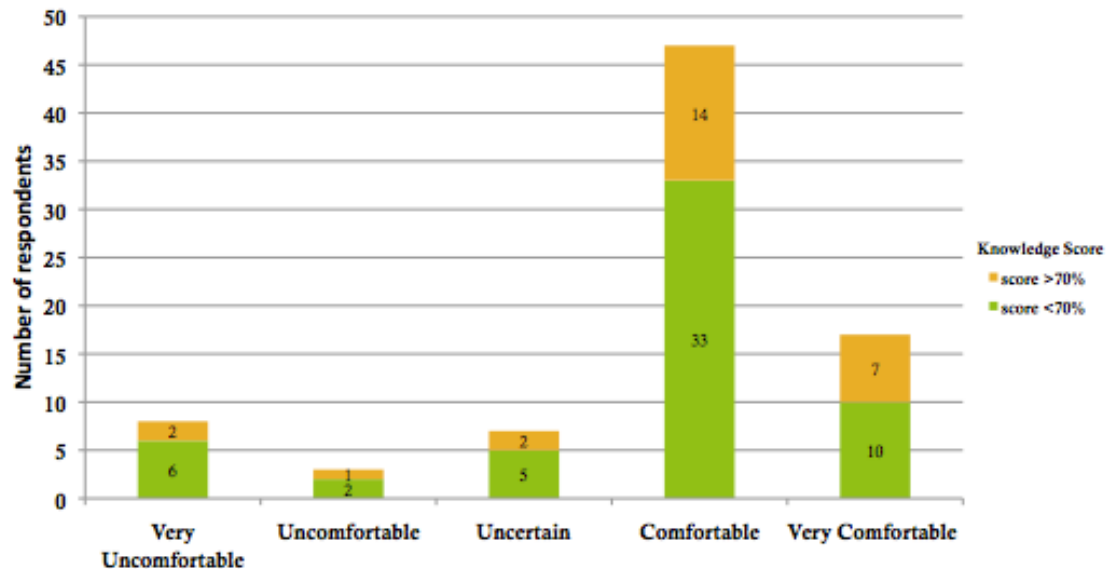


Figure 24: “High scorers” (>70%) and “low scorers” (<70%) by the respondents reported level of comfort in identifying patients that may be at an increased risk of carrying a *BRCA* mutation.

A chi squared test was performed between “high and low scorers” in the knowledge portion of the survey and reported referral to a genetic counselor. No statistically significant difference was found ($p=0.486$). About three quarters, 72.1% (n=31), of respondents that stated they would refer to a genetic counselor after identifying a patient at risk for having a *BRCA* mutation were “low scorers”.

Furthermore, 65% (n=26), of respondents that would not refer to a genetic counselor for further assessment and possible BRCA testing were “low scorers”.

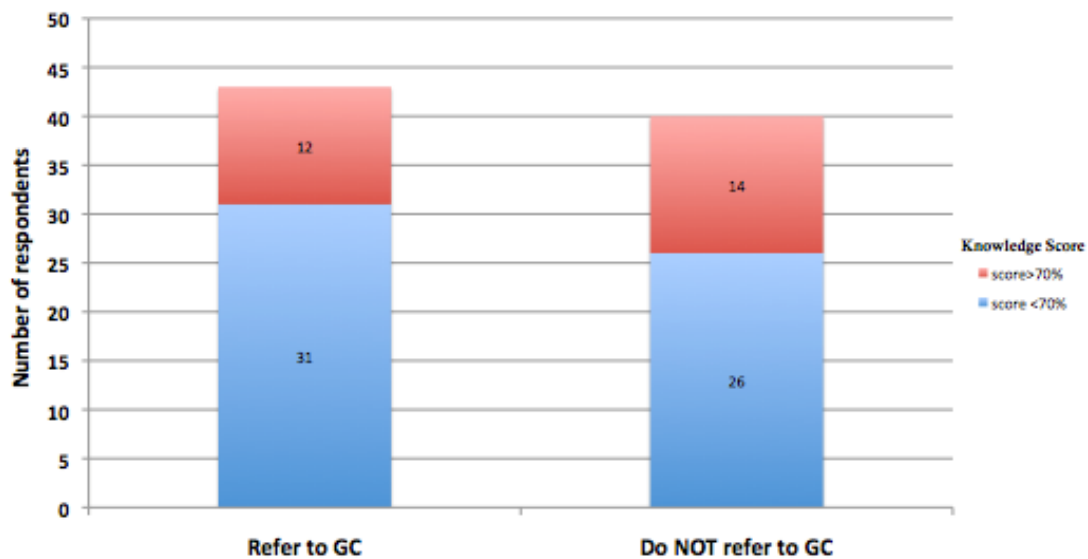


Figure 25: “High scorers” (>70%) and “low scorers” (<70%) by the respondents reported referral patterns to a genetic counselor after identifying a patient that may be at increased risk for carrying a BRCA mutation.

Similarly when evaluating “high and low scorers” by those respondents that would initiate a discussion and order testing themselves, 69.2% (n=27) of respondents that chose this option were found to be low scorers. A chi-squared test was performed and found to not be significant between the two groups (p=0.918).

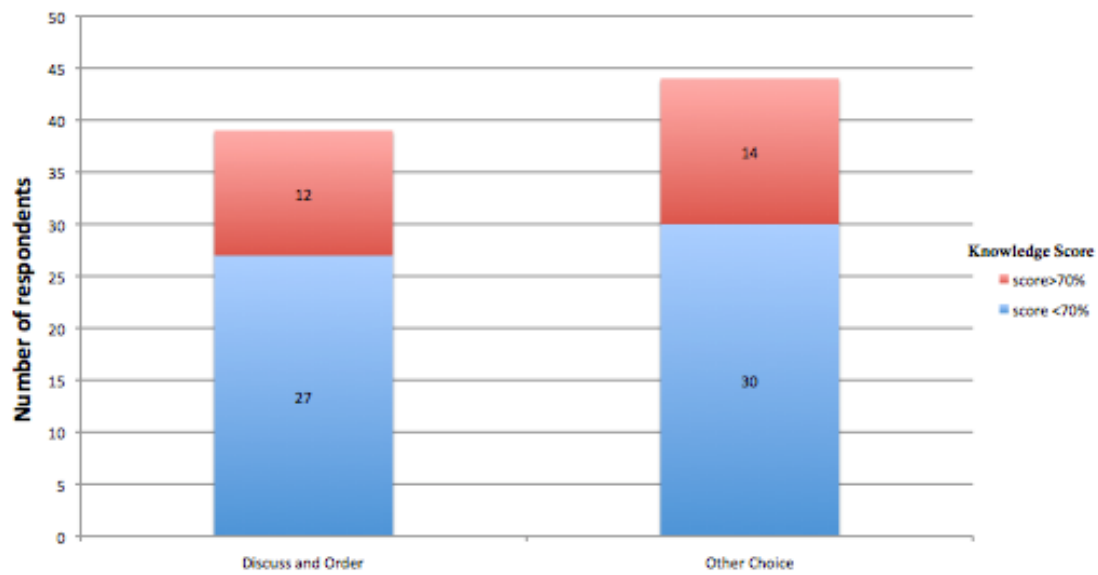


Figure 26: “High scorers” (>70%) and “low scorers” (<70%) in comparison to the respondents reported pattern of discussing HBOC themselves and ordering genetic testing after identifying a patient that may be at increased risk for carrying a *BRCA* mutation. “Other choice” includes: refer the patient to their PCP, refer the patient to a genetic counselor, refer the patient to another specialist, do nothing as it is not important to patient management, or other.

Ordering genetic testing:

The majority (73.7%, n=14) of respondents that indicated they typically never order genetic testing indicated that they did not know what type of testing would be most appropriate for an Ashkenazi Jewish woman with a known familial mutation (Figure 27). One individual (5.3%) in this category indicated that they would order comprehensive *BRACAnalysis*®, two (11.8%) correctly indicated they would order multisite *BRACAnalysis*®, one (5.3%) indicated they would order single site *BRACAnalysis*®, and one (5.3%) indicated they would order *BRACAnalysis*® large rearrangement testing (BART). The majority (54.3%, n=19) of

participants that indicated that they rarely (<1 time/month) order genetic testing responded that they did not know what type of testing would be most appropriate. Eight individuals (22.9%) in this category indicated that they would order comprehensive *BRACAnalysis*®, six (17.1%) indicated they would order single site *BRACAnalysis*®, two (5.7%) indicated they would order *BRACAnalysis*® large rearrangement testing (BART), while no individuals chose the correct response of multisite *BRACAnalysis*®. Of the eleven respondents that indicated that they sometimes (1-2 times/month) order genetic testing, the majority (36.4%, n=4) of respondents incorrectly identified comprehensive *BRACAnalysis*® as the most appropriate testing option for the aforementioned patient. One individual (9.1%) correctly indicated that they would order multisite *BRACAnalysis*®, while three (27.3%) indicated single site *BRACAnalysis*®, one (9.1%) indicated they would order *BRACAnalysis*® large rearrangement testing (BART), and two (18.1%) respondents indicated that they did not know what type of testing would be most appropriate. Of the five respondents that indicated that they often (3-4 times/month) order genetic testing, the majority (80%, n=4) incorrectly identified single site *BRACAnalysis*® as the most appropriate testing option, while only one individual (20%) correctly indicated that they would order multisite *BRACAnalysis*®. No other testing types were chosen by respondents in this category. For those respondents that indicated that they order genetic testing on a regular basis (≥ 5 times/month),

the majority (40%, n=2) incorrectly identified single site *BRACAnalysis*® as the most appropriate testing option, while only one individual (20%) correctly indicated that they would order multisite *BRACAnalysis*®, one individual (20%) indicated they would order comprehensive *BRACAnalysis*®, and one individual (20%) indicated they would order *BRACAnalysis*® large rearrangement testing (BART). There were no respondents in this category that indicated that they did not know which testing would be most appropriate. Finally, there were three individuals that previously did not indicate how often they ordered testing. Of these individuals the majority (66.7%, n=2) indicated that they would order comprehensive *BRACAnalysis*®, while the other respondent (n=33.3%) indicated that they would order single site *BRACAnalysis*®. Of all the respondents across the categories from never ordering genetic testing to ordering genetic testing on a regular basis only five individuals correctly identified that multisite *BRACAnalysis*® would be the most appropriate test for an Ashkenazi Jewish woman with a known familial mutation (Figure 19).

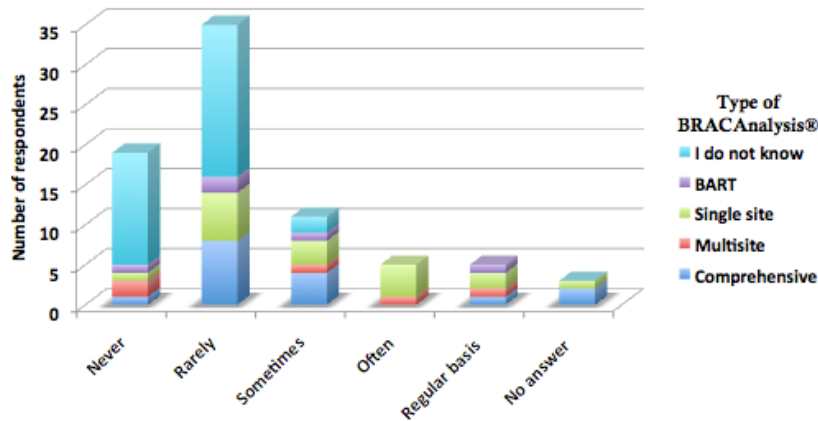


Figure 27: Analysis of the respondents reported frequency of ordering genetic *BRCA* testing by answer choice indicated for the most appropriate type of *BRCA* testing for an Ashkenazi Jewish patient with a known familial *BRCA* mutation

As shown in Figure 7 above, there was a five point likert scale for which respondents could indicate their level of comfort in identifying patients that are at an increased risk of carrying a *BRCA* mutation. Responses between comfort and frequency of ordering genetic testing was further evaluated (Figure 28). Of the eight respondents that indicated that they were very uncomfortable with identifying patients at risk for carrying a *BRCA* mutation, the majority (75%, n=6) indicated that they rarely ordered genetic testing. One respondent (12.5%) indicated that they sometimes (1-2 times/month) order genetic testing, while another respondent (12.5%) indicated that they order genetic testing on a regular basis (≥ 5 times/month). All respondents that indicated they were uncomfortable (n=3) also indicated they never order genetic testing. There were seven respondents that indicated they felt uncertain about their level of comfort in identifying patients at risk for carrying a *BRCA* mutation. Of those respondents, the majority (42.9%, n=3)

indicated that they never order genetic testing, while two (28.6%) indicated that they rarely order genetic testing, one (14.3%) indicated that they sometimes order genetic testing, and one (14.3%) respondent chose not to respond. The majority of respondents (n=47) indicated that they were comfortable with identifying patients at risk for carrying a BRCA mutation. Of these respondents, eight (17%) indicated that they never order genetic testing, twenty four (51.1%) indicated that they rarely order genetic testing, six (12.8%) indicated that they sometimes order genetic testing, three (6.4%) indicated that they often ordered genetic testing, two (4.3%) indicated that they order genetic testing on a regular basis, and four (8.5%) chose not to respond. Finally, of respondents that indicated they were very comfortable (n=17) with identifying patients at risk for carrying a BRCA mutation only two (11.8%) indicated that they ordered genetic testing on a regular basis. Four (23.5%) indicated that they never ordered genetic testing, four (23.5%) indicated that they rarely ordered genetic testing, four (23.5%) indicated that they sometimes ordered genetic testing, two (11.8%) indicated that they often ordered genetic testing, and one (5.9%) chose not to respond.

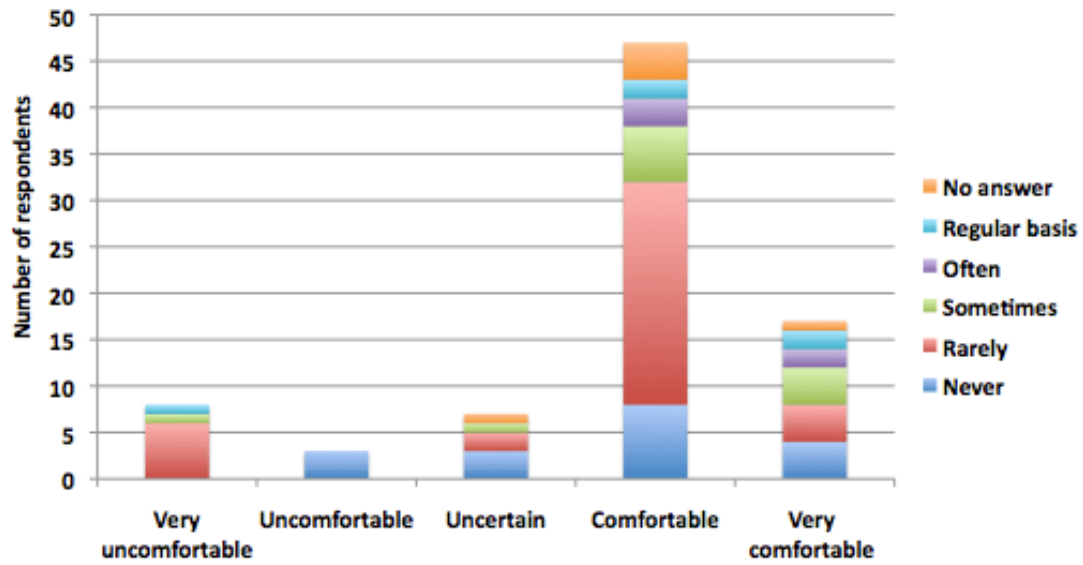


Figure 28: Analysis of the respondents reported comfort level and frequency of ordering genetic *BRCA* testing.

DISCUSSION

In this study, Houston area obstetricians and gynecologists were asked about their knowledge, attitudes, and utilization of *BRCA* testing in their practices. In 2009 the American Congress of Obstetricians and Gynecologists (ACOG) released a practice bulletin, which identified the necessity of evaluating a patient's risk for HBOC as a routine part of obstetric and gynecologic practice [59]. The purpose of this study was to capture the current knowledge of both HBOC and *BRCA* testing among obstetricians and gynecologist in the Houston area, to assess if and how they are utilizing *BRCA* testing, and to determine what they feel their role is with regards to *BRCA* testing.

Study population:

According to the 2008 Socioeconomic Survey of ACOG Fellows our study is representative of the current membership with regards to gender and years in practice [66]. The 2008 survey found that 44.6% of members were female, with average years in practice of 17.59. Furthermore, the 2008 Socioeconomic Survey was consistent with our findings of practice setting indicating that 73.6% of members work in a private practice with an average of 6.3 physicians on site [66]. Our study found that 67.5% of respondents

reported working in a private practice setting with a slightly higher average of 9.36 physicians in their practice.

However, in this study the majority of respondents (83%) identified their primary practice setting as general obstetrics and gynecology, while the national survey found 67.9% of the total members identifying themselves in this group. Similarly while our study population reported 5% to be gynecologists only, 4% gynecologic oncologists, 2% were maternal fetal medicine specialists, 2% were reproductive endocrinologists, and 4% were urogynecologists; the national survey reports 17.9% gynecologists only, 1.9% gynecologic oncologists, 6.1% maternal fetal medicine specialists, 2.8% reproductive endocrinologists, and .9% urogynecologists [66]. In this way, it seems that the population surveyed was not representative of the subspecialties found in the national reported members of ACOG, which can most likely be attributed to our small sample size.

Perceived role and reported comfort in identifying at risk patients:

One of the study aims was to determine what obstetricians and gynecologists feel their role is in regards to *BRCA* testing. An overwhelming 92.7% of respondents indicated that they believe that identifying patients at risk for HBOC is one of their practice responsibilities.

Furthermore, the majority (84.3%) of respondents indicated that Ob/Gyns have the primary responsibility of identifying patients at risk of carrying a *BRCA* mutation (Figure 9). This is supported by the majority of responses received when physicians were asked to indicate what they would do after identifying a patient at risk for carrying a *BRCA* mutation. Respondents indicated that once a patient at an increased risk of carrying a *BRCA* mutation is identified, they would typically either discuss HBOC and ordering *BRCA* testing themselves (53%) and/or refer the patient to a genetic counselor (48.2%).

Our study shows that the majority (77%) of respondents felt very comfortable or comfortable in identifying patients who are at an increased risk of carrying a *BRCA* mutation. A study in 2008 reported a similar level of comfort among 82 physicians, of which 18.3% reported gynecology as their area of practice. This study used a 5-point scale, with 5 being the most comfortable, to measure the group's comfort when identifying potential at risk patients for a hereditary cancer syndrome and discussing genetic information. Their overall average comfort score was found to be 3.7 [67]. In our study a similar 5-point likert scale ranging from very uncomfortable to comfortable was used to assess how Ob/Gyns felt with identifying patients who are at an increased risk of carrying a *BRCA* mutation. Were we to assign

a 1-5 point value to each of our likert scale answer choices, giving very uncomfortable a 1 point value, and very comfortable a 5 point value, we could then calculate that our study found an overall comfort level of 3.85, indicating that the results seen in our study are in line with previous studies that evaluated comfort in identifying patients that may be at risk of carrying a *BRCA* mutation.

It was initially hypothesized that those that stated a higher level of comfort would have higher knowledge of HBOC and *BRCA* testing to support their attitude. However, this study indicates that there is no positive correlation between feeling comfortable identifying patients at an increased risk and knowledge of HBOC and *BRCA* testing. In comparing the knowledge score of each participant with regards to reported comfort in identifying patients at risk (Figure 24), it is seen that the difference in knowledge score is not statistically significantly different between respondents that indicated they were very uncomfortable, uncomfortable, uncertain, comfortable, and very comfortable. Furthermore, the majority (58.8%) of physicians who reported feeling very comfortable in identifying patients at an increased risk of carrying a *BRCA* mutation were found to be low scorers (<70% accuracy) in the knowledge portion of the survey.

Similarly, there was no statistical significance seen between comfort of identifying at risk patients and the reported frequency of ordering genetic testing. A quarter (25%) of respondents that stated they were very uncomfortable with identifying patients that may be at an increased risk for carrying a *BRCA* mutation indicated that they ordered genetic testing at least 1-2 times per month or more. About a third (35.3%) of respondents that stated they were very comfortable with identifying patients that may be at an increased risk for carrying a *BRCA* mutation indicated that they ordered genetic testing at least 1-2 times per month or more.

The lack of a positive correlation seen between reported comfort in identifying at risk patients, knowledge of HBOC/ *BRCA* testing, and frequency of ordering genetic testing is clinically significant for practicing physicians. These results indicate that respondents that felt very comfortable or comfortable in identifying patients at a high risk for carrying a mutation in *BRCA1/2* were just as likely as those respondents that indicated they were very uncomfortable or uncomfortable to answer below 70% of questions correctly on the knowledge portion of the survey. Furthermore, these results show that respondents indicate they are ordering testing even though they may not have the knowledge to appropriately identify patients who are truly at an increased risk for carrying a *BRCA* mutation. This raises two areas of

concern. First, that they are ordering testing on patients who may not truly be at an increased risk for carrying a mutation, thus wasting health care dollars and increasing patient anxiety. Secondly, due to their lack of knowledge, they are likely not correctly identifying patients who would benefit from *BRCA* testing, thus patients who have HBOC are likely going unidentified and therefore not receiving the screening/ surveillance and risk reductions options that could potentially prevent them from developing life threatening cancers.

The US Preventive Services Task Force (USPSTF) issued a practice bulletin, which estimates that about 2% of women would meet the definition for a patient at an increased risk of carrying a *BRCA* mutation [58]. With the USPSTF bulletin in mind, we would expect that physicians that report seeing between 51-100 patients per week to see about 4-8 patients at risk for HBOC and thus carrying a mutation per month; acknowledging that this is just an estimate as some patients may be seen for a follow-up visit in the same week and thus counted twice. However, this study found that only about 10% of respondents indicate that they see patients who they suspect may be at an increased risk for HBOC on a regular basis (>5 times/month) (Figure 11). One possible reason for this discrepancy in the data may be that physicians are not in fact able to identify those patients that are at an increased risk of

carrying a *BRCA* mutation. A previous study in 2003 of 172 gynecologists further supports this conclusion. The 2003 study found that the majority of participants felt comfortable with discussing HBOC with patients that are at an increased risk of carrying a *BRCA* mutation, however, a third of participants also indicated some uncertainty in their basic genetic knowledge [63]. Furthermore, in our study, the majority of respondents (69.2%) that indicated that they would discuss HBOC and order *BRCA* testing had a knowledge score below 70% (Figure 26). Another previous study of 351 primary care physicians found similar results in that there was no association between higher knowledge about breast cancer and having a discussion about risk or ordering *BRCA* genetic testing [68]. This study supports an ongoing trend of physician reported confidence in identifying patients at risk of carrying a *BRCA* mutation, without adequate knowledge to support such attitudes.

Utilization of *BRCA* testing:

About a quarter (26.4%) of respondents indicated that they order genetic testing at least 1-2 times per month or more. Although the majority of our respondents indicated that they do not regularly see a patient at increased risk for HBOC, receive questions from patients about *BRCA*1/2

testing, or order *BRCA* testing, some report that they do (Figure 11). About 8% of respondents reported to see a patient at increased risk for HBOC, 3.6% reported to receive questions about *BRCA1/2* testing, and 6% report to order *BRCA* testing in a typical month.

There was no significant correlation between the number of patients seen per week and the frequencies that physicians report to see patients an increased risk for HBOC, to receive questions from patients regarding *BRCA* testing or to actually order *BRCA* testing. One would have assumed that as the number of patients seen in practice increased there would have been an increase in the number of patients that would be identified as being at an increased risk for HBOC, as well as an increase in the number of patients asking question about *BRCA1/2* testing, and subsequently the frequency of ordering *BRCA* testing. The lack of correlation between these reported practice frequencies and patient loads points to the possibility of other influencing factors. One can conclude that given the overall poor knowledge in regards to HBOC and *BRCA* testing identified through this study, physicians may not feel that they have patients at an increased risk and therefore do not order *BRCA* testing because they are unable to accurately identify such patients.

When comparing respondents that ordered genetic testing at least 1-2 times per month or more with the accuracy of identifying which test would be the most appropriate for an Ashkenazi Jewish woman whose family has a known mutation in a *BRCA* gene, there were only three (14.3%) respondents who were able to correctly identify that multisite *BRCAAnalysis*® was the most appropriate for the given patient. Even with a known family mutation, individuals of Ashkenazi Jewish ancestry should also be offered multisite *BRCAAnalysis*® due to the high carrier frequency of 1/40 found in the Ashkenazi Jewish population. The multisite *BRCAAnalysis*® will cover the three most commonly found mutations that are present in this population. The very low percentage of physicians who correctly answered this question demonstrates the need for more education about which testing is most appropriate based on patient presentation and risk factors. One of the respondents clearly echoed this conclusion with a written comment stating that the survey: “points out need to clarify type of *BRCA* analysis available and which one to use.”

Another goal of this study was to understand what a physician would do once he/she identified a patient that was at an increased risk of being a *BRCA* carrier. The majority of respondents (53%) indicated that they would discuss HBOC and order *BRCA* genetic testing themselves (Figure 12).

However, as previously discussed, the majority of respondents in our study also indicated that they rarely (<1 time per month) order genetic testing (Figure 11).

While most (80.7%) respondents indicated that the cost of testing a greatest barrier that prevented them from ordering *BRCA* genetic testing, just under half (44.6%) felt that the possibility of insurance discrimination was another barrier preventing them from ordering this testing (Figure 10).

Brandt et al (2008) found that about a third of their respondents also cited insurance discrimination as a barrier in ordering genetic testing. In 2008, the Genetic Information Nondiscrimination Act (GINA) was passed, which protects all individuals and their families from being discriminated, both in the workplace and by medical insurance companies, based on genetic information. Education and awareness of GINA, therefore, could ultimately eliminate this perceived barrier.

Just under half (48.2%) of physicians surveyed in this study indicated that they would refer a patient with an increased risk of carrying a *BRCA* mutation to a genetic counselor. Two previous studies found similar incidences of referral to genetic counselors. A 2003 study of 172 German gynecologists found that 58% of gynecologists surveyed recommended genetic counseling to their patients, while only 34% had referred their

patients to a genetic counselor within the past twelve months[63]. Another study found that of the 214 physicians surveyed, 51% had referred to a genetic counselor after identifying a patient at risk for HBOC [69]. Referring to a genetic counselor was also further evaluated with relation to knowledge. In our study, the majority of respondents (72.1%) that indicated that they would refer to a genetic counselor had a knowledge score below 70% (Figure 25). It can be concluded that respondents that would refer to a genetic counselor may see the benefits of utilizing a cancer genetic counselor that can assist with discussing hereditary cancer and facilitate genetic testing. However, identifying which patients may be at an increased risk of carrying a *BRCA* mutation and therefore benefit from a referral to a genetic counselor is the first step in order to utilize this service.

Knowledge regarding HBOC and *BRCA* testing

Our study shows that the overall knowledge of Ob/Gyns surveyed is poor. An overall knowledge score was calculated for each participant. Out of a total of twenty possible points, the mean for all respondents (n=83) was 11.28 with a range of 0-18 points. This point value corresponds to a mean

accuracy rate of 56.4%. No respondents answered all of the knowledge questions correctly. Not surprisingly, the highest scoring group was the gynecologic oncologists as one would assume they regularly see ovarian cancer patients in their practices. A similar European study, which evaluated 243 primary care physicians' knowledge of HBOC via survey, found that the Ob/Gyns in their study population had a lower average knowledge score of 38.6%. Oncologists in this same population were shown to have the highest knowledge with regards to HBOC with an average 68.6% accuracy rate, which is consistent with our study findings [70].

Knowledge regarding cancers that are associated with HBOC was generally good across this study, with one notable exception. Respondents could accurately indicate that both breast and ovarian cancers are associated with HBOC, with 95.2% and 78.3% accuracy, respectively. However, only 24.1% of respondents could correctly identify that prostate cancer is associated with HBOC. The risks of developing prostate cancer for males who carry a *BRCA* mutation, specifically a *BRCA2* mutation, can be as high as 20%. Typically these cancers will be diagnosed at a younger age than in the general population. Increased awareness of the association of prostate cancer with HBOC is another area where education is needed. Another area suggesting the need for increased education was highlighted when

evaluating the respondent's knowledge of the lifetime risks for developing both breast and ovarian cancers for a woman with a known *BRCA* mutation. About half of respondents could accurately indicate that a woman's chance for breast cancer may be as high as 88% and her chance for ovarian cancer may be as high as 44% if she were a carrier of a *BRCA* mutation. While, about 40% of respondents underestimated a woman's risk for developing breast cancer and about 20% underestimated a woman's risk for developing ovarian cancer if she were a carrier of a *BRCA* mutation.

A statistically significant difference was found between the knowledge score and the years since completion of the respondent's primary residency. Our data identified a decrease of approximately one point in the overall knowledge score for every ten years since the completion of residency. A study in 2010, which examined 157 Ob/Gyn residents' knowledge of HBOC and Lynch Syndrome, found that their knowledge was slightly increased as compared to that which was found in our survey [71]. In this 2010 study, 51% of residents could accurately identify the autosomal dominant pattern of inheritance of HBOC, 97% correctly identified ovarian cancer as being associated with HBOC, and 51% incorrectly identified that colon cancer is associated with HBOC. Our study shows slightly decreased knowledge in that: 49% of respondents could identify the autosomal

dominant mode of inheritance of HBOC, 78.3% correctly identified ovarian cancer as a being associated with HBOC, and 53% incorrectly identified that colon cancer is associated with HBOC. According to our study those individuals still in residency should have a slightly increased knowledge score. Another study in 2000, which surveyed 564 ACOG fellows, further supports this conclusion. This study found that younger physicians were more likely to accurately answer questions in the knowledge portion of the survey, which focused on both hereditary cancers and general genetic information [72].

One possible argument could be made that residents score higher as compared to board eligible/certified Ob/Gyns because of the residents' connection with an academic setting. However, no significance was found in our study to support this conclusion. When the knowledge score in this study was arbitrarily stratified as "high scorers" (above 70% correct) and "low scorers" (below 70% correct) it was seen that there was no significance between the primary practice setting and knowledge. In this way it appears that those respondents that practiced at an academic institution did not show an added benefit that may have otherwise been presumed based on the connection with an academic institution, in

comparison to those that indicated they primarily practiced in a private practice.

Strengths and Limitations:

Since the ACOG practice bulletin in 2009, there have been no studies, to our knowledge, that have addressed whether or not OB/ Gyns are in agreement with these practice guidelines and how well they are adhering to them. This study seems to be the first study that has focused on the attitudes, utilizations, and knowledge of HBOC and *BRCA* in US Ob/Gyns. Through the knowledge portion of the survey, we were able to identify areas that need further attention for universal benefit for both physicians and patients. These areas include both identifying patients that may be at an increased risk for HBOC and identifying cancers that are associated with HBOC. This study also captured the attitudes of physicians with regards to their role in identifying patients and in barriers that may prevent them from ordering *BRCA* genetic testing. Indicating that the majority of patients feel comfortable with identifying patients that may be at an increased risk of carrying a *BRCA* mutation and that perceived barriers to *BRCA* genetic testing include the cost of testing and the fear of insurance discrimination.

While our sample of Ob/Gyns reached across various hospital systems in the Houston area, the overall sample size was small (n=83). Due to the small sample size, there was not an adequate amount of respondents that fell into each subspecialty. In this way the study was limited in terms of the ability for further stratification and analysis by specialty. While this study's population is representative of the greater Houston area, one may not be able to generalize these results to other areas of the country. Furthermore, all of the factors measured in this study were based on the self-reporting of our respondents, and may not accurately reflect true practice behaviors. Another possible limitation is the presence of selection bias that may have resulted due to the voluntary and thus self-selection of the study sample from our target population. It is possible that the physicians who responded and are part of our study sample may have a heightened interest in HBOC. If this were the case, then the findings reported in this study may be skewed towards those physicians who feel that identifying at risk patients is important, those that may utilize testing more often, and those that may have a higher amount of knowledge than their peers who chose not to complete our survey. It is quite possible that results would actually be less favorable in an unbiased sample. Another limitation of this study is that two formats of the survey that were distributed. While some questions clearly stated to

choose only one answer, some participants with hard copy versions of the survey chose more than one answer. Moreover, participants with the hard copy version were free to go back to previous questions to change their answers or write in answers. The online version prevented participants from going back to previously answered questions and allowed limited areas for write in answers. Finally, the survey distributed was not a validated survey, as it was created specifically for this study.

Final Conclusions and Future Studies:

This study shows that the majority of Ob/Gyns feel that it is their role to identify patients that may be at an increased risk of having a *BRCA* mutation. Overall, reported comfort in identifying patients that may be at and increased risk of having a *BRCA* mutation is high. Most Ob/Gyns would agree that they are comfortable or very comfortable with this task. Furthermore, most Ob/Gyns report that they would discuss HBOC and order *BRCA* testing themselves once they have identified patients that may be at an increased risk. However, only about a quarter of participants indicated that they order *BRCA* genetic testing one to two times per month, or more. Finally, this study demonstrates that the overall knowledge of HBOC and *BRCA* testing is poor. Thus, this study points out the need for more

education regarding HBOC, molecular *BRCA* testing, and strategies for identifying patients that may be at risk for having a mutation in a *BRCA* gene. Furthermore, it emphasizes the importance of raising awareness to current practice guidelines and recommendations that can assist obstetricians and gynecologist to better identify and manage patients that may be at an increased risk of having HBOC, which could have otherwise been overlooked.

Future directions of this study are to replicate the study across a larger population of Ob/ Gyns to capture the attitudes, utilization, and knowledge across a more diverse population. An education module with pre and post testing could also be implemented to capture the significance of education about HBOC and *BRCA* testing. Furthermore, another study to examine how physicians are identifying patients that are at an increased risk may help explain the reported level of comfort in identifying patients at an increased risk of having a *BRCA* mutation that was seen in this study. Another direction that could be taken is to adapt the survey questions created here to analyze other physician's knowledge about different hereditary cancers or genetic conditions. Results of a survey like this could prove beneficial in demonstrating the need for more genetics training, with the ultimate goal of providing better patient care.

APPENDIX A

Part I.

1. What is your gender?
 - ☐ Male
 - ☐ Female

2. How many years has it been since the completion of your primary residency?

3. Are you board certified in Obstetrics and Gynecology?
 - ☐ Yes
 - ☐ No

4. Are you boarded in any sub-specialty?
 - ☐ No
 - ☐ Yes, please indicate which one(s) below:
 - i. Gynecologic Oncology
 - ii. Maternal Fetal Medicine
 - iii. Reproductive Endocrinology
 - iv. Urogynecology
 - v. Other: _____

5. Which of the following best describes your area of practice?
 - ☐ General Obstetrics and Gynecology
 - ☐ Gynecology only
 - ☐ Obstetrics only
 - ☐ Gynecologic oncology
 - ☐ Maternal fetal medicine
 - ☐ Reproductive endocrinology
 - ☐ Urogynecology
 - ☐ Other _____

6. What is your primary practice setting? **Choose all that apply.**
 - ☐ Private Practice- please indicate the number of **Ob/Gyns** in your group _____
 - ☐ Academic Institution/University Medical Center
 - ☐ Other _____

7. On average, how many patients do you see in the **outpatient setting** per **week**?
 - ☐ <50
 - ☐ 51-100

- ☐ 101-150
- ☐ 151-200
- ☐ >200



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Part II.

1. How comfortable do you feel identifying patients who are at an increased risk of carrying a BRCA mutation?

☐ ☐ ☐ ☐ ☐
 Very Uncomfortable Uncomfortable Uncertain Comfortable Very Comfortable

2. Please indicate your answer choice by marking the appropriate column below:

	Yes	No
That it is one of your practice responsibilities to identify patients who may carry a mutation in BRCA1/2?		
That your management of a patient would change if you knew she carried a mutation in BRCA1/2?		

3. Who do you feel has the **primary** responsibility of identifying patients who may be at an increased risk of carrying a mutation in BRCA1/2?

- ☐ Obstetrician/ Gynecologist
- ☐ General Practitioner/ Primary Care Physician
- ☐ Radiologist
- ☐ Oncologist
- ☐ Other _____

4. What barriers do you feel prevent you from ordering genetic testing of the BRCA genes?

Chose all that apply.

- ☐ Cost of the testing
- ☐ The possibility of insurance discrimination if patient is found to be a carrier
- ☐ Lack of patient interest/ uptake
- ☐ Time constraints in my clinic
- ☐ Lack of knowledge regarding which patients are eligible for testing
- ☐ I do not feel that I have any patients who are at an increased risk of having a BRCA mutation
- ☐ I do not feel that it is relevant/ important to the care of my patients

☐ Other _____



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Part III.

1. Please indicate your answer choice by marking the appropriate column below:

On average, how many times each <u>month</u> do you...	Never	Rarely (<1 time/mo)	Sometimes (1-2 times/mo)	Often (3-4 times/mo)	On a regular basis (≥ 5 times/mo)
See a patient that you suspect has an increased risk for HBOC?					
Receive questions from patients about the heredity of breast cancer?					
Receive questions from patients about BRCA1/2 testing?					
Initiate a conversation regarding genetic testing for BRCA1/2 with your patients?					
Order genetic testing for BRCA1/2?					
Refer a patient to a genetic counselor, or other specialist, in order to discuss genetic testing for BRCA1/2?					

2. If you identify a patient who you believe is at risk for carrying a mutation in BRCA1/2, what would you do?

- ☐ Discuss hereditary breast and ovarian cancer and order the testing yourself
- ☐ Refer the patient to their primary care physician for testing
- ☐ Refer the patient to a genetic counselor for risk assessment and possible testing

- ☐ Refer the patient to another specialist. Please specify which type of specialist:

- ☐ Nothing, because you do not feel that it would change your management of the patient

1. Which of the following patients would you consider at an increased risk for having a mutation in BRCA1 or BRCA2?	Yes	No
A patient who was diagnosed with breast cancer at 45 years but has no other family history of breast cancer?		
A patient whose mother was diagnosed with breast cancer at 60 years and whose maternal grandmother was diagnosed with breast cancer at the age of 70 years?		
A patient who was diagnosed with ovarian cancer at the age of 55 years?		



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- ☐ Other _____

Part IV.

1-2. Please indicate your answer choice by marking the appropriate column below:

A patient who is Ashkenazi Jewish and was diagnosed with breast cancer at the age of 60 years?		
A patient whose brother was diagnosed with breast cancer?		
A patient whose paternal grandmother was diagnosed with breast cancer at the age of 50 and whose paternal aunt was diagnosed with breast cancer at 49 years old?		
A patient whose paternal cousin was diagnosed with endometrial cancer at 45 and whose paternal aunt was diagnosed with colon cancer at 51?		
A patient who has a family member with breast cancer, regardless of age.		

2. Which of the following cancers are associated with BRCA mutations?	Yes	No
Breast cancer		
Colon cancer		
High grade serous or endometrioid ovarian cancer		
Mucinous ovarian cancer		
Prostate cancer		
Uterine cancer		
Fallopian tube cancer		

3. What is the lifetime risk for developing **breast** cancer for a woman who has a known BRCA mutation?

- ☐ Up to 22%
- ☐ Up to 44%
- ☐ Up to 88%
- ☐ Virtually 100%
- ☐ I do not know



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4. What is the lifetime risk for developing **ovarian** cancer for a woman who has a known BRCA mutation?

- ☐ Up to 22%
- ☐ Up to 44%
- ☐ Up to 88%
- ☐ Virtually 100%

☐ I do not know

5. What is the chance of a woman having a mutation in BRCA1/2 if she has a first degree relative with a known BRCA mutation?

☐ 0%

☐ 25%

☐ 50%

☐ 100%

☐ This is dependent upon whether it is a maternal or paternal relative

☐ I do not know

6. A woman can inherit a mutation in BRCA1/2:

☐ From her mother only

☐ From her father only

☐ From either her mother or her father

☐ These mutations are not typically inherited, it is most likely that the mutation started in the affected individual

☐ I do not know

7. What testing would you order for an Ashkenazi Jewish patient with a known familial mutation in BRCA1/2?

☐ Comprehensive BRAC Analysis

☐ Multisite BRAC Analysis

☐ Single Site BRAC Analysis

☐ BRAC Analysis Large Rearrangement Testing (BART)

☐ I do not know

Please provide us with any comments regarding this survey, identifying patients at risk for hereditary breast and ovarian cancer (HBOC) or BRCA testing:



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APPENDIX B

Research study (Survey) Regarding Obstetricians and Gynecologists knowledge, attitudes toward, and utilization of BRCA testing

You are invited to take part in a research project called, "Knowledge, attitudes toward, and utilization of BRCA testing," conducted by Salma Nassef, of the University of Texas Health Science Center. For this research project, she will be called the Principal Investigator or PI.

The purpose of this research study is to assess obstetricians and gynecologists' medical background, experience, and opinions regarding the utilization of BRCA testing for their patient population. This study is composed of multiple-choice questions, which we hope will allow us to better understand current practice regarding this topic. Space is available for additional comments should you find this necessary. There are no other alternative ways to participate in this study without filling out the survey below. There are no known risks for your participation in this study.

Completion of this anonymous survey is voluntary and for research purposes only. It should take less than 15 minutes to complete this survey. All responses are completely confidential, and you will not be personally identified in any reports or publications of this study. Data will be summarized and presented as part of a thesis project at The University of Texas Graduate School of Biomedical Sciences at Houston. By completing and submitting the questionnaire, you are implying consent to have your answers used and shared among collaborators for this study. There is no financial compensation for taking this survey.

Although the results of this study will be useful for doctors and other health professionals, there may be no direct benefit to you for participating in this study. You can refuse to answer or skip any questions or stop taking the survey at any time. Refusing to take part or stopping at any point during the survey will involve no penalty. If you decide to participate in the study, it is very important that you answer the questions as honestly as you can.

If you have any questions or concerns, please contact Salma Nassef or Cathy Sullivan, MS, CGC at 713-500-6381. Thank you very much for your input regarding this important issue.

Sincerely,

Salma Nassef
Genetic Counseling Student
UT Health Science Center at Houston
Graduate School of Biomedical Sciences
Principal Investigator

Cathy M. Sullivan, MS, CGC
Genetic Counselor/Clinical Instructor
UT Health Science Center at Houston
Department of Obstetrics, Gynecology and Reproductive Sciences
Committee Chair

Manju Monga, MD
Senior Faculty

Maternal Fetal Medicine
Department of Obstetrics and Gynecology
Baylor College of Medicine
Committee Member

Jon Gogola, MD
Chief of Staff Memorial Hermann Memorial City
Greater Houston Obstetrics and Gynecology
Associates, LLP
Committee Member



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VITA

Salma A. Nassef was born in Houston, Texas on August 2, 1987, to Mona Younes and Ahmed Nassef. After graduating from St. Agnes Academy, in Houston, Texas in 2005, Salma went on to the University of Houston Honors College to pursue a degree in health education. She graduated with summa cum laude in May 2009 with a Bachelor of Science in health education and minor in biology. She entered the University of Texas Genetic Counseling Program in the fall of 2010 and graduated with a Master of Science in Genetic Counseling in May 2012.