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Genetic Screening for Breast Cancer in the Primary Care Setting

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GENETIC SCREENING FOR BREAST CANCER IN THE PRIMARY CARE SETTING

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Abstract

The purpose of this project was to increase adherence to the U.S. Preventive Services Task Force and National Comprehensive Cancer Network guidelines for breast cancer screening and genetic testing. Screening for breast cancer risk factors including genetic testing helps reduce the incidence of breast cancer. A protocol was developed based on national clinical guidelines to increase screening and genetic testing for breast cancer. Provider responsibilities included screening all patients 18 and older for risks factors of breast cancer, referring patients with a significant risk based on the screening for genetic testing and providing referrals for genetic counseling once genetic testing was complete. One hundred fifty-four (47%) of the patients meeting inclusion criteria were screened with 25 (19%) having a positive screen. Fourteen (56%) patients with a positive screen opted for genetic testing, one patient was confirmed having a clinically significant mutation in the BRCA1 gene. One of the fourteen patients was identified as having a 35% remaining lifetime breast cancer risk and one patient was identified as having a non-clinically significant mutated gene. Three patients were referred to genetic counseling. One patient followed up with a genetic counselor. Ten (25%) patients meeting genetic testing criteria declined testing. BRCA gene mutations are associated with breast cancer as well as ovarian, melanoma, pancreatic, and prostate cancers. Providers and patients need additional education on the benefits of genetic testing in identifying patients at risk for breast cancer. Early detection and implementation of preventive measures can help reduce morbidity and mortality rates.

Keywords: breast cancer screening, genetic testing, BRCA mutation

Genetic Screening for Breast Cancer in Primary Care Setting

It is estimated that there will be 2,088,849 new cases of breast cancer worldwide in 2018 with a mortality rate of 626,679 or 30% (Bray et al., 2018). Ten percent of these breast cancers likely resulted from hereditary causes, with more than 50% of genetic mutations occurring in the breast cancer gene one (BRCA1) and breast cancer gene two (BRCA2) (Bray et al., 2018). Up to 80% of people at risk of getting breast cancer have not received genetic testing, mainly because they do not meet the breast screening guidelines that were established more than 20 years ago (Beitsch et al., 2018). The practice guidelines have neither been updated to reflect advances in genetic testing that can provide clinicians with more information regarding cancer risks nor have the practice guidelines been updated to reflect the need to screen men for breast cancer. Due to the high mortality rate associated with breast cancer in both women and men, an intervention implementing an evidence-based practice screening tool in a primary care clinic was chosen for this project with the expectation that it would increase the number of people being screened. Screening more patients would help identify those individuals who might be at high risk for mutations in the BRCA genes (Bray et al., 2018). Genetic testing provides confirmation of mutated genes that may potentially contribute to the development of cancer, allowing individuals with these mutations to implement preventive measures such as lifestyle changes or starting mammograms earlier and more frequently (Keating & Pace, 2018). On average, women living in the United States have a 12.4% or a 1 in 8 risk of being diagnosed with breast cancer in their lifetime (DeSantis, Ma, Sauer, Newman, & Jemal, 2017). Mutations in the BRCA genes that cause breast cancer in women have also been linked to causing breast and prostate cancer in men (Bray et al., 2018). A recent genomic screening in 2018 of 50,000 people showed that over 80%

of individuals did not know they had identifiable genetic risks (Beitsch et al., 2018). Although mammograms and self-breast exams have been included in recommended screening guidelines, these screening guidelines do not apply to men and recent studies have shown that these screening methods may be contraindicated to use in the screening of young women (Keating & Pace, 2018). Furthermore, surveys have shown that majority of primary care providers do not routinely screen for breast cancer using either the old or current screening guidelines (Gornick et al., 2018).

Statement of the Problem

Breast cancer is the most common cancer diagnosed among women in the United States and is the second leading cause of cancer death in women (DeSantis et al., 2017). Approximately 41,000 people passed away from breast cancer in 2017 (DeSantis et al., 2017). It is estimated that in 2018, there were 266,120 new cases of women diagnosed with breast cancer, along with 2,550 new cases in men in the United States alone (American Cancer Society, 2018). These are large numbers that could be reduced significantly with preventive measures including performing early screening for genetic testing (DeSantis et al., 2017). Between 250,000 and 415,000 men and women are at a high risk of being diagnosed with breast cancer that is potentially preventable with early detection (King, Levy-Lahand, & Lahad, 2014). Data from the National Cancer Institute (2012) shows the 10 year frequency and probability of developing breast cancer among U.S. women by age and over the course of a lifetime. Table 1 summarizes these findings.

Table 1

Age Specific Probability of Developing Breast Cancer

Age	10 Year Risk	10 Year Probability
20	1 in 1,567	0.1%
30	1 in 227	0.44%
40	1 in 68	1.47%
50	1 in 42	2.38%
60	1 in 28	3.56%
70	1 in 26	3.82%
Lifetime risk	1 in 8	12.4%

BRCA1 and BRCA2 mutations are equally common in men as in women and are inherited equally from their mothers and fathers (King et al., 2014). For men, the risk of being diagnosed with breast cancer is about 1 in 833, with an estimated 480 deaths annually (American Cancer Society, 2018). Although these numbers are far less dramatic than for women, the mortality rate is significant at a rate of approximately 58%. This may be attributed to the fact that there are no breast cancer screening guidelines for men, thus by the time men are diagnosed with breast cancer, there is a high probability of metastasis of more advanced cancers which usually results in a poorer prognosis (American Cancer Society, 2018). In general, the survival rates improve if breast cancer is detected early (American Cancer Society, 2018). Figure 1 shows 5 year survival rates among men correlated to the diagnosed stage of cancer as noted by the American Cancer Society (2018).

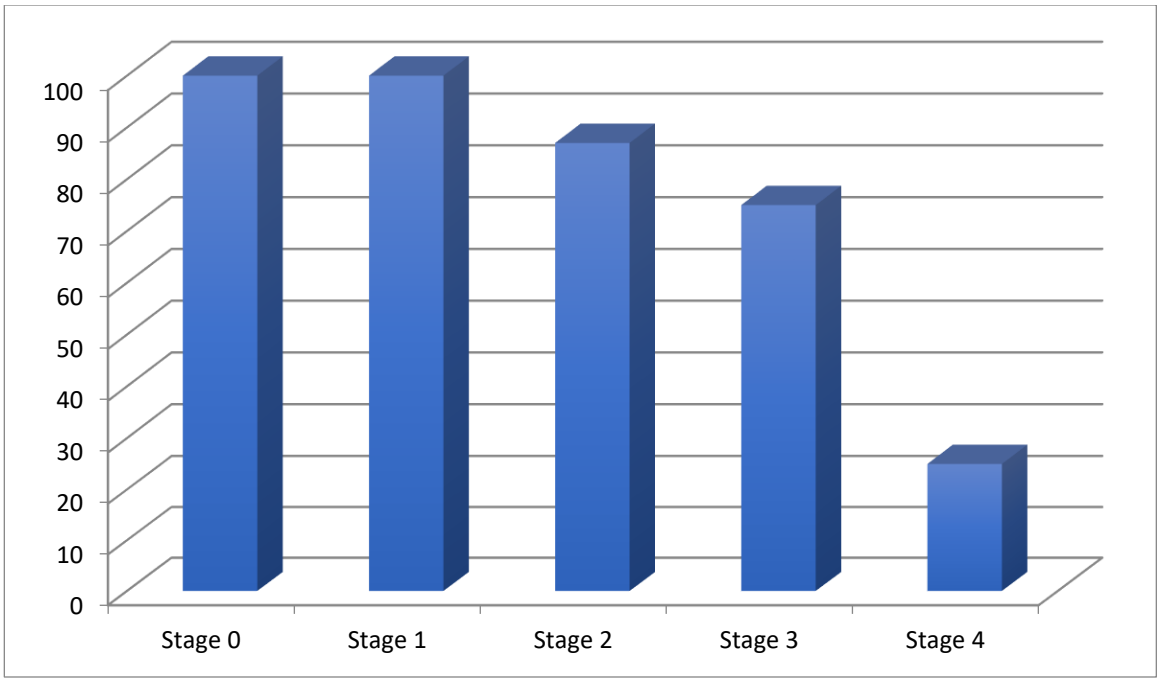

Figure 1. Male breast cancer 5-year survival rates by stage of cancer.

Studies have shown harm from over diagnosing breast cancers related to false-positives from mammography (Keating & Pace, 2018). Evidence from several randomized clinical trials suggest that 19% of women diagnosed by mammogram screenings are considered over diagnosed, subjecting women to treatment without any benefit (Keating & Pace, 2018). Over the past 9 years, there have been many changes in the recommendations for breast cancer screenings (Keating & Pace, 2018). In 2009, the U.S. Preventive Services Task Force (USPSTF) recognized evidence of harm from mammograms such as unnecessary surgeries, medications, further imaging and biopsies which has resulted in revisions to the taskforce's recommendations that now include biannual mammograms for women aged 40 years to 49 years (Keating & Pace, 2018). In 2016, 80% of the 871 primary care physicians that were surveyed still recommended annual screenings for women starting at age 40 years, which is contrary to the USPSTF and American Cancer Society (ACS) guideline recommendations (Keating & Pace, 2018). A study

showed 132 per 100,000 women were over diagnosed for cancer that would never show clinical signs or symptoms in the women's lifetime utilizing mammograms (Welch, Prorok, O'Malley, & Kramer, 2016). Since many studies have linked over diagnosing breast cancer with false-positives from mammograms, the USPSTF and the ACS have recommended the use of family history screening tools over mammograms in young men and women (Keating & Pace, 2018).

Gornick et al. (2018) surveyed 537 newly diagnosed breast cancer patients to determine their common knowledge regarding genetic testing. The results showed that patients' overall knowledge of genetic testing regarding BRCA1 and BRCA2 was low (29.8%). Gornick et al. (2018) found that interest in genetic testing was increasing and should be discussed as an option for screening within the primary care clinic. A recent study pointed out the clinical importance of utilizing multi-gene testing within the primary care setting as well as the fact that genetic testing guidelines are developing rapidly resulting in multiple revisions to genetic testing guidelines (Beitsch et al., 2018). Furthermore, genetic testing criteria have become more complicated, yet these criteria have not been sufficiently re-evaluated (Beitsch et al., 2018). It is estimated that 1.2 to 1.3 million women with a history of breast cancer have not undergone genetic testing despite USPSTF and the ACS' evidence-based practice guidelines supporting this type of testing as a standard of care (Childers, Childers, Maggard-Gibbons, & Macinko et al., 2017). Furthermore, over 70% of eligible patients with breast cancer have never discussed genetic testing with a health care provider (Childers et al., 2017). There is increasing evidence, which supports the benefits of identifying BRCA gene mutations in early breast cancer to evaluate the risk of recurrence (Nilsson et al., 2017).

Assessment

The clinic where the evidenced based practice project was implemented is located in the northeast side of San Antonio, Texas. The clinic is privately owned and staffed with one physician, one nurse practitioner, an office manager, two administrative personnel, and three medical assistants (MA) that are bilingual in English and Spanish. Each provider typically sees about 15 to 20 patients a day, with the majority of patients being private insurance holders. Figure 2 provides a summary of the ethnic groups seen in the clinic and figure 3 provides a summary of the age groups seen in the clinic. As shown, the clinic sees primarily Caucasian patients between the ages of 45-64 years.

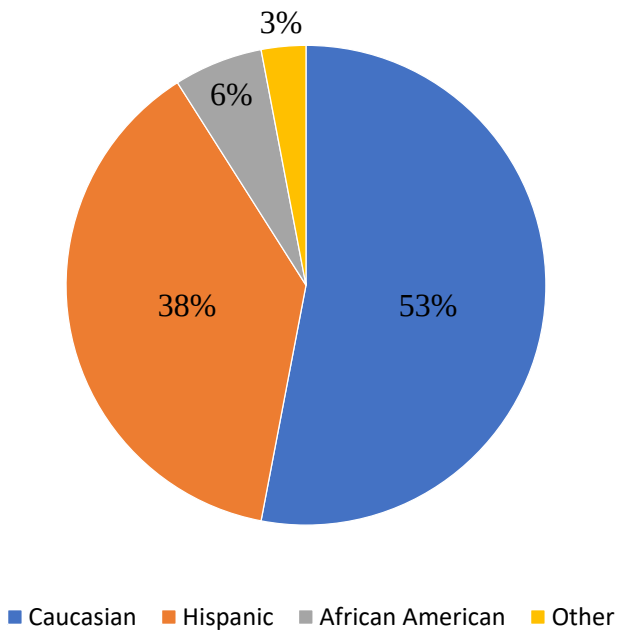

Figure 2. Ethnicity of the patient population within the clinic.

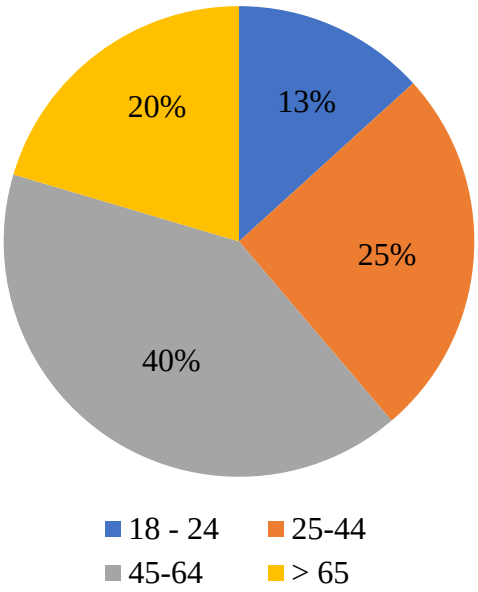

Figure 3. Age groups of the patient population within the clinic.

This clinic did not screen for breast cancer, nor did they offer genetic testing prior to this project intervention. During the microsystem assessment 100 patient charts were audited, which revealed that 42% of the patients met the national recommended guidelines to be offered genetic testing. Many organizations defer to the USPSTF guidelines, because this group of health experts review the strength of the evidence found in the research and determine the benefits and harms each reviewed method poses to patients (USPSTF, 2018a). The USPSTF makes recommendations based off their reviews of the evidence to help guide healthcare providers in managing their patients appropriately. The USPSTF national guidelines for genetic testing recommend that patients who have had one family member diagnosed with either breast, colon, or uterine cancer under the age of 49 years be considered to have an increased risk for potentially harmful mutations in BRCA1 and BRCA2 (Hampel, Bennett, Buchanan, Pearlman, & Wiesner, 2015). The guidelines also state if a family member has an ovarian or pancreatic cancer at any

age, then they too should be considered a high risk for BRCA 1 and BRCA 2 mutations and should be offered genetic testing (Hampel et al., 2015).

Organization's Readiness for Change

Upon review of the USPSTF guidelines and the results of the microsystem assessment it was determined in consultation with the key stakeholders that the clinic was not aligned with the current national guidelines. Both providers had personal experiences with cancer affecting family members thus they were interested in learning more regarding genetic screening and testing. Both providers were already aware that genetic testing for cancer existed, however they were unaware of the practice guidelines that determine which patients should be screened. This interest in practice guidelines for genetic screening and testing is what made the key stakeholders ready to implement my project. They had expressed an interest in offering genetic screening and testing to their patients and were aware that they needed education on the national practice guidelines for screening.

After identifying that a problem existed in the clinic, I developed a project to implement a process that would screen, test, and provide referrals to patients at high risk for BRCA mutations based on the USPSTF guidelines. A short meeting was held with the office manager and each provider individually to fully explain the project's intent and to create a protocol that involved all of the stakeholders. The staff and providers were able to verbalize an understanding of the project's purpose, objectives and interventions. The providers and staff expressed a willingness to participate in this project implementing the evidence-based USPSTF guidelines for BRCA testing in the clinic as a method of improving patient care for both women and men in this patient population.

Project Identification

Purpose and Objectives

The purpose of this project was to implement an evidence-based practiced screening process that included genetic counseling and genetic testing for patients who were considered at high risk for breast cancer in order to improve patient outcomes according to the USPSTF guidelines. The USPSTF guidelines recommend screening all patients, both men and women, and when appropriate, provide genetic testing and referral for genetic counseling to ascertain genetic risks for gene mutations associated with breast cancer.

The objectives for this evidence-based practice project were to:

1. Increase patient screenings for risk factors associated with breast cancer from the pre-intervention rate of 0% to 80% by the completion of the 5th week of the project.
2. Increase the percentage of genetic testing from 0% to 80% in those patients identified as high risk based on screening.
3. Increase the percentage of referrals for patients with genetic mutations to genetic counseling from the pre-intervention rate of 0% to 95%.

Anticipated Outcomes

Prior to the start of my project it was anticipated that implementation of the screening tool would result in the clinic experiencing an increased number of patients being identified as high risk for breast cancer, thus possibly leading to genetic testing and subsequent genetic counseling. Since I anticipated that the clinic would experience an increase in genetic screenings, genetic testing, and genetic counseling referrals, I also predicted that the providers would be willing to continue the implemented interventions, increasing the likelihood that the project would be sustainable.

Summary and Strength of Evidence

Melnyk and Fineout-Overholt's (2015) system of grading the quality and level of evidence was used for this project. The quality of the evidence was rated using a I-IV scale and the level of evidence was rated using a I-VII scale. Specifics regarding the criteria that Melnyk and Fineout-Overholt (2015) define for the numerical rating scales can be found in table 2 and table 3, respectively.

Table 2

Quality of Evidence

Quality of Evidence	Criteria
I	Acceptable quality: No concerns
II	Limitations in quality: Minor flaw or inconsistencies in the evidence
III	Major limitations in quality: Many flaws and inconsistencies in the evidence
IV	Not acceptable: Major flaws in the evidence

Evidence relevant to this project was identified with a comprehensive literature search. Searches were performed using PubMed and CINAHL. In addition, the Cochrane Library and the National Guideline Clearinghouse databases were searched. Searches were conducted using the key words *BRCA, genetic testing, mammograms, breast cancer* and *cancer genes*. The reference lists in the selected articles were also reviewed for pertinent evidence. Research articles from the primary care settings, oncology settings, as well as position statements and guidelines from professional associations and societies were also reviewed. Based on this literature review

15 articles were reviewed and rated.

Table 3

Level of Evidence

Level of Evidence	Study Design
I	Systematic reviews and meta-analysis of randomized controlled studies
II	Randomized controlled studies
III	Non-randomized controlled studies (quasi-experimental)
IV	Case-control or cohort studies
V	Systematic reviews of qualitative or descriptive studies
VI	Qualitative or descriptive studies
VII	Opinion of authorities and/or reports of expert committees

Intensive screening for breast cancer is associated with an increase in false-positive results, unnecessary imaging, and unneeded surgery (USPSTF, 2018b). Other studies have confirmed that mammograms can result in higher rates of false-positives (King et al., 2014). False positive results lead to prescribing medications such as tamoxifen and raloxefine which increases the risk in women for thromboembolic events, cataracts and endometrial cancer (King et al., 2014). Additionally, women identified as being at high risk for breast cancer by mammograms have had unneeded surgeries resulting in complications such as hematomas, contractures, numbness, pain, infection, swelling, bleeding, pulmonary embolisms, and decreased sexual function due to changes in the body (USPSTF, 2018b).

Henderson, Hubbard, Sprague, Zhu, & Kerlikowske (2015) conducted a study that showed women who had false-positive mammogram results that led to additional imaging and

testing were at a higher risk of having breast cancer within the next decade. During the 10 year follow-up of 12,022,560 people, 48,735 cancers were diagnosed (Henderson et al., 2015). When compared to women with a true-negative examination, women with a false-positive with additional imaging recommendation had increased risk of developing breast cancer as did women with a false-positive with a biopsy recommendation (Henderson et al., 2015). Women with a false-positive result had persistently increased risk of developing breast cancer 10 years after the false-positive examination (Henderson et al., 2015). There is no definitive explanation regarding why false-positive mammograms appear to be linked to a slightly higher risk of invasive disease but it was hypothesized that the breast tissue changes that lead to the false-positive mammogram result might in fact be predictive of future breast tissue changes (Henderson et al., 2015). Many studies have concluded that subtle changes on mammograms may be an early clue to cancer before actual cancer exists (Puliti et al., 2012). It is also important to note that these finding has been seen in multiple studies. Studies with large sample sizes of women and extended lengths of follow-up have contributed to more evidence linking false-positive results with a higher risk of invasive breast cancer later in life (Puliti et al., 2012). Approximately 67% of women 40 years of age and older have had a mammogram screening biannually with 16% of the first mammogram and 10% of subsequent mammograms resulting in false-positives (Henderson et al., 2015). Over a period of 10 years, the probability of having at least one false-positive mammogram is 61% for women who were screened annually and 42% for women who were screened biannually (Henderson et al., 2015).

These results are consistent with several studies, such as the study by Euler-Chelpin, Risor, Thorsted, and Vejborg (2012) that found a 67% increased risk for breast cancer among women with false-positives. Another study that was conducted over the course of 17 years found

that false-positives from mammograms involving fine needle aspiration cytology or biopsy had a significantly higher risk for breast cancer than women who had additional imaging procedures alone (Castells et al., 2013). In this study, the overall cancer detection rate was 2.89 cases for every 1,000 mammogram screenings (Castells et al., 2013). The detection rate for women with a history of a false-positive result involving additional imaging was 4.53 per 1,000 mammogram screenings, and those involving a fine-needle aspiration were 7.09 per 1,000 screenings (Castells et al., 2013). The study identified other factors associated with higher detection rates including having a first-degree family history of breast cancer (Castells et al., 2013). Additionally, a study conducted in the United Kingdom, found that women who had a false-positive result from their first mammogram, had a higher interval cancer rate than women with true negatives and also had more advanced stages of cancer (McCann, Stockton, & Godward, 2002). However, as previously mentioned, there is insufficient evidence to determine the association between false-positives and high risks of developing cancer. This study concluded that false-positive mammographies leading to unnecessary assessment of cancer free women has unintended associated costs (McCann et al., 2002). First, there are psychological costs associated with the inconvenience of the procedure and increased anxiety in women that were falsely identified (McCann et al., 2002). Second, there are the direct financial costs associated with performing the procedures (McCann et al., 2002).

In a nonrandomized comparison study by Riedl et al. (2015), BRCA mutation carriers and women with a high familial risk for breast cancer were offered triple and single diagnostic screenings with mammography, ultrasound, and magnetic resonance imaging (MRI) every 12 months. Diagnostic performance was compared between individual modalities and their combinations. Additional comparisons included age, mutation status and breast density. There

were 559 women with 1,365 completed imaging rounds included in this study (Riedl et al., 2015). The sensitivity of MRI (90.0%) was significantly higher than that of mammography (37.5%) and ultrasound (37.5%) (Riedl et al., 2015). Out of 40 cancer types, 18 were detected by MRI alone and two cancers were found by mammography alone (Riedl et al., 2015). The triple modality approach, which included all three diagnostics, yielded the highest detection rate, but also had higher false-positives and costs (Riedl et al., 2015). Age, mutation status, and breast density had no influence on the sensitivity of MRI and did not affect the superiority of MRI over mammography and ultrasound (Riedl et al., 2015).

Current evidence suggests that genetic testing can accurately detect BRCA mutations with little to no risk of harm associated with testing in both men and women (USPSTF, 2018). However, consideration of screening for BRCA mutations should begin once the individual reaches 18, the age of consent (King et al., 2014). In 1995, the American Society of Human Genetics (ASHG) and American College of Medical Genetics and Genomics (ACMG) issued a joint report that offered points to consider for genetic testing in children. The clinical context of that report focused on decisions about testing for single-gene disorders in response to either a family history or within-population screening programs (Botkin et al., 2015). The social context of that report included limited data about the psychosocial impact of such testing in children. The ASHG and ACMG recommended that clinicians and parents consider medical benefits related to diagnosis, prognosis, and interventions as the best justification for testing in children (Botkin et al., 2015). Additionally, the report acknowledged that there was limited information about risks and benefits of genetic testing in children thus the report recommended deferral of testing due to this uncertainty. The report has been influential in encouraging caution when testing children, but often has been over-interpreted as a stricter prohibition of predictive testing in children for

adult-onset conditions than was intended (Botkin et al., 2015). There has been a significant increase in research regarding the impact of predictive testing in high-risk families since the first ASHG ACMG pediatric testing statement, which was established over 20 years ago (Botkin et al., 2015). To date, this limited research has not found evidence of significant psychosocial harms in children (Botkin et al., 2015). Currently, the ASHG now offers the following recommendations:

- Unless there is a clinical intervention appropriate in childhood, parents should be encouraged to defer predictive or pre-dispositional testing for adult-onset conditions until adulthood or at least until the child is an older adolescent who can participate in decision making in a relatively mature manner (Botkin et al., 2015).
- Adolescents should be encouraged to defer predictive or pre-dispositional testing for adult-onset conditions until adulthood, because of the complexity of the potential impact of the information at formative life stages (Botkin et al., 2015).
- Providers should offer to explore the reasons why parents or adolescents are interested in predictive or pre-dispositional testing for adult-onset conditions. Providers can acknowledge that, in some cases, testing might be a reasonable decision, but decisions should follow a thorough deliberation (Botkin et al., 2015).

More than 90% of hereditary cases of breast cancer are thought to be a result of a mutation in BRCA1 and BRCA2 (Paluch-Simon et al., 2016). A founder mutation or founder variant is a genetic alteration observed in high frequency within a group, in which one or more of the ancestors was a carrier of the altered gene (National Cancer Institute [NIH], 2018). Over 2,000 different mutations have been identified in BRCA1 and BRCA 2 genes with founder mutations being the most prevalent in some populations (Paluch-Simon et al., 2016). For

example, up to 2.5% of the general Ashkenazi Jewish population harbor a mutation in either the BRCA1 (C.5266dupC) or BRCA2 (c.5946delT) (Paluch-Simon et al., 2016).

A recent study with a rather large sample consisting of 8,000 men studied the association between relatives who were carriers of BRCA gene mutations. All participants were healthy, cancer-free men that were tested for genetic BRCA1 and BRCA2 mutations. Out of the 8,000 men, 175 tested positive for having BRCA1 or BRCA2 genetic mutations (King et al., 2014). Female relatives of the 175 men were then tested for the same gene disorders and were found to be carriers of the same BRCA mutations, placing them at a very high risk for cancer (King et al., 2014). The evidence supports offering genetic testing to those with personal or family history of cancer, and to those who are relatives of confirmed carriers (King et al., 2014).

The reviewed evidence consistently agreed that genetic testing is still rather new and as newer, more advanced equipment is developed, more research is still needed. With that being said, much of the level I evidence recommends reviewing and revising the current genetic testing guidelines to reflect current evidence and recent trials. Several of the level I studies support the recommendations that mammograms should not be the sole basis of screening men and women for breast cancer. The evidence suggests that there is a benefit of BRCA genotyping patients who are newly diagnosed with breast cancer and recommends genetically testing men and women for mutations that suggest an increase likelihood of developing cancer allowing for early implementation of preventive measures.

Nelson et al. (2013) reviewed 70 studies evaluating the evidence on the benefits and harms of risks assessments, genetic counseling and genetic testing. Results showed those who received counseling post genetic testing experienced less depression and worry regarding both low and high-risk genetic results (Nelson et al., 2013). Although evidence such as this suggesting

that offering genetic counseling with genetic testing reduces depression and anxiety, recent studies have shown that providers are not adhering to these recommendations (Armstrong et al., 2015). A study by Armstrong et al. (2015) identified factors associated with use of BRCA testing to assess whether delivery of genetic counseling and testing services was adhered to as part of the professional guidelines and measures the impact on patient-reported outcomes. This study analyzed data from providers throughout the United States and collected data from 11,159 women whose provider ordered BRCA testing between December 2011 and December 2012. Findings revealed that only 1,334 (36.8%) women received genetic counseling prior to genetic testing with the lowest rates 130 (12.3%) among patients of obstetricians and gynecologists (Armstrong et al., 2015). The most commonly reported patient reason for not receiving counseling was due to lack of provider recommendation (Armstrong et al., 2015). This study also concluded that the patients that did receive genetic counseling demonstrated greater knowledge about BRCA mutations, greater understanding of the genetic information, and expressed greater satisfaction (Armstrong et al., 2015).

During the review of the evidence, it is apparent that there is very little research concerning breast cancer in men. It is under acknowledged clinically and socially as a real risk to men's health, even though breast cancer in men persists as a critical health issue with complex ramifications for those affected (Sirieix et al., 2018). Breast cancer in men accounts for 1% of all breast cancer and management is still largely based on breast cancer management in women (Sirieix et al., 2018). Only a small amount of retrospective series on metastatic cases have been reported so far (Sirieix et al., 2018). Currently there is a multi-center project that aims to collect data from clinical trials and comprehensive cancer centers to improve the customized management of breast cancer in men. So far, the only conclusive finding is that compared to

women, the prognosis and treatment effects for male breast cancer are the same (Sirieix et al., 2018). Unfortunately, studies examining male breast cancer are not routinely funded (Sirieix et al., 2018). Recently the National Comprehensive Cancer Network (NCCN) (2019) started recommending that men age 35 years or older start performing self-breast exams and have an annual breast exam performed by providers. It is evident, that more research is needed to be able to offer early preventive measure to both men and women and if necessary, early interventions to reduce morbidity and mortality rates for these patients.

Methods

Project Intervention

Prior to implementation of this project several meetings were held with the clinic providers and staff based on their roles in implementing the project. A demonstrational meeting was held for the front desk personnel and MAs to allow them to visualize the workflow of the intervention and to ask questions about the implementation process. Another meeting was held on the same day with the laboratory technician to verify that she understood all of the components in the genetic testing kit that needed to be completed in order to process patient samples. The laboratory kit contained one lavender tube and a consent form (see appendix B). The laboratory technician completed a successful return demonstration of how to process the genetic kits. The laboratory technician was familiar with the genetic kit as she had previously processed some samples the previous year. A final meeting was held with both providers to explain the workflow of the intervention and to identify possible barriers to implementation.

Starting on day 1 of implementation, each patient 18 years of age and older entering the clinic was given an electronic tablet issued by the clinic's genetic lab company of choice, Myriad Genetics, which contained an electronic hereditary cancer risk survey. Myriad Genetics was the

clinic's preference because this company currently offered a 35-gene panel (see appendix C) that tests for nine types of cancers and 11 genes (see appendix D) that are not only specific to breast cancer, but also to ovarian cancer, melanoma, pancreatic cancer and prostate cancer. This was important for the clinic because the results of a recent study showed that those identified with BRCA1 mutations had a higher incidence of breast cancer, ovarian cancer and melanoma (Mersch et al., 2015). This same study showed that BRCA2 mutations were reported to increase the risk of developing pancreatic cancer and prostate cancer (Mersch et al., 2015). The electronic tablets containing the online screening survey were handed to the patients during check in by the front desk receptionist and patients were asked to complete the screening survey. Once the electronic tablet screening survey was completed, the tablet was handed back to the front desk receptionist. The electronic tablet screening survey, MyRisk Screening Survey, is an online screening tool by Myriad Genetics that utilizes the USPSTF and the NCCN national clinical guidelines for screening tools in genetic testing. The MyRisk Screening Survey incorporates the national clinical guideline which state if the patient has one family member diagnosed with either breast cancer, colon cancer, or uterine cancer under the age of 49 years, then they should be deemed as having an increased risk for potentially harmful mutations in breast cancer susceptibility genes (Hampel, Bennett, Buchanan, Pearlman, & Wiesner, 2015). Another consider is if a family member has had ovarian cancer or pancreatic cancer at any age, then they too should be deemed as having an increased risk for mutations in the BRCA1 and BRCA2 genes (Hampel et al., 2015). All patients meeting any of these criteria should be offered genetic testing to be in compliance with current national clinical guidelines.

Once the electronic screening survey was completed, a risk score was generated recommending either performing genetic testing (see appendix E) or not performing genetic

testing (see appendix F). The receptionist would then print out and attach the risk score report to the patient's chart, and the MAs would place the entire chart outside the patient's room for the providers as per their usual protocols. The only difference was the charts now contained the patients' risk score reports. The providers reviewed the risk score reports and explained recommendations for genetic testing along with the pros and cons of genetic testing. The providers were educated about the USPSTF national guidelines recommending offering genetic counseling prior to testing, but both providers declined this part of the intervention. The providers stated that insurance companies would not pay for genetic counseling prior to genetic testing. Instead, the providers performed basic genetic counseling themselves to educate the patients about genetic testing discussing the fact that genetic testing does not detect cancer, but rather determines the genetic risk of developing cancer based on any mutations in genes. If patients were screened as high risk, the providers would encourage genetic testing to be performed. If a patient agreed to genetic testing, the providers would review the consent form supplied in the testing kits with the patient and a signature was obtained consenting to the testing.

Once the consent form was signed, the provider would walk the patient to the in-house laboratory to have their blood drawn by the laboratory technician using a lavender tube. The laboratory technician would then place the specimen in a pre-posted package setting it aside for pick up by FedEx. Once the genetic company received the specimen, the company would contact the patient's insurance and determine if the genetic testing would be covered. All genetic testing was reported as being covered so no missed opportunities occurred for this reason. The average turn-around time to receive results was approximately 10 to 14 business days. Each provider would receive a notification via email informing them that results had been uploaded into the

database and were ready for viewing. Results indicated the inherited genetic risk of developing cancer. Based on the presence of mutated genes, a report was generated that provided a percentage risk of developing breast cancer within 5 years and a percentage risk of developing cancer over one's lifetime (see appendix G). For example, results associated with a high-risk patient may state that the patient has a 38% chance of developing breast cancer within 5 years and a 60% chance of developing breast cancer over the course of the patient's lifetime. Results could also indicate that a patient was at low risk for developing breast cancer if no signs of genetic mutations existed for any of the breast cancer genes (see appendix H), in which case the provider would inform the patients of the results over the telephone. Patient's that had genetic mutations were scheduled by the front desk receptionists to be seen in the clinic to discuss the results and were then educated by the provider on preventive measures and lifestyle modifications such as quitting smoking, exercising regularly, and increasing foods associated with higher levels of antioxidants to reduce their chances of developing breast cancer (American Cancer Society, 2018). The providers also educated the patients about additional and alternative screening measures. These recommendations included those listed by the USPSTF (2018b) for BRCA mutation carriers to reduce risk for cancer or cancer related deaths such as intensive cancer screening, risk reducing medications, and risk reducing surgeries. Medications such as tamoxifen and raloxifene have been shown to reduce the incidence of invasive breast cancer in high risk women, but have not been studied in men (USPSTF, 2018b). The patients were also educated that risk reducing surgeries such as mastectomy and salpingooophorectomy significantly reduce the risk of developing breast cancer (USPSTF, 2018b). The USPSTF (2018b) also recommends women who have been genetically identified as being high risk for

developing breast cancer to start receiving mammograms twice annually and if currently only receiving mammograms annually, then switching to screening twice a year.

After the primary care providers discussed the results and recommendations with the patient, the providers offered a referral to one of the local genetic counselors based on the patient's insurance coverage. A referral to a geneticist counselor was recommended to reduce the incidence of the patient developing anxiety or depression due to having received results (Nelson et al., 2013). If the patient agreed to attend genetic counseling, the receptionist would submit the referral. The patients who had declined a genetic counseling referral only received the basic recommendations from the provider that was previously mentioned. There were no incidences where the insurance did not cover the genetic counseling and there were no patients who declined a referral based on their personal insurance coverage.

Organization Barriers and Facilitators

Barriers. The organization experienced a few barriers to implementing the interventions as planned. These barriers included failure to screen all patients 18 years and older, loss of wi-fi connectivity and software updates required with the electronic tablets, patients not understanding how to use the tablets as well as patients not willing to participate after receiving the patient education.

Initially the front desk receptionists kept forgetting to hand out an electronic tablet to each patient who was 18 years of age and older. However, after another meeting with the front desk receptionists to re-educate the importance of the screenings, they were more consistent with screening every eligible patient by week 2.

At times the electronic tablets would have some connectivity issues, or the electronic tablet software needed to be updated. The front office receptionists attempted to reset the

electronic tablets to correct these issues, but if this intervention did not correct the problem, no other attempts were made. These electronic tablets were not available to use until I fixed the issues, which resulted in multiple missed opportunities between week 1 and week 3.

The most significant barrier occurred with elderly patients who did not know how to use the electronic tablet or did not understand the survey questions. This required the front desk receptionists to assist these patients in completing the survey as they were the first person available to the patients. During the pre-intervention stage of the project, the receptionists were asked to complete the survey so they would have a good understanding of how it worked, what to expect and how to answer certain screening questions should the patients have any questions. The front office receptionists successfully assisted each patient that required assistance, thus no missed opportunities were attributed to this barrier.

However, there were many misconceptions among the patients regarding the screening and the testing that may have altered their decision to participate in the project. Some common misconceptions verbalized by the patients included:

- “I don’t have any kids, so it doesn’t matter.”
- “There is nothing I can do if I have the mutated gene.”
- “I get mammograms, so I don’t need to get tested.”
- “I probably wouldn’t have to worry either way since I’m a male.”
- “I’m too old to have to worry about genetic testing for breast cancer.”

Facilitators. Facilitators to implementing the project interventions included staff familiarity with BRCA genetic testing, the clinic’s affiliation with a genetic laboratory company, patients’ willingness to participate in the project, and staff familiarity with processing the laboratory kits and consent forms.

The clinic's nurse practitioner was familiar with the genetic testing process since she had previously processed a few patients for genetic testing in 2017. However, these patients were not screened or tested accordingly to any guideline and were only tested due to the patient's own concerns of having breast cancer. Both providers were already familiar with the genetic laboratory company's processes and already had the lab kits needed for blood draws in storage. The laboratory technician was also familiar with obtaining the specimens since she was the one who performed the testing in 2017. The clinic had a previous affiliation with the genetic laboratory company used for this project because this company processed the genetic tests in 2017. As a result of already having an affiliation in place, the genetic company provided the electronic tablets and laboratory kits to the clinic at no cost.

Patients were also facilitators to this project, as the majority of eligible patients were interested in completing the electronic tablet screening survey. Some of the reasons that patients participated in the project were patients possessing personal knowledge about genetic testing, curiosity and interest about genetic testing, personal predispositions that motivated patients to have genetic testing done, and some patients having friends or family that received genetic testing and recommended the screening to the patient.

Ethical Considerations

As with any project, it is important to consider ethical considerations. When researching similar studies, no one reported patients experiencing any harm from participating in a cancer risk assessment (Moyer, 2014). However, as previously mentioned prior studies have shown an increased in anxiety and depression after meeting criteria for genetic testing or after receiving results. By the same token, other studies have reported a decrease in anxiety, depression, worry and an increase in the accuracy of risk perception after counseling (Moyer, 2014). After

disclosing this information to the providers, an agreement was reached that the providers would provide the initial genetic education themselves because they felt that an initial genetic counseling session would not be covered by insurance prior to testing. However, both providers agreed that a post genetic testing referral would be implemented into the project interventions.

According to the American College of Obstetricians and Gynecologists (ACOG) (2014), another ethical dilemma that should be considered is having a formal consent, which explains that genetic testing may have important consequences or require difficult choices. For example, patients should be informed that the test might reveal that they have, are at risk for, or are a carrier of a specific disease (ACOG, 2014). The results of genetic testing may require difficult decisions to be made regarding current or future health choices, insurance coverage, career, marriage, or reproductive options (ACOG, 2014). The providers provided a consent form to every patient who agreed to genetic testing. The consent form included information regarding the purpose of testing, the testing procedure, as well as the risks, benefits and limitations of genetic testing. Also included in the consent form was a description about how test result findings are reported and what these descriptions mean. The descriptions were defined as:

- Positive: A mutation that is associated with an increased risk for hereditary cancer was identified.
- Negative: A mutation was not identified in any of the genes included as a part of your testing.
- Uncertain: A genetic change was detected but it is not known if this change is linked to cancer risk.

The full consent form can be found in appendix B.

A provider ethical dilemma is the inability of the providers to warn the at-risk relatives of the genetic mutations. Genetic testing is absolutely confidential. Although the provider may inform the patient of familial implications for at-risk relatives, confidentiality and federal laws restrict providers from disclosing any genetic information to relatives without consent of the patient (Knoppers et al., 1998). It is important that consents for genetic testing provide a warning to patients that they may be faced with this dilemma and they should consider having genetic counseling prior to testing (ACOG, 2014).

This project was referred to the University of The Incarnate Word Institutional Review Board (IRB) for review and was deemed not regulated research. Authorization (NRR [19-037]) was given to proceed with the project since it did not require IRB approval.

Results

This project lasted 5 weeks, with 154 of 329 eligible patients being approached for screening using the electronic screening survey. Out of the 154 eligible patients that were asked to complete the electronic screening survey, 129 (40%) of them completed it. Twenty-five (19%) of the 129 patients screened had positive screens that resulted in a recommendation for genetic testing based on their family and personal history. Fourteen (56%) of the 25 patients chose to have genetic testing done. Figure 4 shows the patients who had positive high risks screens recommending genetic testing per each week and Figure 5 shows the patients that proceeded with genetic testing each week.

Three women (21.4%) who consented for genetic testing were identified as having a high risk of developing breast cancer. One female patient was identified as having a clinically significant mutation in the BRCA1 gene. This patient had an estimated 46% - 87% risk of getting breast cancer by the age of 70 years, whereas the general population for her age group only had a

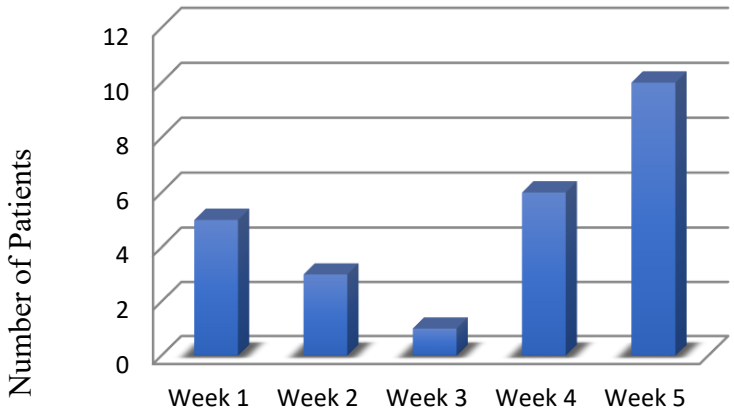

Figure 4. High risk screens.

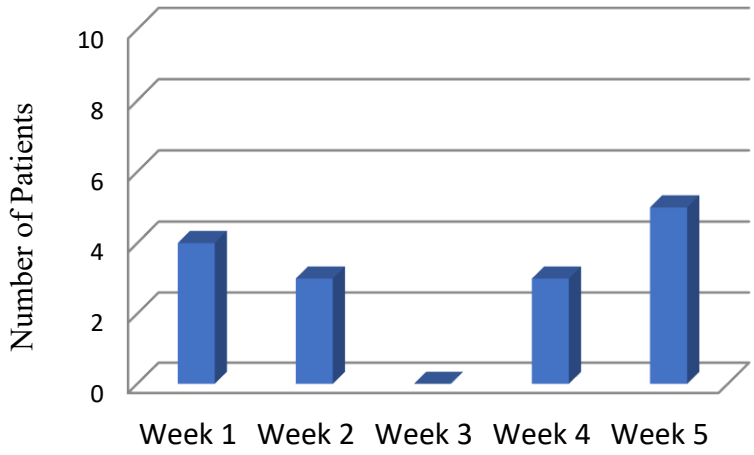

Figure 5. Patients who received genetic testing.

7% risk. The second female patient was identified as having a 35% remaining lifetime risk based on her family history. The third female patient was found to have had a mutated gene, with uncertain clinical significance due to insufficient data to determine if the variant was linked to an increased risk for any type of cancer. Myriad's genetic protocol for this type of finding is to

follow up with the patient if and when new research studies identify any new additional information regarding the uncertain mutations.

Since the implementation of the project, all three (100%) patients with confirmed high risks have been referred to genetic counseling. As of to date, one followed up with the genetics counselor to review her results.

The number of genetic testing opportunities offered by each provider varied significantly. Provider one explained that she had a family history of cancer and felt it was important to offer this service to all patients. Provider two also expressed the importance of genetic testing, but he did not want to make the patients feel pressured into getting genetic testing. Table 4 shows the overall weekly screening rates for the clinic whereas table 5 shows the weekly testing rates by each provider. Table 6 shows the comparison between the pre-intervention rates for each project objective and the post-intervention rates for each project objective.

Table 4

Weekly Screening Rate

	Screenings	Denied Screenings
Week 1	19	8
Week 2	15	3
Week 3	7	10
Week 4	24	3
Week 5	64	1

Table 5

Weekly Genetic Testing Rate by Provider

	Provider 1	Provider 2
Week 1	4	0
Week 2	2	1
Week 3	0	0
Week 4	3	0
Week 5	3	2

Table 6

Objective Comparisons

	Objective Goal	Pre-Intervention Rate	Post-Intervention Rate	Objective Met
Patient Screening	80%	0%	40%	Not met
Genetic Testing	80%	0%	56%	Not met
Genetic Counseling	95%	0%	100%	Met

Discussion

The electronic hereditary cancer risk survey was not given consistently to patients for the first four weeks of implementation. Due to some of the barriers mentioned such as losing wi-fi connectivity, electronic tablets in need of software updates, and patients' lack of willingness to participate, the clinic was unable to maximize the number of patients screened. On several occasions, I would sit with the front desk receptionists to review the project and interventions clarifying any questions they had. During these times I would also review functionality of the electronic tablets to teach the front desk receptionists how to fix some basic errors such as resetting the wi-fi, restarting the tablet and downloading software. By frequently visiting with the front desk receptionists, they became more familiar with the project, and operating the electronic tablets as well as learning the impact the project has for the clinic's patients. This resulted in more efficiency and consistency in the last two weeks of the project.

Analysis of the data revealed no significant similarities among the three women who were found to have genetic mutations of BRCA1 or BRCA2. Table 7 highlights patient demographics and reproductive history of the three women who tested positive for genetic mutations of the BRCA1/BRCA2 genes.

Table 7

Comparison of Patients Identified with BRCA Gene Mutations

	Age of Menarche	Age at First Live Birth	Hormone Replacement Therapy	Race
Patient 1	13	21	No	Caucasian
Patient 2	12	25	Yes	Hispanic
Patient 3	15	21	No	Caucasian

These results differ from larger sample size studies that revealed that BRCA mutation prevalence differed in women diagnosed with breast cancer based on ethnicity and race (Greenup et al., 2013). Figure 6 shows the BRCA mutation prevalence rates by ethnicity as identified by Greenup et al. (2013). This differs from findings from this project, which revealed a more homogenous distribution of patients who had a higher risk of breast cancer based on the electronic screening. Table 7 shows the ethnicity of the 14 women who had genetic testing done based on the initial screening in the clinic. The difference in distribution may be attributed to the fact the primary ethnicity of this clinic's patient population was Caucasian.

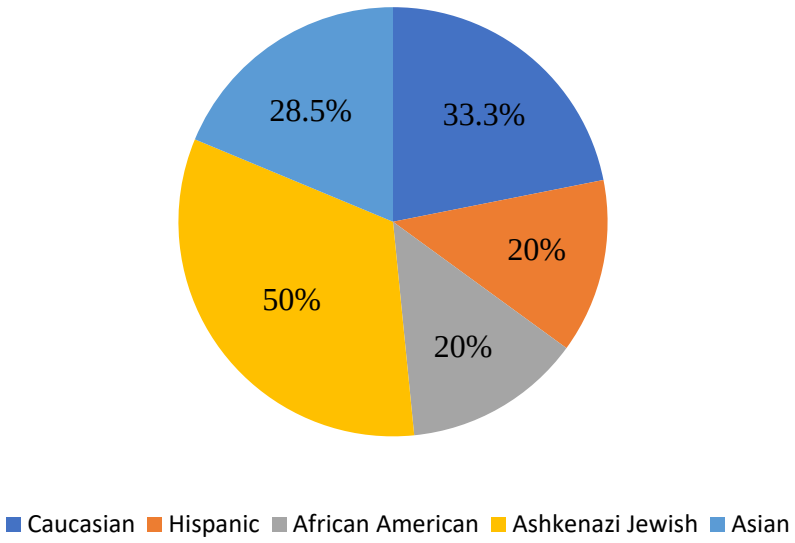

Figure 6. BRCA mutation prevalence by ethnicity.

In the study by King et al. (2014), the evidence supports offering genetic testing to those with personal or family history of cancer and to those who are relatives of confirmed carriers. Results from this project revealed three out of 14 (21%) patients with a family history of cancer had an increased risk for developing breast cancer. King et al. (2014), found that the combined risk of developing either breast or ovarian cancer was 60% (±7%) by age 60 years and 83% (±7%) by age 80 years in BRCA1 mutation carriers. For BRCA2 mutation carriers the risk was 33% (±9%) by age 60 years and 76% (±13%) by age 80 years (King et al., 2014). All three women in this project identified as having a high risk for developing breast cancer were 50 years of age or older. The one patient that had a BRCA1 significant gene mutation was 65 years of age. The two patients who had a high risk for developing breast cancer that were in their 50's differ from King et al.'s (2014) findings whereas the one 65-year-old patient with the BRCA 1 significant gene mutation is consistent with King et al.'s (2014) findings.

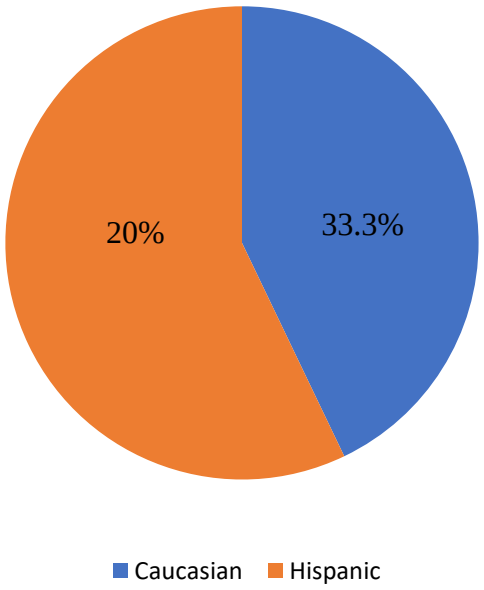

Figure 7. Clinic ethnicity of women complete genetic testing.

The summary of evidence provided plenty of evidence that genetic counseling is a benefit to patients who are receiving genetic counseling as it decreases anxiety and depression and increases understanding of genetic testing results. Unfortunately, the evidence also revealed that providers are not routinely adhering to this recommendation (Armstrong et al., 2015). This was similar to findings from this project, as both providers declined offering genetic counseling prior to genetic testing based on patient cost concerns. They did however adhere to the USPSTF's (2018a) recommendations of referring patients to a geneticist counselor following genetic testing. Armstrong et al. (2015) identified that out of the 11,159 patients who received genetic testing, only 1,334 (36.8%) women received genetic counseling prior to genetic testing. Interestingly enough, this project found that one of the reasons for the lack of pre-genetic testing referrals was due to lack of provider recommendations which is consistent with findings by Armstrong et al. (2015).

A study conducted by Struewing et al. (1997) found that the NCCN guidelines at the time regarding genetic testing under identified patients with BRCA1/BRCA2 genetic mutations. The study randomly selected 1,000 volunteers who had completed a family history survey and provided a blood sample with permission to analyze it for mutations in the BRCA1 and BRCA2 genes. Out of the 1,000 men and women tested, 120 participants were found to have BRCA gene mutations (Struewing et al., 1997). Of the 120 participants who carried a BRCA gene mutation, 31 did not report a family history of breast or ovarian cancer among first- or second-degree relatives (Struewing et al., 1997). This led to a recommendation to revise guidelines for breast cancer screening to include additional familial history such as the ones used for this project's interventions. It is interesting to note that few changes have been made to the genetic screening recommendations from the NCCN over the past 20 years. When comparing this project's results with other studies such as Struewing et al. (1997) and Beitsch et al. (2018), the similarities in results are interesting. Table 8 provides a side-by-side comparison of this project's results with these two studies.

Table 8

Results Comparison of Patients Identified with Having BRCA Gene Mutations

Studies	Sample Size	Results
This project	14	7%
Struewing et al. (1997)	1000	12%
Beitsch et al. (2018)	959	9%

Factors that may have influenced the findings from this project that prevent any assumptions being made about these similarities include the small size of this project's population as well as the homogeneity of the clinic's population and the type of insurance of the clinic patients. No men agreed to participate in genetic screening for this project. Therefore it is difficult to know whether any correlation exists between personal and family history of cancer and genetic mutations in the BRCA1/BRCA2 genes. Furthermore, the majority of patients in this clinic population are private pay patients or commercial health insurance, which provides these patients preventive health care resources that would be unavailable to underinsured or uninsured patients. The dichotomous distribution of patients in the clinic (Hispanic and Caucasian) may have also contributed to findings from the electronic risk screening survey and genetic testing results. Many researchers used a more homogenous population of Ashkenazi Jewish people when analyzing BRCA gene mutations since there is a much higher than average risk for developing breast cancer in this population as stated in the following articles, King et al. (2014), Walsh et al. (2017), and Struewing et al. (1997). Further research regarding the influence of gender and ethnicity on BRCA1/BRCA2 mutations is needed.

Limitations

There were several issues with the electronic tablets during the initial implementation of the electronic risk screening survey as previously discussed which may have affected the overall screening, testing and referral rates. Out of 329 eligible patients that presented to the clinic during the implementation period, only 154 (46.8%) of the patients were asked to complete the electronic risk screening survey. Failure to ask the remaining 175 (53.2%) patients most likely affected the genetic testing rates and subsequently the ability of the clinic to identify patients with BRCA gene mutations.

Additional limitations included the one provider who was not as assertive in recommending genetic screening as the other provider. Personal bias regarding genetic testing influenced both providers participation in the project. This most likely affected the testing rates. The number of weeks allotted for this project intervention may have also affected the results, since the intervention was not operational as intended until the last week.

Recommendations

The clinic has continued with the intervention of utilizing the electronic tablet screening surveys. The nurse practitioner provider informed me that she has continued testing patients and following up with a referral to a geneticist counselor. However, the physician provider has completely stopped screening all patients for breast cancer using the project implementation plan. The nurse practitioner provider verbalized that she would speak with the physician to recommend continuing the intervention. With only one provider participating in the project plan, approximately 50% of the clinic's patients that are 18 years and older will be screened. I would recommend that the front desk receptionists continue distributing the tablets to patients who are 18 years and older when they check in to the clinic. This seemed to be the most time efficient workflow for the clinic personnel and the patients. I would also recommend the clinic getting additional tablets from the genetic testing company in order to help increase the number of screenings that can be completed when an electronic tablet experiences loss wi-fi connectivity or needs software updates. The nurse practitioner provider of this clinic believes that the number of BRCA gene mutations is significant when considering the number of patients participating in the project. This has resulted in the nurse practitioner provider continuing the project interventions. Perhaps with time and continued implementation of the project the physician provider may decide to reinstate the project interventions into his practice.

Implications for Practice

In 2018, there were no patients identified as being at high risk for breast cancer in this clinic's population since no type of breast cancer screening was being implemented. As a result, there were also no referrals to genetic counseling in 2018. As of to date since the implementation of this project, three (21.4%) patients of the 14 tested have been identified as having a high risk of developing breast cancer, and all three women were referred to a geneticist counselor. One of these women was confirmed as having a clinically significant BRCA1 gene mutation; another one of the women had a mutated gene with unknown clinical significance; and the third women was found to have no mutated genes but was still identified as having a very high risk for breast cancer due to familial history. Implementation of this project also resulted in informing 101 (78%) patients that they were at very low risk of developing breast cancer.

The results of this quality improvement project demonstrate that screening for genetic risks aids in identifying those individuals at high risk for developing breast cancer thereby encouraging clinicians to develop plans of care that can help minimize these genetic predispositions for breast cancer and increase surveillance for breast cancer in these patients. Although the project was implemented in a primary care clinic, a similar protocol would be suitable for other specialty clinics such as an obstetrics or gynecology clinic since BRCA gene mutations also predispose patients to ovarian cancer. Using a modified version of this protocol in primary care or urology could also identify men with BRCA genetic mutations that not only predispose them to developing breast cancer but also increases their risk of developing prostate cancer. Genetic screening protocols could even be implemented in an oncology setting, as it is recommended that patients get genetic testing done at time of diagnoses (Childers et al., 2017).

There are numerous hereditary genetic screening tools available for screening for breast cancer risks. Some that have been recommended by the USPSTF include the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool and the FHS-7 model (USPSTF, 2018). These screening tools are free for providers to use thus providing clinics with a cost-effective method to screen for cancer causing genetic mutations.

Implementation of this project has helped a patient to identify the specific gene that has contributed to so many deaths in her family. This has allowed the patient to inform her siblings, children, nieces and nephews about the specific gene mutation that runs in their family. Knowing what gene mutations a patient has allows for specific testing, which is ultimately less expensive, and can bring peace of mind to family members once the genetic mutation is ruled out (D'Andrea et al., 2016). More importantly, the patient's insurance will now cover biannual mammograms instead of limiting the patient to an annual mammogram.

Conclusion

Healthcare providers have the ability to utilize clinical practice guidelines to potentially have a significant impact on their patient populations. Operationalization of a genetic screening/testing protocol similar to this one can aid providers in potentially saving lives of patients who would otherwise have no idea that they are at high risk for breast cancer. The importance of identifying inherited genetic mutations extends beyond the initial treatment period. It allows providers to develop treatment plans that include prevention measures that can help negate these genetic mutations and increase surveillance of those patients that test positive as well as informing other family members of their risk.

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APPENDIX A: Evidentiary Table for Summary of Evidence

Reference	Purpose	Design/Sample Setting	FIndings/Implications	Quality of Evidence	Level of Evidence
U.S. Preventive Services Task Force (2018b).	Purpose: Establishes clinical practice guidelines	Design: N/A, Clinical Practice Guideline Sample: N/A	The USPSTF recommends that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with one of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (*BRCA1* or *BRCA2*). Adequate evidence suggests that the overall harms of detection of and early intervention for potentially harmful BRCA mutations are small to moderate. Implications: The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.	I	VII
King, M. C., Levy-Lahad, E., & Lahad, A. (2014).	Purpose: To determine genetic mutations among women who have male relatives who have a familial history of cancer	Design: Randomized controlled study Sample: 8,000 men and women	Findings: The study found adequate evidence that the overall harms of testing, detection, and early intervention are small to moderate. There was also a correlation of genetic mutations in descendants of males with a familial history of cancer particularly those males with genetic mutations. Implications: Population-based screening of women for BRCA1 and BRCA2 should become a routine part of clinical practice.	I	II
Henderson, L. M., Hubbard, A.	Purpose: To	Design: Quasi-	Findings: Women with a history of	II	III

Reference	Purpose	Design/Sample Setting	FIndings/Implications	Quality of Evidence	Level of Evidence
R., Sprague, B. L., Zhu, W., & Kerlikowske, K. (2015).	determine whether the relationship between a history of a false-positive screening mammogram result and the risk of developing breast cancer varies according to the type of recommendations associated with the false-positive results or by mammographic breast density.	experimental Sample: Included women ages 40 to 74 years of age, who received a mammogram between 1994 and 2009 with a sample size of 12,022,560.	a false positive screening mammogram or who received a biopsy recommendation were at increased risk of developing breast cancer for at least a decade, suggesting that prior false positive screening results may be useful in risk prediction models. Implications: The findings suggest that false positive mammography results should be considered in risk prediction models to better stratify women into risk categories that may be used to personalize breast cancer screening and primary prevention strategies for individual women.		
Puliti, D., Duffy, S. W., Miccinesi, G., Koning, H. D., Lynge, E., Zappa, M., & Paci, E. (2012).	Purpose: To determine an estimate rate of over diagnosis of breast cancer using mammograms.	Design: Systematic reviews of qualitative studies Sample: 13 studies	Findings: Determined that false-positive results are linked with higher risk of invasive breast cancer later in life. Implications: Estimation of the underlying expected incidence in the absence of screening is crucial to obtaining reliable estimates of over diagnosis.	II	V
Euler-Chelpin, V. M., Risor, M. L., Thorsted, L. B., & Vejborg, I. (2012).	Purpose: Assess the risk of screened-detected breast cancer in women with false positive results.	Design: Systematic reviews of qualitative and descriptive studies Sample: 6,094,515 screenings	Findings: Concluded that women with false positive results are at increased risk for breast cancer. Implications: Advised to actively encourage women with false positives results for regular breast screening as the potential benefit from screening is higher than in women with false positives than with negative tests.	II	V
Castells, X., Roman, M., Romero, A., Blanch, J., Zubizarreta, R., Ascunce, N., … Sala, M. (2013).	Purpose: To evaluate the association of false-positive results with the cancer detection risk in subsequent screening participations over a 17-year period.	Design: Cohort study Sample: 762, 506 women	Findings: False positives showed an increased cancer detection risk in subsequent screenings. False positives involving a cytology or biopsy were associated with a significantly higher risk of cancer detection than false positives leading to additional imaging procedures Implications: In the context of mammographic screening in which large cohorts of women were assessed every 2 years, personalized risk information could be useful to improve the effectiveness of breast cancer screening by emphasizing the need for returning for further screening in women with false-positive results.	I	IV

Reference	Purpose	Design/Sample Setting	FIndings/Implications	Quality of Evidence	Level of Evidence
McCann, J., Stockton, D., & Godward, S. (2002).	Purpose: To quantify the increased risk with increasing anxiety an increased risk of subsequent interval cancer associated with false-positive mammograms. To evaluate whether it extends to cancers detected at rescreening and determine whether cancers differ between women who have and have not experienced false-positive mammographies.	Design: Cohort study Sample: 140,387 women	Findings: Women experiencing false-positive mammographies at first screen were less likely to return for subsequent screens than were non-assessed women, yet these women were more likely to have increased cancers and larger cancers when subsequent interval screenings or second screens were performed Implications: A possible explanation for the increased risk of cancer in women following false-positive mammography might be the characteristic of women's breasts makes it difficult to interpret mammographically and predisposes these women to the risk of a false-positive result which in itself is a risk factor for breast cancer.	I	IV
Riedl, C. C., Nikolaus, L., Bernhart, C., Weber, M., Bernathova, M., Tea, M.M,… Helbich, H. T. (2015).	Purpose: To evaluate the breast cancer screening efficacy of mammography, ultrasound, and magnetic resonance imaging (MRI) in a high-risk population and in various population subgroups.	Design: Non-randomized study Sample: 559 women	Findings: MRI allows early detection of familial type breast cancer regardless of patient age, breast density, or risk status. The use of MRI in women with a high familial risk for breast cancer has a significantly higher sensitivity for invasive and preinvasive cancers than mammography and ultrasound. Implications: Considering high cost and false-positive rates associated with the addition of screening modalities and considering the high sensitivity of MRI alone, the use of MRI alone as a screening modality in high-risk patients should be considered, thus maximizing identification of cancers and reducing costs and false-positive findings results	II	III
Botkin, R. J., Belmont, W. J., Berg, S. J., Berkman, E. J., Bombard, Y., Holm, A. I., . . . Mclnerney, D. J. (2015).	Purpose: Establishes standard of care.	Design: N/A, Clinical Practice Guideline Sample: N/A	Findings: To date, this limited research has not found evidence of significant psychosocial harm when genetically testing children. Implications: Providers should offer to explore the reasons why parents or adolescents are interested in predictive or pre-dispositional testing for adult-onset conditions in children. Providers can acknowledge that, in some cases, testing might be a reasonable decision, but decisions should follow a thorough discussion with parents.	I	VII

Reference	Purpose	Design/Sample Setting	FIndings/Implications	Quality of Evidence	Level of Evidence
Paluch-Shimon, S., Cardoso, F., Sessa, C., Balmana, J., Cardoso, M. J., Gilbert, F., & Senkus, E. (2016).	Purpose: Establishes clinical practice guidelines	Design: N/A Clinical Practice Guideline. Sample: N/A	Findings: Follow-up counseling outlining options for screening for early detection, risk-reducing measures and issues pertaining to fertility in women who have not completed becoming pregnant is fundamental. Implications: If available, genetic mutation carriers should be encouraged to participate in dedicated high-risk follow-up clinics that specifically focus on follow-up and screening of individuals with a known hereditary cancer syndrome.	I	VII
Nelson, H. D., Pappas, M., Zakher, B., Mitchell, J. P., Okinaka-Hu, L., & Fu, R. (2014).	Purpose: To review new evidence on the benefits and harms of genetic counseling and genetic testing for BRCA.	Design: Systematic reviews of randomized studies Sample: 70 studies	Findings: Genetic counseling decreases anxiety and depression regarding cancer and improves understanding of genetic testing results. Implications: No trials evaluated the effectives of intensive screening or risk reducing medications in genetic mutation carriers, although false positive rates, unneeded imaging, and unneeded surgeries were higher with screening.	II	V
Armstrong, J., Toscano, M., Kotchko, N., Friedman, S., Schwartz, M. D., Virgo, K,... Sutphen, R. (2015).	Purpose: To identify factors associated with use of BRCA testing to assess whether delivery of genetic counseling and testing services adheres to professional guidelines and measure the impact on patient-reported outcomes.	Design: Systematic review of qualitative and descriptive studies Sample: 11,159	Findings: Despite improved patient knowledge, understanding, and satisfaction among patients who receive genetic counseling by a genetics clinician, as well as multiple guidelines emphasizing the importance of genetic counseling, most U.S. women undergoing BRCA genetic testing do not receive this counseling service. Lack of physician recommendation is the most commonly reported reason. Implications: This finding demonstrates the important gaps in clinical genetic services. Mandated coverage of genetic counseling services as a preventive service without patient cost sharing should contribute to improving clinical genetics services and associated outcomes in the future.	II	V
Siriex, J., Fraisse, J., Mathoulin-Pelissier, S., Leheurteur, M., Vanlemmens, L., Jouannaud, C.,... Frenel, J. S. (2018).	Purpose: Providing a large comprehensive analysis of metastatic breast cancer in men.	Design: Randomized control study. Sample: 16,701	Findings: Men who received hormonal therapy when compared to a matched cohort of women showed slightly higher survival rates from breast cancer. Implications: More biological information is needed to improve the customized management of metastatic breast cancer in men.	II	II

Reference	Purpose	Design/Sample Setting	FIndings/Implications	Quality of Evidence	Level of Evidence
National Comprehensive Cancer Network [NCCN] (2019).	Purpose: To update clinical practice guidelines for breast cancer screening in men.	N/A Clinical Practice Guideline.	Findings: Recommends that men age 35 years or older start performing self-breast exams and have an annual breast exam performed by providers.	I	VII

Appendix B: Informed Consent for Hereditary Cancer Genetic Testing

Instructions for Healthcare Providers:
- **This document is provided for your convenience and can be used at your discretion**
- **Some states may have specific documentation requirements for informed consent**

Informed Consent for Hereditary Cancer Genetic Testing

Introduction This form describes the benefits, risks, and limitations of genetic testing for inherited susceptibility to cancer. This is a voluntary test and you may wish to seek genetic counseling prior to signing this form. Read this form carefully before making your decision about testing.

Purpose This test analyzes a specific gene or gene(s) for genetic changes called mutations. The gene(s) analyzed are associated with specific hereditary cancer risks. This test will help determine if a person has a significantly increased risk of developing certain tumors due to a mutation(s) in a cancer-predisposing gene(s). Genetic testing allows a more precise estimate of an individual's risk for hereditary cancer than personal and family history alone. In some cases the results of this testing may also provide information about risks for non-cancer related medical conditions.

Test Procedure Usually, a tube(s) of blood will be drawn or a saliva sample will be obtained and sent to Myriad Genetic Laboratories, Inc. ("Myriad"). In some instances other types of cells will be submitted. Myriad will analyze the DNA of a specific gene or genes to look for mutations associated with specific hereditary cancer risks. Additional information about the testing and the genes analyzed for each of the specific tests available can be found on Myriad's patient website at http://www.MySupport360.com.

Test Results and Interpretation Your results should be evaluated in the context of personal and family health history, the results of physical examination, laboratory and hospital tests, and the clinical impression of your healthcare provider. Possible result outcomes include positive, negative and uncertain.

- Positive – A mutation that is associated with an increased risk for hereditary cancer was identified. Knowing this information may help you and your doctor make more informed choices about your health care, such as screening, risk-reducing surgeries and preventive medication strategies.
- Negative – A mutation was not identified in any of the genes included as part of your testing.
    - If you are the first person tested in your family, you still have at least the same risk of cancer as does a person in the general population. You may still be at greater than average risk for hereditary cancer due to a genetic predisposition that cannot be detected by this test, either in the gene(s) for which you were tested or in another gene linked to hereditary cancer.
    - If you test negative for a mutation known to be in your family, you may be considered to have the same genetic risks as others in the general population.
- Uncertain – A genetic change was detected but it is not known if this change is linked to cancer risk. You still have at least the same risk of cancer as the general population. In addition, you may still be at greater than average risk due to this change or a genetic predisposition that cannot be detected by this test, either in the gene(s) for which you were tested or in another gene linked to hereditary cancer.

Genetic tests results have implications for blood relatives. In consultation with an appropriate healthcare provider, you may wish to discuss sharing your test results with certain blood relatives who may be at risk. If you decide to do this, you should also consider the best way to make this disclosure.

Myriad keeps test results confidential and is fully in compliance with all Health Insurance Portability and Accountability Act (HIPAA) regulations. Myriad will only release your test results to your healthcare provider, his or her designee, or to another healthcare provider as directed by you (or a person legally authorized to act on your behalf) in writing, or otherwise as required by federal and state laws.

Benefits Your genetic test results may help you and your doctor make more informed choices about your health care, such as screening, risk-reducing surgeries and preventive medication strategies.

The identification of gene mutation(s) in a family enables other blood relatives to determine whether or not they share the same hereditary cancer risks. If you are positive, you should discuss with your healthcare provider how hereditary cancer is inherited and learn about the chance your children and blood relatives may have inherited the same mutation(s) in the gene(s) tested.

If you test negative for a known mutation in your family, you cannot pass on that mutation to your children and you may be considered to have the same genetic risks for cancer as others in the general population.

Risks Genetic testing requires DNA most often provided from a sample of blood or from a saliva sample. Side effects of having blood drawn are uncommon, but may include dizziness, fainting, soreness, bleeding, bruising and rarely, infection.

To address concerns regarding possible health insurance discrimination, most states and the federal government have enacted laws to prohibit genetic discrimination. In addition, some states have enacted laws that limit use of this information by life insurers and by employers. Furthermore, broad federal legislation prohibits unauthorized disclosure of confidential personal health information.

Limitations This test analyzes only certain important gene(s) associated with specific hereditary cancer risks. Genetic testing clarifies cancer risks for only those cancers related to the genes analyzed.

If you are found to be a carrier of a gene that predisposes you to cancer, there may be differing opinions among physicians about the best steps to take. Your medical care is best determined by you in consultation with your healthcare provider.

Analysis for a specific genetic variant of uncertain significance may be considered investigational and may not provide additional cancer risk information to blood relatives.

For the State of New York The State of New York requires that no tests other than those authorized shall be performed on the biological sample and that the sample shall be destroyed at the end of the testing process or not more than sixty days after the sample was taken.

Financial Responsibility Genetic testing of appropriate individuals is typically reimbursed by health insurance or covered by HMOs. You are responsible for any cost of the genetic test not reimbursed by insurance.

New Information and Future Correspondence Due to the dynamics of this field, there continues to be new information and data that may change the interpretation of your test results. It is recommended that you keep in contact with your healthcare provider, at least annually, to learn of any changes to the interpretation of your results or new developments in cancer genetics and to provide any updates to your personal or family history which may affect your cancer risks.

Patient Consent Statement:

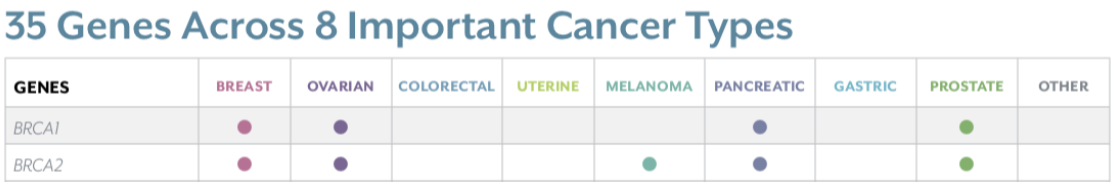
By signing below, I, the patient having the test performed, acknowledge that:

- I have been offered the opportunity to ask questions and discuss with my healthcare provider the benefits and limitations of the genetic test(s) to be performed as indicated on the associated test request form or follow-on tests ordered by my healthcare provider.
- I have discussed with the medical practitioner ordering this test the reliability of positive or negative test results and the level of certainty that a positive test result for that disease or condition serves as a predictor of such disease.
- I have been informed about the availability and importance of genetic counseling and provided with written information identifying an appropriate healthcare provider from whom I might obtain such counseling.
- I have read this document in its entirety and realize I may retain a copy for my records.
- I consent to being tested for predisposition to hereditary cancer and I will discuss the results and appropriate medical management with my healthcare provider.
- I am the owner of my medical history and test results. My healthcare practitioner should not discuss or disclose my test results and associated medical history to a third party, unless related to treatment or payment for treatment, without my express written authorization.

_____	_____
Name of patient having testing (please print)	Date of Birth
_____	_____
Signature of patient (or legal guardian*)	Date & Time of Signature

*Genetic testing on children under the age of 18 requires that the ordering healthcare provider obtain an informed consent from a parent or legal guardian. If legal guardian, specify relationship to the patient:_____

Appendix C: BRCA1/BRCA2 Influence on Cancer Types



Appendix D: Genes Related to Breast Cancer

GENES	BREAST
BRCA1	●
BRCA2	●
MLH1	
MSH2	
MSH6	
PMS2	
EPCAM	
APC	
MUTYH Biallelic	
MUTYH Monoallelic	
CDKN2A (p16INK4a)	
CDKN2A (p14ARF)	
CDK4	
TP53	●
PTEN	●
STK11	●
CDH1	●
BMPR1A	
SMAD4	
PALB2	●
CHEK2	●
ATM	●
NBN	●
BARD1	●
BRIP1	
RAD51C	
RAD51D	
POLD1	
POLE	
GREM1	
HOXB13	
AXIN2	
MSH3	
NTHL1	
RNF43	
GALNT12	
RPS20	

Appendix E: myGeneHistory Hereditary Cancer Screening Positive Summary Result Page

myGeneHistory™ Hereditary Cancer Screening Result

myGeneHistory by Myriad Genetic Laboratories
THIS IS NOT A LAB REPORT

myGeneHistory compiles information provided by a patient and compares it to society guidelines for hereditary cancer testing. These results are designed to help guide you in assessing a patient's risk for hereditary cancer and to help determine whether genetic testing is warranted.

Patient [redacted] Date of Birth: [redacted] Gender: F Provider: [redacted] Date Taken: 03/27/2019

Ancestry: Hispanic/Latino

Summary

Based on the patient's answers, they appear to meet society guidelines for hereditary cancer testing (specific guidelines listed below).

This patient may be a candidate for Myriad myRisk® Hereditary Cancer testing. Make sure to discuss these results with your patient.

Qualifying Criteria

NCCN
- First or second degree relative diagnosed with breast cancer at age 45 or younger
- First or second degree relative with ovarian cancer at any age

USPSTF
- 1st or 2nd degree relative with breast cancer before age 50
- 1st or 2nd degree relative with ovarian cancer

Cancer Diagnoses

- Self, Colorectal Polyps, age 61
- Aunt Maternal, Breast, age 50
- Aunt Maternal, Ovarian, age 75
- Aunt Paternal, Breast, age 45

Appendix F: myGeneHistory Hereditary Cancer Screening Negative Summary Result Page

myGeneHistory™ Hereditary Cancer Screening Result

myGeneHistory by Myriad Genetic Laboratories
THIS IS NOT A LAB REPORT

myGeneHistory compiles information provided by a patient and compares it to society guidelines for hereditary cancer testing. These results are designed to help guide you in assessing a patient's risk for hereditary cancer and to help determine whether genetic testing is warranted.

Patient [redacted] Date of Birth: [redacted] Gender: Provider: [redacted] Date Taken:

Ancestry:

Summary

Based on the patient's answers, they do not appear to meet any society guidelines for hereditary cancer testing:

- Hereditary Breast and Ovarian Cancer syndrome
- Lynch syndrome
- FAP syndrome

However, it is important to discuss your patient's personal and family history of cancer with them.

Qualifying Criteria | Cancer Diagnoses

USPSTF
- Doesn't currently meet criteria

NCCN
- Doesn't currently meet criteria

ADDITIONAL INFORMATION

About The Patient's Answers
The above result is based on a comparison of the patient's answers with nationally recognized society guidelines for hereditary cancer. If you'd like to learn more about the different society guidelines for hereditary cancer, you can visit the following websites:

- National Comprehensive Cancer Network (NCCN): https://www.nccn.org/patients/guidelines/cancers.aspx
- U.S. Preventive Services Task Force (USPSTF): https://www.uspreventiveservicestaskforce.org/Page/Name/about-the-uspstf

Important Notice
This screening application does not provide a comprehensive assessment of the NCCN testing criteria and does not account for certain risk factors, including the following:

- Hereditary Breast and Ovarian Cancer syndrome
  - A previously identified BRCA mucation
- Lynch syndrome
  - MSI High histology before age 60
    - Mucinous
    - Signet ring
    - Tumor infiltrating lymphocytes
    - Crohn's-like lymphocytic reaction histology
    - Medullary growth pattern
  - A previously identified Lynch syndrome mutation

There are several Lynch syndrome related cancers that were not evaluated in this screening. If your patient has had a personal and/or family history of the following cancers, they might be at risk for Lynch syndrome:

- Stomach
- Small intestine
- Hepatobiliary tract
- Upper urinary tract
- Brain
- Skin

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1 of 1

Appendix G: myRisk Genetic Result Breast Cancer Patient riskScore Page

CONFIDENTIAL

53369266
53369266

myRisk Genetic Result

Name: [redacted] DOB: [redacted] Accession #: [redacted] Report Date: Mar 19, 2019

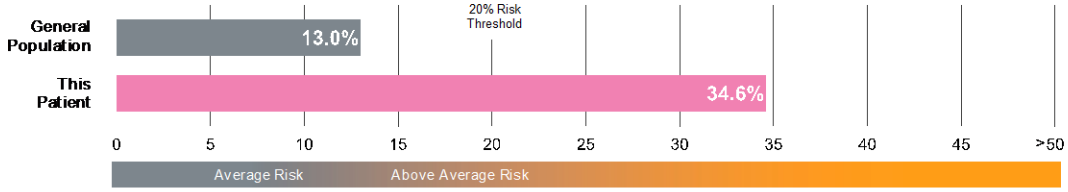
Breast Cancer riskScore™

MYRIAD myRisk® Hereditary Cancer | riskScore™ BREAST CANCER

Breast Cancer riskScore™:
34.6%

RESULT: 34.6% Remaining Lifetime Risk for Breast Cancer
1.4% 5-Year Risk for Breast Cancer

Breast Cancer riskScore™ - Remaining Lifetime Risk



BREAST CANCER RISKSCORE™ INTERPRETATION

The breast cancer riskScore™ provides an estimate of the remaining lifetime risk for breast cancer. A risk estimate at or above 20% is associated with specific modified medical recommendations, including consideration of more aggressive breast cancer screening and additional risk reduction measures. If applicable, details of these recommendations are provided in the accompanying myRisk Medical Management Tool or other supplemental material. Women with a risk estimate below 20% may still be appropriate for consideration of modified medical management based on other clinical factors or estimates from other breast cancer risk models, such as Tyrer-Cuzick, Claus, and Gail.

BREAST CANCER RISKSCORE™ ANALYSIS DESCRIPTION

The breast cancer riskScore™ provides 5-year and remaining lifetime breast cancer risks, based on an analysis of genetic markers combined with patient clinical and family history data. The Technical Specifications summary (https://www.myriadpro.com/documents-and-forms/technical-specifications/) describes the riskScore™ eligibility criteria, analysis, method, performance and interpretive criteria of this test. Data from 86 biomarkers are analyzed during next generation sequencing (NGS). The allele status of these markers is weighted and combined with patient clinical and family history data in the riskScore™ calculation. The Clinical and Cancer Family History Information section of this report displays the data used for this analysis and explains important limitations on the accuracy of riskScore (including significant over- or under-estimates of breast cancer risk) that can be caused by errors and/or omissions in the reported clinical and family history data.

TYRER-CUZICK BREAST CANCER RISK CALCULATION

REMAINING LIFETIME BREAST CANCER RISK: 27.5%	5-YEAR BREAST CANCER RISK: 1.1%

The National Comprehensive Cancer Network (NCCN) provides medical management recommendations for women with an estimated remaining lifetime breast cancer risk greater than 20% based on Tyrer-Cuzick. These recommendations are summarized on the myRisk Management Tool (MMT). If an MMT is not included with this report, current management recommendations from the NCCN Breast Cancer Screening and Diagnosis panel can be accessed at www.nccn.org. Version 7.02 of the Tyrer-Cuzick model was used for this risk estimate. Tyrer-Cuzick model Versions 7.02 and 8.0 are available for download at the EMS-Trials website, http://www.ems-trials.org/riskevaluator.

Please contact Myriad Medical Services at 1-800-469-7423 X 3850 to discuss any questions regarding this result.

This Authorized Signature pertains to this laboratory report:

Benjamin B. Roa, PhD
Diplomate AEMG
Laboratory Director
Johnathan M. Lancaster, MD, PhD
Diplomate ABOG, FACOG, FACS
Chief Medical Officer

These test results should only be used in conjunction with the patient's clinical history and any previous analysis of appropriate family members. The patient's clinical history and test results should not be disclosed to a third party, unless related to treatment or payment for treatment, without the patient's express written authorization. It is strongly recommended that these results be communicated to the patient in a setting that includes appropriate genetic consultation. This test was developed and its performance characteristics determined by Myriad Genetic Laboratories. It has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that clearance or approval for laboratory-developed tests is not required.

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Appendix H: myRisk Genetic Result Breast Cancer Low Risk Summary Page

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Integrated BRAC*Analysis*® with Myriad myRisk® Hereditary Cancer

myRisk Genetic Result

MYRIAD myRisk® Hereditary Cancer | Powered by myVision®

RECEIVING HEALTHCARE PROVIDER	SPECIMEN		PATIENT	
[redacted]	Specimen Type:	**Blood**	Name:	[redacted]
	Draw Date:	**Mar 11, 2019**	Date of Birth:	
	Accession Date:	**Mar 13, 2019**	Patient ID:	
	Report Date:	**Mar 19, 2019**	Gender:	
			Accession #:	
			Requisition #:	

GENETIC RESULT: NEGATIVE - NO CLINICALLY SIGNIFICANT MUTATION IDENTIFIED

Note: "CLINICALLY SIGNIFICANT," as defined in this report, is a genetic change that is associated with the potential to alter medical intervention.

CLINICAL HISTORY ANALYSIS: NO ADDITIONAL MANAGEMENT GUIDELINES IDENTIFIED BASED ON THE CLINICAL HISTORY PROVIDED

Other clinical factors may influence individualized management. This analysis may be incomplete if details about cancer diagnoses, ages, family relationships or other factors were omitted or ambiguous.

ADDITIONAL FINDINGS: VARIANT(S) OF UNCERTAIN SIGNIFICANCE (VUS) IDENTIFIED

GENE	VARIANT(S) OF UNCERTAIN SIGNIFICANCE	INTERPRETATION
AXIN2	c.1615G>A (p.Val539Met)	**UNCERTAIN CLINICAL SIGNIFICANCE** There are currently insufficient data to determine if these variants cause increased cancer risk.

Details About Non-Clinically Significant Variants: All individuals carry DNA changes (i.e., variants), and most variants do not increase an individual's risk of cancer or other diseases. When identified, variants of uncertain significance (VUS) are reported. Likely benign variants (Favor Polymorphisms) and benign variants (Polymorphisms) are not reported and available data indicate that these variants most likely do not cause increased cancer risk. Present evidence does not suggest that non-clinically significant variant findings be used to modify patient medical management beyond what is indicated by the personal and family history and any other clinically significant findings.

Variant Classification: Myriad's myVision™ Variant Classification Program performs ongoing evaluations of variant classifications. In certain cases, healthcare providers may be contacted for more clinical information or to arrange family testing to aid in variant classification. When new evidence about a variant is identified and determined to result in clinical significance and management change, that information will automatically be made available to the healthcare provider through an amended report.

ADDITIONAL INFORMATION

Genes Analyzed: Unless otherwise noted sequencing and large rearrangement analyses were performed on the following genes:

APC, *ATM*, *AXIN2*, *BARD1*, *BMPR1A*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CDK4*, *CDKN2A*, *CHEK2*, *EPCAM* (large rearrangement only), *HOXB13* (sequencing only), *GALNT12*, *MLH1*, *MSH2*, *MSH3* (excluding repetitive portions of exon 1), *MSH6*, *MUTYH*, *NBN*, *NTHL1*, *PALB2*, *PMS2*, *PTEN*, *RAD51C*, *RAD51D*, *RNF43*, *RPS20*, *SMAD4*, *STK11*, *TP53*. Sequencing was performed for select regions of *POLE* and *POLD1*, and large rearrangement analysis was performed for select regions of *GREM1* (see technical specifications).

** Other genes not analyzed with this test may also be associated with cancer.

Indication for Testing: It is our understanding that this individual was identified for testing due to a personal or family history suggestive of a hereditary predisposition for cancer.

Associated Cancer Risks and Clinical Management: Please see the "myRisk Management Tool" associated with this report for a summary of cancer risk and professional society medical management guidelines that may be useful in developing a plan for this patient based on test results and reported personal/family history, if applicable. Testing of other family members may assist in the interpretation of this patient's test result.

Analysis Description: The Technical Specifications summary (https://www.myriadpro.com/documents-and-forms/technical-specifications/) describes the analysis, method, performance, nomenclature, and interpretive criteria of this test. Current testing technologies are unable to definitively determine whether a variant is germline or somatic in origin, which may significantly impact risk estimates and medical management; therefore, these results should be correlated with this patient's personal and family history. The interpretation of this test may also be impacted if the patient has a hematologic malignancy or an allogeneic bone marrow transplant.