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ACCURACY OF THE BRCAPRO RISK ASSESSMENT MODEL IN MALES PRESENTING TO MD ANDERSON FOR BRCA TESTING

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PRESENTING TO MD ANDERSON FOR *BRCA* TESTING

by

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A

THESIS

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The University of Texas Health Science Center at Houston
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The University of Texas
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Graduate School of Biomedical Sciences
In Partial Fulfillment

of the Requirements

for the Degree of

MASTER OF SCIENCE

by

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Houston, TX

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ACCURACY OF THE BRCAPRO RISK ASSESSMENT MODEL IN MALES

PRESENTING TO MD ANDERSON FOR *BRCA* TESTING

Publication No. _____

Carolyn A. Garby, B.S.

Supervisory Professor: Banu Arun, M.D.

Hereditary Breast and Ovarian Cancer (HBOC) syndrome is due to mutations in *BRCA1* and *BRCA2* genes. Women with HBOC have high risks to develop breast and ovarian cancers. Males with HBOC are commonly overlooked because male breast cancer is rare and other male cancer risks such as prostate and pancreatic cancers are relatively low. *BRCA* genetic testing is indicated for men as it is currently estimated that 4-40% of male breast cancers result from a *BRCA1* or *BRCA2* mutation (Ottini, 2010) and management recommendations can be made based on genetic test results. Risk assessment models are available to provide the individualized likelihood to have a *BRCA* mutation. Only one study has been conducted to date to evaluate the accuracy of BRCAPro in males and was based on a cohort of Italian males and utilized an older version of BRCAPro.

The objective of this study is to determine if BRCAPro5.1 is a valid risk assessment model for males who present to MD Anderson Cancer Center for *BRCA* genetic testing. BRCAPro has been previously validated for determining the probability of carrying a *BRCA* mutation, however has not been further examined particularly in males.

The total cohort consisted of 152 males who had undergone *BRCA* genetic testing. The cohort was stratified by indication for genetic counseling. Indications included having a known familial *BRCA* mutation, having a personal diagnosis of a *BRCA*-related cancer, or having a family history suggestive of HBOC. Overall there were 22 (14.47%) *BRCA1*+ males and 25 (16.45%) *BRCA2*+ males. Receiver operating characteristic curves were constructed for the cohort overall, for each particular indication, as well as for each cancer subtype. Our findings revealed that the BRCAPro5.1 model had perfect discriminating

ability at a threshold of 56.2 for males with breast cancer, however only 2 (4.35%) of 46 were found to have *BRCA2* mutations.

These results are significantly lower than the high approximation (40%) reported in previous literature. BRCAPro does perform well in certain situations for men. Future investigation of male breast cancer and men at risk for *BRCA* mutations is necessary to provide a more accurate risk assessment.

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BACKGROUND

Introduction

Hereditary Breast and Ovarian Cancer (HBOC) is a hereditary cancer syndrome caused by mutations in the *BRCA1* and *BRCA2* genes and is inherited in an autosomal dominant manner. Since the discovery of *BRCA1* and *BRCA2* genes in 1994 and 1995, respectively [1,2] there have been many research studies conducted on this topic. The *BRCA1* gene is located on chromosome 17q21, consists of 1,863 amino acids, and plays an important role in DNA repair, cell-cycle-checkpoint control, protein ubiquitylation and chromatin remodeling [3]. The *BRCA2* gene is located on chromosome 13q12.3 and consists of 3,418 amino acids. To date, the exact function of *BRCA2* is not as well known, however both *BRCA1* and *BRCA2* play important roles in DNA repair, more specifically in homologous recombination [3]. Inheriting a *BRCA1* or a *BRCA2* mutation puts both males and females at risk to develop certain types of cancers at earlier ages than the general population.

Mutations in *BRCA1* and *BRCA2* confer the highest risk for women to develop breast and ovarian cancers. Women who are found to be *BRCA1* mutation carriers have up to an 85% lifetime risk of developing breast cancer and a 45% lifetime risk of developing ovarian cancer [4]. For women who are *BRCA2* mutation carriers, the lifetime risks to develop breast and ovarian cancer are up to an 84% risk and an up to a 27% risk, respectively [5]. These numbers are increased well above the general population lifetime risks for a woman to develop breast cancer and ovarian cancer. According to Surveillance, Epidemiology and End Results (SEER) the general lifetime population risk for women to develop breast cancer is 12.29% [6]. SEER data estimates that the general population lifetime risk for women to

develop ovarian cancer is 1.40% [6]. The vast majority of information known about *BRCA1* and *BRCA2* is through research conducted on women with *BRCA* mutations.

BRCA1 and *BRCA2* mutations are also associated with an increased risk for men to develop male breast cancer and prostate cancer with a higher risk conferred by having a *BRCA2* mutation [7]. The general population lifetime risk for men to develop prostate cancer is 16% [8]. The general population lifetime risk for men to develop breast cancer is 0.1% [9]. Both male and female *BRCA2* mutation carriers are at an increased risk to develop pancreatic cancers with up to a 7% lifetime risk seen for males and up to a 3% lifetime risk seen for females [5].

Male Breast Cancer

Male breast cancer is extremely rare and only accounts for 1% of all breast cancers [10]. In the United States, it is estimated that there are approximately 1,970 new cases of male breast cancer diagnosed each year with 390 deaths resulting from male breast cancer [10]. Male breast cancer usually first comes to attention due to one or more of the following symptoms: painless subareolar lump, nipple retraction, or bleeding from the nipple [11]. In comparison female breast cancers are commonly diagnosed through one of two methods, which include screening measures such as breast mammograms, MRIs, and ultrasounds or when the tumor has grown to a size that creates a lump that is palpable on physical exam [12]. Less common signs and symptoms in female breast cancers include breast pain or heaviness, swelling, thickening or redness of the skin covering the breast, nipple discharge, and changes to the nipple such as erosion, inversion, or tenderness [12]. Screening mammography starting at age 40 for women in the general population is universally

recommended [13]. The advances made in screening technology along with addition in adjuvant advances can be attributed to the 2.2% per year decrease seen in breast cancer mortality rates in the United States since 1990 [5].

Male breast cancers historically differ from female breast cancers in several different aspects. Male breast cancers, when compared to female breast cancers, are diagnosed at later ages and at more advanced clinical stages, with greater tumor sizes and more frequent involvement of the lymph nodes [9]. In comparison to the mean age of diagnosis of breast cancer in women of 62 years, male breast cancer is diagnosed five years later, with the mean age of diagnosis for male breast cancer being 67 years [11]. A similarity seen between male and female breast cancer is that there is a slight preponderance of left-sided disease over right-sided disease [11].

Tumor marker status for male breast cancers differs when compared to female breast cancers, as these markers are much more likely to be both estrogen and progesterone receptor positive. More than 90% of male breast cancers are found to be estrogen receptor positive, with the majority also being progesterone receptor positive at approximately 81% [11,14]. Male breast cancers are most commonly found to be HER2 negative, with estimation that only 10% of male breast cancer tumors demonstrate HER2 amplification [15].

The Surveillance, Epidemiology, and End Results (SEER) registry collected data on breast cancer from 1973 through 2005 and has a collection of 5,494 male breast cancer cases [9]. The SEER data set found that in their male breast cancer cases, 11% were diagnosed with ductal carcinoma in situ [9]. Most frequently, male breast cancer is confirmed by pathology to be invasive ductal carcinoma [11]. In male breast cancer, the histology

subtypes of lobular, mucinous, medullary and papillary account for only about 5% of cases [11]. The risk to develop breast cancer increases at a steady linear rate in regard to age for males with a peak being reached at approximately 75 years of age [9]. The linear rate observed in male breast cancers is in contrast to the bimodal distribution, also known as Clemmesen's hook, seen in regard to age of diagnosis for females [9]. The incidence of male breast cancer varies based on race, for example black males having a higher incidence of 1.8 per 100,000 as compared to white males having an incidence of 1.1 per 100,000 [9].

Male Breast Cancer Risk Factors

There are many different factors that may increase a male's risk to develop breast cancer in his lifetime. In addition to mutations in *BRCA1* and *BRCA2*, there are other genetic factors that have been suggested as conferring an increased risk for male breast cancer, more specifically mutations in *PTEN*, *CHEK2* [9]. The risks for male breast cancer associated with mutations in *PTEN*, *CHEK2* are substantially lower than the risk for male breast cancer with a *BRCA1* or *BRCA2* mutation. Klinefelter syndrome, a sex chromosome disorder diagnosed with karyotype of XXY, has been described as occurring in 3% to 7.5% of males with breast cancer [9,11]. Individuals with Klinefelter syndrome have been suggested to have up to a 50 times higher risk to develop breast cancer in comparison to males in the general population [16]. Determining the exact risk factor for male breast cancer in regard to Klinefelter syndrome is complicated due to the relative rarity of these two factors.

Gynecomastia is defined as the abnormal development of large mammary glands resulting in breast enlargement in males [16]. It is thought that gynecomastia is a risk factor

for the development of male breast cancer due to an increased amount of breast tissue. Gynecomastia is the most common benign breast condition noted in males, occurring in approximately 30% of healthy men [11,17]. Having at least one female relative diagnosed with breast cancer increases a man's likelihood to develop breast cancer 2.5 times [11]. In summary, risk factors for the development of male breast cancer include genetic mutations, hormonal and personal factors, family history of breast cancer, and environmental factors. Both males and females who receive chest wall radiation for various indications such as treatment for Hodgkin's lymphoma are at increased risk to develop breast cancer [11]. Several risk factors have been proposed to exist with male breast cancer and include alcohol use, liver disease, obesity, electromagnetic field radiation and diet; although further investigation is needed at this point to prove associations [11].

Treatment for Male Breast Cancer

As previously stated, male breast cancer is rare; due to this fact there have only been retrospective analyses performed in evaluating treatment options for male breast cancer at this point in time. Treatment choices for male breast cancer are similar to the options available for female breast cancer and include surgery, adjuvant therapy, radiation and chemoprevention [18]. In regard to surgical options, males generally undergo a modified radical mastectomy due to the relatively small amount of male breast tissue along with the fact that most male breast tumors are centrally located [19]. Male breast cancer patients are more likely than their female counterparts to receive radiation due to the presence of advanced disease [20]. Since the vast majority of male breast cancers are estrogen and progesterone positive tumors, the chemoprevention agent Tamoxifen has recently been

studied in this patient population based on data established in female breast cancers that this agent improves survival along with decreasing recurrences of breast cancer [18]. There are concerns that need to be considered when prescribing hormonal agents like Tamoxifen to male patients, such as potential undesirable side effects, which may cause males to discontinue this treatment [21]. Pemmaraju et al. (2011) recently carried out a retrospective review of 64 male breast cancer patients who were treated with Tamoxifen and found that 20.3% of patients altogether discontinued Tamoxifen citing specific side effects. In addition to clinicians continuing to increase patient awareness of unpleasant side effects, more research is needed focused on evaluating the use of Tamoxifen in males.

Prostate Cancer

Prostate cancer is currently the most commonly diagnosed male cancer in North America [22]. It is estimated that in 2011, 240,000 men will be diagnosed with prostate cancer and result in 34,000 deaths [8]. It has been established that *BRCA2* carriers have between a 2-5 relative risk for prostate cancer, whereas *BRCA1* carriers have between a 1-3 relative risk [21]. The NCCN® guidelines recommend that both the risks and benefits of screening for prostate cancer be discussed with male *BRCA* carriers at age 40. The American Cancer Society recommends that men at high risk for developing prostate cancer should begin having specific antigen tests (PSA) and digital rectal examinations (DRE) at age 40. The American Cancer Society defines high risk as males who have multiple relatives with prostate cancer, which is an important distinction to make since this definition does not specifically include *BRCA* carriers. However, the utility of prostate screening is currently a subject of contention and disagreement among many medical professionals. It

will be imperative in the coming years for both male *BRCA* carriers as well as men in the general population to stay abreast on research regarding this topic.

Prostate Cancer Risk Factors and Treatment

There are numerous risk factors that are known to increase the risk for prostate cancer in males. Increasing age, positive family history, and being of African American heritage are the risk factors that have been found to be most strongly associated with prostate cancer [23]. “The median age of diagnosis of prostate cancer is 67 years and the median age of death is 81 years” [22]. Men who have at a first degree relative diagnosed with prostate cancer are at a two-fold increased risk to develop prostate cancer in comparison to their counterparts with no apparent family history [24]. For reasons not well understood at this point in time, African American males have a higher incidence of prostate cancer and are also more likely to receive the diagnosis at an advanced stage of disease when compared to Caucasian and Hispanic males [23].

Once a prostate cancer is detected there are numerous different approaches to managing the disease, often times decisions are based on several different factors such as the patient’s age, if the cancer has spread, other medical conditions, along with the patient’s overall health [25]. There are several different treatment options when the prostate cancer has not metastasized and include watchful waiting, radical prostatectomy, radiation therapy either internal or external, hormone therapy, and cryotherapy [25].

Pancreatic Cancer

Of all cancers diagnosed in the United States, pancreatic cancers are the fourth deadliest [26]. Although rare in occurrence, representing only 3% of cancers each year, pancreatic cancer accounts for 6% of all cancer related deaths [10] (Jemal et al, 2007). It is estimated that 10% of pancreatic cancers are due to heritable genetic mutations and/or familial patterning of inheritance [27,28]. *BRCA* mutation carriers are at increased risk to develop pancreatic cancer, with *BRCA2* carriers having around a 5% lifetime risk to develop pancreatic cancer [5]. It is estimated that *BRCA1* mutation carriers have approximately a 2.26 increased risk to develop pancreatic cancer in comparison to the general population [29]. In the Ashkenazi Jewish population, there is a particular *BRCA2* mutation, 6174delT, that has been found in families who have higher incidences of pancreatic cancer [26]. In the Ashkenazi Jewish population *BRCA2* mutations have been found to be associated with 10% of unselected, apparently sporadic pancreatic cancers [30]. Unfortunately at this point in time there are not reliable methods for screening and early detection of pancreatic cancers, even though individuals at increased risk based on gene mutations or family history could benefit from such screening. Detecting small pancreatic cancers along with premalignant lesions of the pancreas is complicated by the fact that neither lesion shows symptoms [26]. If an individual is identified as being at an increased risk for the development of pancreatic cancer, there are several available ongoing clinical trials looking to identify the most reliable screening method for this patient population.

Pancreatic Cancer Risk Factors and Treatment

Pancreatic cancer is considered to be multifactorial in its development. Risk factors include smoking, family history of chronic pancreatitis, advancing age, male sex, diabetes mellitus, obesity, non-O blood type, occupational exposures such as nickel, and diet [31]. Possible risk factors for pancreatic cancer may include *Helicobacter pylori* infection and periodontal disease [29]. Another genetic risk factor for developing pancreatic cancer is seen in individuals with hereditary pancreatitis, which is a rare inherited form of chronic pancreatitis caused by germline *PRSSI* mutations [32]. Notably a positive history of cigarette smoking and/or use of other tobacco products is present in 20% of all patients with pancreatic tumors [33].

For pancreatic cancer patients, the only potentially curative treatment is a pancreatectomy, for which only 15-20% of patients will qualify for this course of treatment [32]. In comparison to patients with unresectable pancreatic tumors, patients who undergo a pancreatectomy have a higher 5-year survival rate, although it is still relatively low with the 5 year survival rate being 25-30% in node-negative patients and 10% in node-positive patients [30].

***BRCA* Testing in males who present with *BRCA* associated cancers**

BRCA genetic testing is indicated in this patient population as it is currently estimated that up to 40% of male breast cancers result from a *BRCA2* mutation whereas up to 4% of cases are estimated to result from a *BRCA1* mutation [7,14,34]. Males who are known *BRCA1* mutation carriers are quoted as having a 5.8% lifetime risk to develop breast cancer, whereas males with a known *BRCA2* mutation have a 6.9% lifetime risk to develop

breast cancer, which is 80-100 times increased above the general population risk [7]. The general population lifetime risk to develop breast cancer for males is 0.1% [9]. Mutations in both *BRCA* genes also confer an increased risk for males to develop prostate and pancreatic cancers [7]. In regard to *BRCA* mutations it is more common for males with breast cancer to be *BRCA2* mutation carriers. Although one study found that more than one-third of the *BRCA* mutations that were identified in their cohort of 76 men with breast cancer were *BRCA1* [35]. A predisposition to develop other cancers such as melanoma and stomach cancer may also exist due to *BRCA1* and *BRCA2* mutations [22].

Screening Recommendations

The National Comprehensive Cancer Network® has put forth screening guidelines for men who are found to be *BRCA1* or *BRCA2* mutation carriers. The NCCN® is comprised of 21 cancer centers and is considered to be a leading authority providing expert opinions in the field of cancer. The NCCN 2011 guidelines for male *BRCA1* and *BRCA2* mutation carriers include:

“breast self-exam training and education starting at age 35, clinical breast exam , every 6-12 months, starting at age 35 years, consider baseline mammogram at age 40; annual mammogram if gynecomastia or parenchymal/glandular breast density on baseline study, as well as adhere to screening guidelines for prostate cancer.” [36]

In males undergoing mammography, the sensitivity is reported to be 92% with 90% specificity in the diagnosis of male breast cancers [11,37]. Because of their increased lifetime cancer risks, it is important to identify males with *BRCA1* and *BRCA2* mutations early so that screening can be implemented in the hopes of preventing cancer altogether.

Clinical *BRCA* Testing

Myriad Genetic Laboratories first made testing for *BRCA1* and *BRCA2* mutations available in 1996 [38]. Currently, genetic counselors and other health care providers utilize statistical models along with clinical judgment to determine if individuals are candidates for *BRCA* genetic testing. Indications for *BRCA* genetic testing include a personal history of early onset breast and/or ovarian cancer and positive family history the family history features that are suggestive of a hereditary form of breast and ovarian cancer include: close relatives with breast, ovarian or other related cancers, premenopausal breast cancer diagnoses, multiple related cancers in an individual, male breast cancer, similar cancers in multiple generations, and Ashkenazi Jewish ancestry. The NCCN® recommends offering *BRCA* testing to any male diagnosed with breast cancer in order to investigate the possibility of a genetic cause; therefore it is routine practice in the clinical setting [36] [39].

When considering *BRCA* genetic testing, it is important to understand the different types of tests that are currently available. If an individual reports being of Ashkenazi Jewish ancestry, it is most appropriate to begin testing with the Ashkenazi Jewish Multisite 3 *BRCA*Analysis® test. This is due to the fact that the majority of mutations in Ashkenazi Jewish individuals occur in one of three common founder mutations two in *BRCA1* (187delAG, 5385insC) and one in *BRCA2* (6174delT) [35]. If there is a known *BRCA* mutation within a family, testing should first be ordered for that particular known familial mutation, however if this individual is found to have an Ashkenazi Jewish founder mutation then the multi-site panel should be ordered for their family members. In both of these cases, if a negative test result is obtained, there is always the option to additional *BRCA* testing. Therefore, one patient could have multiple types of *BRCA* testing ordered. Comprehensive

BRCA genetic testing should be the first line of testing ordered for individuals without a known familial mutation or any report of Ashkenazi Jewish ancestry. Comprehensive testing involves sequencing both *BRCA1* and *BRCA2*. BRACAnalysis Large Rearrangement Test® (BART) is testing offered through Myriad clinically as of August 2006 and involves testing for large rearrangements, deletions or duplications that are otherwise missed by sequencing. The yield for mutations found by BART is relatively low, although varies based on ethnic groups.

After *BRCA* testing is ordered there are three possible test results that a patient can receive. The first test result is that of a positive result, meaning a mutation was detected. Individuals with a positive test result should follow screening recommendations such as those outlined by the NCCN® and encourage other family members to seek genetic counseling and be tested for the mutation that was identified. A negative test result means that no mutation was identified based on the testing ordered. Individuals who receive this result should be considered for additional reflex testing if either their personal and/or family history is highly suggestive of HBOC. Lastly, there is the result of a variant of uncertain significance meaning that a sequence change was identified, however it is unclear whether that specific change is deleterious or a polymorphism.

Risk Assessment Models for Genetic Mutations

Certain cancer genetic risk assessment models are used by clinicians to give their patients an individualized risk to develop a particular cancer or the chance to have a *BRCA* mutation, which in turn can assist patients in making informed decisions about undergoing genetic testing. Three men from Duke University Institute for Statistics and Decision

Sciences created BRCAPro [40]. BRCAPro has been validated as an accurate counseling tool for determining the probability of carrying *BRCA1* and *BRCA2* mutations [41].

BRCAPro utilizes personal history and family history of first and second-degree relatives' diagnoses of cancer in addition to other characteristics such as hormone receptor status (breast cancer), oophorectomy, ethnicity, and Ashkenazi Jewish ancestry to provide an accurate risk assessment. BRCAPro is a risk assessment model based on Baye's theorem, which takes into account both affected and unaffected individuals to calculate an individual's conditional probability to have a mutation in either *BRCA1* or *BRCA2*. In the case of BRCAPro, the condition is having a personal history of cancer, family history of cancer, or both. The question generated by BRCAPro is "given this pattern of affected and unaffected relatives, what is the probability that this individual carries a mutation in one of the BRCA genes?" [40]. *CancerGene* Version 5.1 is available as a free online download, and includes BRCAPro (UT Southwestern Medical Center of Dallas © 1998-2010). BRCAPro version 5.1 has been updated to include race-specific calculations and uses Myriad BRCA prevalence tables from February 2010.

The overall accuracy of this model is dependent on both the frequency and penetrance of *BRCA* mutations in the specific population of interest [42]. An initial limitation of BRCAPro as a risk assessment model is that it was developed and thus first validated in individuals, mainly women, of Ashkenazi Jewish or European descent and therefore may not be as meaningful or useful in minority populations [42]. Minority populations represent less than 10% of individuals who uptake *BRCA* genetic testing, according to data from Myriad Genetic Laboratories [42]. The small number of minorities who have undergone *BRCA* genetic testing only further complicates the issue of validating

BRCAPro in these populations. However, one study conducted in 2009 studied a total of 292 minority families which included African Americans, Hispanics, Asian-Americans, Native Americans as well as a few other less represented minorities in the United States, who had at least one family member who had undergone *BRCA* mutational testing in order to access BRCAPro's ability to accurately detect mutation carriers. This study found that BRCAPro performed the most reliably in Hispanics with the highest AUC of 0.83, and the least reliably in African Americans with an AUC of 0.68 [42]. Similar to the small number of studies that have focused on validating BRCAPro use in minority populations, relatively no studies have focused on the utilization of this model in males.

Zanna et al, (2010) found in their study of 102 Italian men with breast cancer, that BRCAPro had the highest combination of sensitivity, specificity, negative predictive value, and positive predictive value out of four different risk assessment models [34]. However, further research is needed for the male breast cancer population and males in general undergoing *BRCA* genetic testing.

One recent study found the BRCAPro model was overestimating the relative contribution that female bilateral breast cancer had on the likelihood of detecting either a *BRCA1* or *BRCA2* mutation in their cohort of 66 women with a personal history of bilateral breast cancer [43]. Further investigation into male breast cancer may produce findings similar to Ready et al, (2009) in regard to BRCAPro overestimating their likelihood to be *BRCA* mutation carriers.

Objective

The objective of this study was to determine if BRCAPro is a valid risk assessment model to use for all males who present for *BRCA* genetic testing. Findings from this study will help clinicians offering testing to male breast cancer patients or who have a significant family history that is suggestive of HBOC to determine the most appropriate testing candidates and accurately assess their risk to test positive. Additionally, this study may facilitate the development of a new risk assessment model specifically for males, if the BRCAPro model is not validated in this study population.

METHODS AND MATERIALS

This study was a retrospective chart review of all males who have presented to MD Anderson Cancer Center for genetic counseling in the high-risk genetics clinics and had *BRCA* testing performed. A chart review through MD Anderson Cancer Center's electronic medical record (EMR) was performed to obtain relevant information for study participants. The specific aim of this study was to determine if BRCAPro version 5.1 is a valid risk assessment tool in affected males who have undergone *BRCA* genetic testing. Males who had undergone predictive testing, or those with a known familial mutation (KFM) were included in this study, however were analyzed separately from males affected with a *BRCA* related cancer that presented as the index case in their family for *BRCA* testing. We hypothesized that BRCAPro5.1 will overestimate the likelihood for a male to have either a *BRCA1* or *BRCA2* mutation.

Study Approval

The University of Texas-Houston Health Science Center's Institutional Review Board approved this study on July 25th, 2011. The Committee for the Protection of Human Subjects of MD Anderson approved this study on November 3rd, 2011.

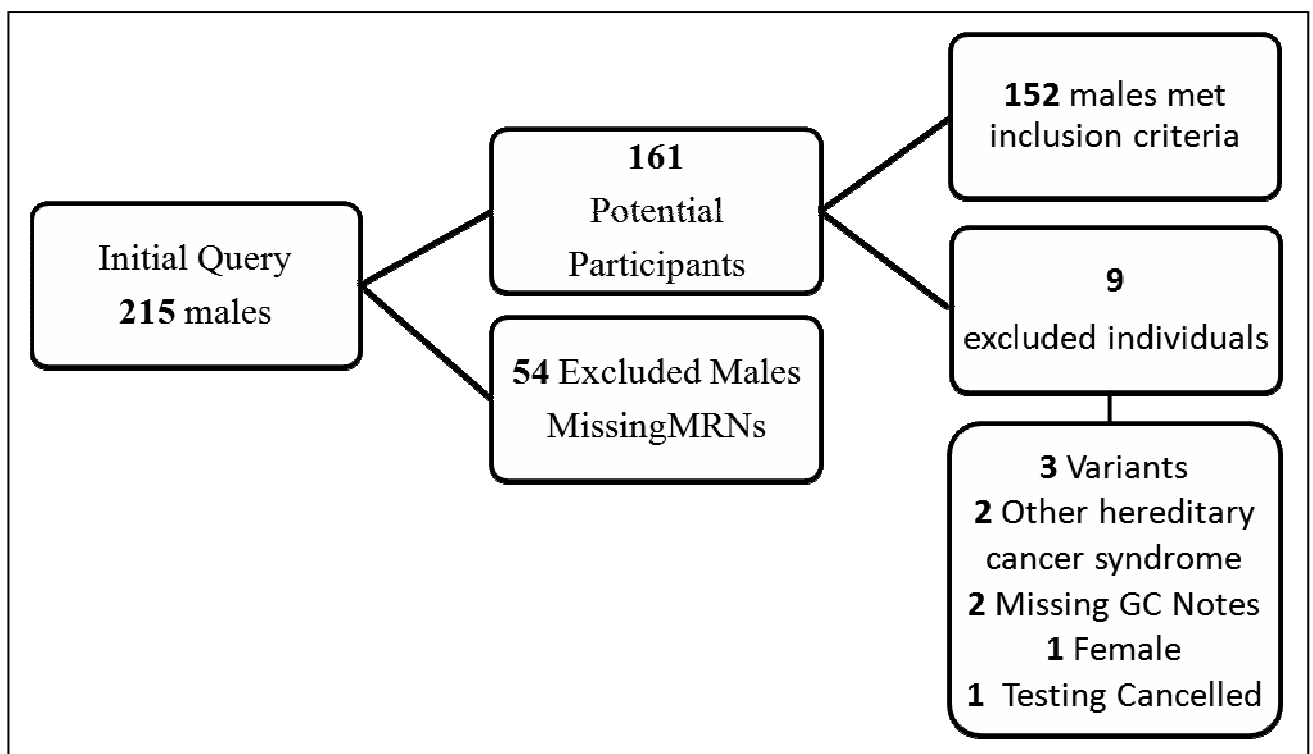
Study Population

The study population consisted of 152 MD Anderson Cancer Center male patients who underwent *BRCA* testing through Myriad Genetics Laboratory in Salt Lake City, Utah. However, one study participant had *BRCA* testing performed through Oxford Radcliffe Hospitals Genetics Laboratories in Oxford, OX.

Ascertainment

An IRB approved research database at MD Anderson Cancer Center was used to identify potential study participants. The study population included patients seen at MD Anderson between February 1997 to September 2011. An initial query revealed 215 males had presented to MD Anderson for *BRCA* testing, however 54 of these patients were excluded based on the fact that they were missing medical record numbers. A total of 161 patients were identified as potential study participants and their fulfillment of the inclusion criteria was confirmed during review of their medical records. Of the 161 patients, in total nine were excluded because they did not meet the inclusion criteria of the study. The following individuals were excluded from our data: women, individuals who did not have electronic medical records on file, individuals who did not have a genetic counseling note as reliable family history could not be obtained, males with a variant of uncertain significance and no deleterious mutation, males who were identified to have another hereditary cancer syndrome aside from HBOC and males whose *BRCA* testing was never performed. Males who were noted to have a variant of uncertain significance in either *BRCA1* or *BRCA2* that were classified as suspected deleterious were included due to the fact that these individuals are treated from a clinical standpoint as having a mutation. Males who were noted to have a variant of uncertain significance in either *BRCA1* or *BRCA2* classified as a favored polymorphism were included and treated as a negative result. Males who were diagnosed with ductal carcinoma in situ (DCIS) were included in the cohort and entered into BRCAPro as having DCIS at their age of diagnosis as opposed to entering their DCIS as invasive breast cancer developing 10 years after the DCIS.

Figure 1: Flowchart of final study population



BRCAPro Risk Calculation

All study participants had their individual BRCAPro numbers calculated by entering both their personal and family history into the BRCAPro 5.1 model, which generates both a pedigree and risk calculation. Study participants' ethnicities were recorded by self-report at their genetic counseling appointment. Males who were diagnosed with ductal carcinoma in situ (DCIS) were included in the cohort and entered into BRCAPro as having DCIS at their age of diagnosis as opposed to entering their DCIS as invasive breast cancer developing 10 years after the DCIS. Males who were undergoing predictive testing had their KFM entered into the program to most accurately predict their own likelihood to test positive.

Data Collection

The study population's medical records at MD Anderson Cancer Center were reviewed December 2011 through March 2012. The information extracted from the medical records is displayed in table 1.

Table 1 Information Obtained from Chart Review through MD Anderson EMR

Demographic and General Information Indication for genetic counseling Date of birth Ethnicity including Ashkenazi Jewish Age of diagnosis of all cancer diagnoses Height and weight (at initial appointment) to calculate BMI Gynecomastia if noted on physical exam (at initial appointment)
Tumor Information Receptor status of breast tumor Pathology of tumor History of previous biopsy Treatment options
Family History First and second degree relatives (sometimes third degree) with reported cancer diagnoses Gender of family members Ages of diagnoses of these cancers if reported Ages of deaths of these individuals if reported Pedigrees constructed from the genetic counseling appointment
Testing Information Type of testing ordered Date of testing Testing result

Statistical Analysis

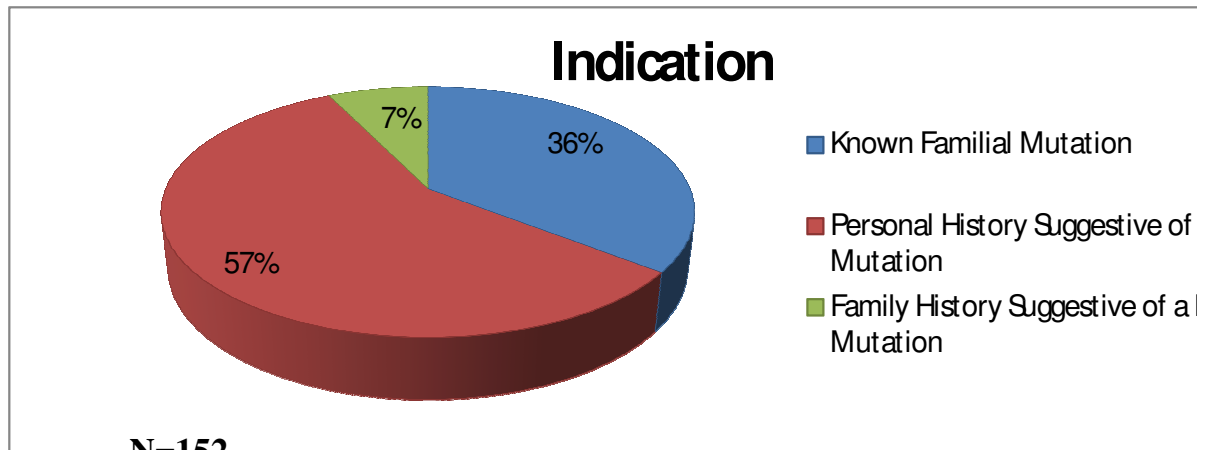
Numerous computer programs were utilized to analyze this data set. Access 2010 was used to create a secure password protected database for all information collected from the chart review portion. Microsoft Excel 2010 was used as a means of organizing the data. STATA 10.0 was used to perform descriptive statistics.

We constructed receiver operating characteristic (ROC) curves to evaluate the discriminatory value of the BRCAPro5.1 model. ROC curves are constructed by plotting the sensitivity on the y axis against 1-specificity on the x axis. When discussing the likelihood of having a *BRCA* mutation, sensitivity and specificity have equal importance since it can be argued harm could be afflicted for calling either false positives or false negatives. Therefore, in order to set our threshold value for our ROC curve, the Youden's index (J) was calculated, since it was determined that both sensitivity and specificity are equally critical. The maximum theoretical value for J is 1, in the case of a test having perfect discriminatory value or the ability to accurately determine individuals who will test positive from those who will test negative.

RESULTS

In total 152 male patients were included in our cohort; 57% (87/152) presented for *BRCA* testing due to a personal history that was suggestive of a *BRCA* mutation as defined as having a personal diagnosis of male breast cancer, pancreatic cancer and/or prostate cancer, 36% of our patients were seen for predictive testing with a KFM and 7% presented to clinic due to a family history that was suggestive of a *BRCA* mutation (Figure 1). Table 1 summarizes the number of study participants seen for each indication with 54 males presenting to clinic with a KFM, 87 males presenting to clinic due to a personal history suggestive of a *BRCA* mutation (diagnosis of male breast cancer, prostate, pancreas) and 11 males presenting to clinic due to a family history suggestive of a *BRCA* mutation. A family history suggestive of a *BRCA* mutation included males of Ashkenazi Jewish ancestry, first and/or second degree relatives with early age of onset and higher than expected diagnoses of *BRCA* related cancers in family members (breast, ovarian, prostate, pancreatic). Therefore, the majority of our study cohort was seen due to a personal cancer history that was suggestive of a *BRCA* mutation. Results from our study were stratified based on the indication for having *BRCA* testing, as these groups were analyzed separately from one another.

Figure 2: Indication for *BRCA* Testing



Demographics

The vast majority of our study population was Caucasian with a total of 94 males (61.84%). This number increases to 129 males (84.87%) if you add in the ethnic group who reported themselves as Ashkenazi Jewish which is a subset of Caucasian. The ethnicity of our cohort is summarized in Table 2.

The overall mean age of the study cohort at the time they presented for *BRCA* testing was found to be 57.43 with a standard deviation of 14.59 and a range from 19 to 88 years. When looking at the dataset stratified by indication, it was noted that the lowest mean age was 51.06 with a standard deviation of 17.81 and a range from 19 to 79 years for individuals who were undergoing predictive testing. The highest mean age of 61.31 with a standard deviation of 14.59 was seen for individuals who had a personal cancer diagnosis suggestive of a *BRCA* mutation. The findings for the age of our study population are summarized in Table 2.

When looking at the vital status of our study cohort, it was seen that overall the majority of participants were still living (80.26%; n=122) when our chart review was

performed, while 30 males were deceased representing 19.74% of the cohort. The majority of deceased males had a personal history of cancer, (93.3%, n=28). The vital status of the study participants from the time of the chart review are summarized in Table 2.

Table 2: Demographic Information of Study Cohort

Variable		Known Familial Mutation	Personal History	Family History	Overall
N		54 (35.53%)	87 (57.24%)	11 (7.24%)	152
Age (Mean, SD)		51.06 (17.81)	61.31 (11.36)	58.36 (8.26)	57.43 (14.59)
Ethnicity	Caucasian	38 (70.37%)	52 (59.77%)	4 (36.36%)	94 (61.84%)
	Ashkenazi	8 (14.82%)	20 (22.99%)	7 (63.64%)	35 (23.03%)
	Hispanic	8 (14.82%)	6 (6.90%)	0	14 (9.21%)
	Black	0	4 (4.60%)	0	4 (2.63%)
	Asian	0	4 (4.60%)	0	4 (2.63%)
	Other	0	1 (1.15%)	0	1 (0.66%)
Vital Status	Alive	51 (41.80%)	63 (51.64%)	8 (6.56%)	122 (80.26%)
	Deceased	2 (6.67%)	28 (93.33%)	0 (0.00%)	30 (19.74%)

Of our total cohort, 46 (30.26%) males were noted to have invasive breast cancer or DCIS. The majority of males with breast cancer, 44, had an indication of having a personal diagnosis of cancer, whereas the other 2 breast cancers were diagnosed in males who had a KFM. The overall mean age of diagnosis for breast cancer not subdivided by indication was 60.13 with a standard deviation of 10.83 and a range from 24 years to 87 years. The most common pathology was ductal accounting for 38 (82.61%) of all the breast cancers diagnosed. The least common breast pathology was mixed lobular and ductal as it was found in only 1 study participant (2.17%). The majority of breast cancers diagnosed were both ER+ and PR+ with 40 breast cancers being ER+ and 38 breast cancers being PR+, which represented 86.96% and 82.61% respectively of all the breast cancers

diagnosed. The findings of breast cancers diagnosed, breast cancer subtype and tumor marker status are summarized in Table 3.

Table 3: Breast Cancer Information and Subtype by Indication

Variable		Known Familial Mutation (n=54)	Personal History (n=87)	Family History (n=11)	Overall (n=152)
Breast Cancer Present		2 (3.70%)	44 (50.57%)	0	46 (30.26%)
Age of Diagnosis (Mean, SD)		62.50 (3.54)	60.02 (11.06)	0	60.13 (10.83)
Breast Cancer Pathology	Ductal	2 (100%)	36 (81.82%)	0	38 (82.61%)
	DCIS	0	5 (11.36%)	0	5 (10.87%)
	Papillary	0	2 (4.55%)	0	2 (4.35%)
	Ductal and Lobular	0	1 (2.27%)	0	1 (2.17%)
Tumor Markers	ER+	2 (100%)	38 (86.36%)	0	40 (86.96%)
	PR+	2 (100%)	36 (81.82%)	0	38 (82.61%)
	Her2neu+	1 (50%)	3 (6.82%)	0	4 (8.70%)

In addition to breast cancer, males in our study were noted to have several other *BRCA* associated cancers. Across all three indications, prostate cancer was diagnosed in 21 males, which represented 13.82% of the entire study population. Overall the mean age of diagnosis of prostate cancer was 57.47 with a standard deviation of 6.33 and a range from 47-70. Of the 21 prostate cases diagnosed, 16 cases were diagnosed in males seen due to their cancer diagnosis while 5 cases of prostate cancers were diagnosed in males seen due to having a KFM. Across all three indications, pancreatic cancer was diagnosed in 39 patients

(25.66%). Pancreatic cancer had a mean age of diagnosis of 56.16 years with a standard deviation of 10.64 and a range from 34 to 80 years. Additionally, other cancer diagnoses were also collected from the medical records. Overall the mean age of diagnosis of other cancers was 58.60 with a standard deviation of 13.26 and a range from 33 to 80 years. Of the 54 males seen for an indication of a KFM, 10 (18.52%) were noted to have other cancers that are not currently known to be associated with *BRCA* mutations and included: bladder cancer, squamous cell carcinoma of the tongue, appendix cancer, colon cancer, basal cell carcinoma, and duodenum. Of the 87 males seen for a personal cancer diagnosis suggestive of a *BRCA* mutation, 21 (24.14%) were noted to have other additional cancer diagnoses which included: basal cell carcinoma, pituitary cancer, bladder cancer, duodenal cancer, colon cancer, clear cell carcinoma, thyroid cancer, lung cancer, squamous cell carcinoma, esophageal cancer, and Non-Hodgkin's lymphoma. Of the 11 males seen for a family history suggestive of a *BRCA* mutation, 4 (9.09%) were noted to have a cancer diagnosis and included: adenocarcinoma of unknown primary, lymphoma, anal cancer, and duodenal cancer. The findings of other cancers, aside from breast cancer, diagnosed in our study cohort can be found in Table 4.

Table 4: Other Cancer Diagnoses by Indication

Other Cancers	Known Familial Mutation (n=54)	Personal History (n=87)	Family History (n=11)	Overall (n=152)
Prostate Cancer	5 (9.26%)	16 (18.39%)	0	21 (13.82%)
Age of Diagnosis (Mean, SD)	53.6 (4.56)	58.69 (6.43)	0	57.47 (6.33)
Pancreatic Cancer	4 (7.41%)	35 (40.23%)	0	39 (25.66%)
Age of Diagnosis (Mean, SD)	45.33 (3.06)	57.09 (10.56)	0	56.16 (10.64)
Other Cancers	10 (18.52%)	21 (24.14%)	4 (9.09%)	35 (23.03%)
Age of Diagnosis (Mean, SD)	57.00 (14.70)	62.61 (9.49)	59.25 (10.18)	58.60 (13.26)

Several variables were looked at within our study to observe if there were particular trends or associations in regard to male breast cancer. These variables included gynecomastia, a history of a previous biopsy, radiation exposure, and if study participants chose to have a prophylactic mastectomy of their unaffected breast after receiving their breast cancer diagnosis. Overall the numbers were very low for these miscellaneous findings and are summarized in Table 5.

Table 5: Miscellaneous Information for Study Cohort by Indication

Miscellaneous Findings	Known Familial Mutation (n=54)	Personal History (n=87)	Family History (n=11)	Overall (n=152)
Gynecomastia	1 (1.85%)	2 (2.30%)	0	3 (1.97%)
Previous biopsy	0	2 (2.30%)	0	2 (1.32%)
Radiation exposure	0	7 (8.05%)	1 (9.10%)	8 (5.26%)
Prophylactic mastectomy	0	2 (2.30%)	0	2 (1.32%)

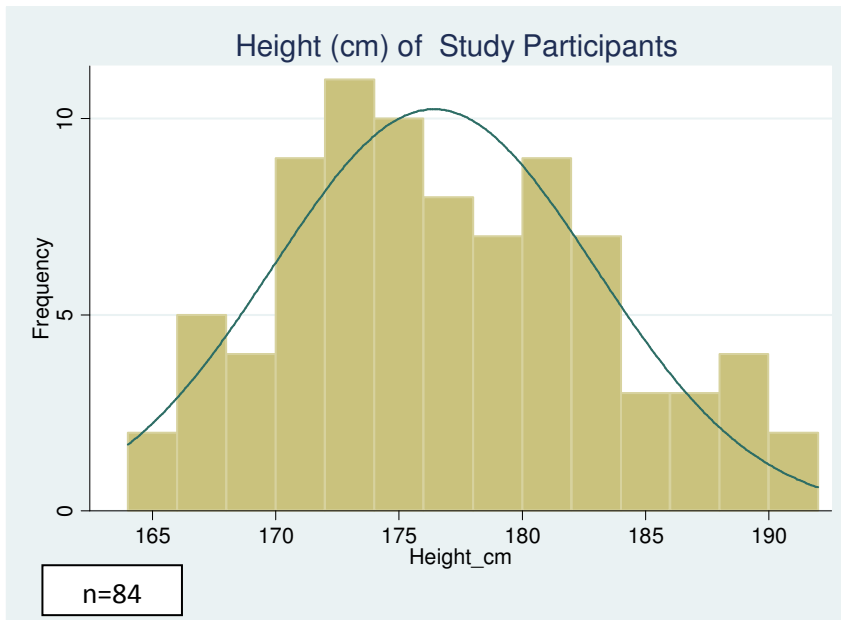
Table 6 summarizes the number of first and second degree relatives diagnosed with particular cancers per family of our study participants. Cancers included in this table are those known to be associated with *BRCA* mutations and included: breast cancer, male breast cancer, ovarian cancer, breast and ovarian cancer in the same individual, prostate and pancreatic cancer. Other cancers diagnosed in first and second degree relatives that are not known to be associated with *BRCA* mutations were collected from the electronic medical record and stored in our database; however, were not reported in this table. The family history data is subdivided by the three indications males for seen for genetic counseling.

Table 6: Family History (First and Second Degree Relatives) Information Per Family

Variable	Known Familial Mutation (n=54)	Personal History (n=87)	Family History (n=11)
Family History (Per Family)	Total number Mean (SD)	Total number Mean (SD)	Total number Mean (SD)
Individuals with breast cancer	70 2.55 (1.28)	75 0.86 (0.95)	20 1 (1.83)
Individuals with male breast cancer	2 0.037 (0.19)	0	2 0.18 (0.40)
Individuals with ovarian cancer	28 0.52 (0.72)	10 0.11 (0.35)	1 0.17 (0.30)
Individuals with prostate cancer	5 0.09 (0.29)	34 0.39 (0.75)	1 0.17 (0.30)
Individuals with pancreatic cancer	8 0.15 (0.45)	7 0.51 (0.31)	5 0.45 (1.2)
Individuals with breast and ovarian cancer	8 0.15 (0.41)	0	0

Of the 152 males in our study, 84 had a height recorded at the time of their initial visit to MD Anderson (Figure 3). Therefore 68 males were missing a measurement for height from their patient history database. It is seen that the height is normally distributed. The mean for height in cm was 176.42 with a standard deviation of 6.54. The range of values recorded for height in cm was 164 to 191. The p-value obtained from the skewness test was 0.289.

Figure 3: Height (cm) of Study Participants



Of the 152 males in our study, 87 had a weight recorded at the time of their initial visit to MD Anderson (Figure 3). Therefore 65 males were missing a measurement for weight from their patient history database. It is seen that weight is not normally distributed within our cohort. By looking at the graph it is seen to be skewed to the left, as several males were noted to be overweight. The median for weight in kg was 87 with the IQR being from 77 at the 25th percentile to 97 at the 75th percentile. The p-value obtained from the skewness test was <0.001 .

Figure 4: Weight (kg) of Study Participants

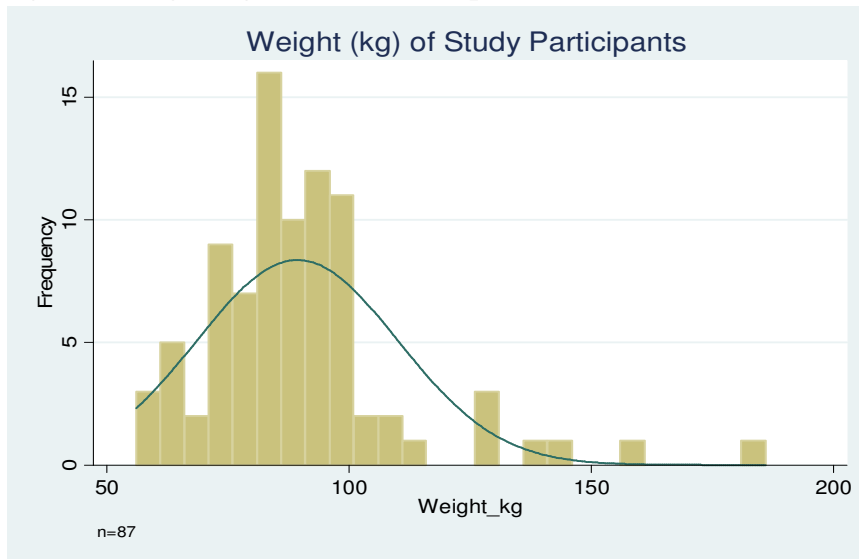
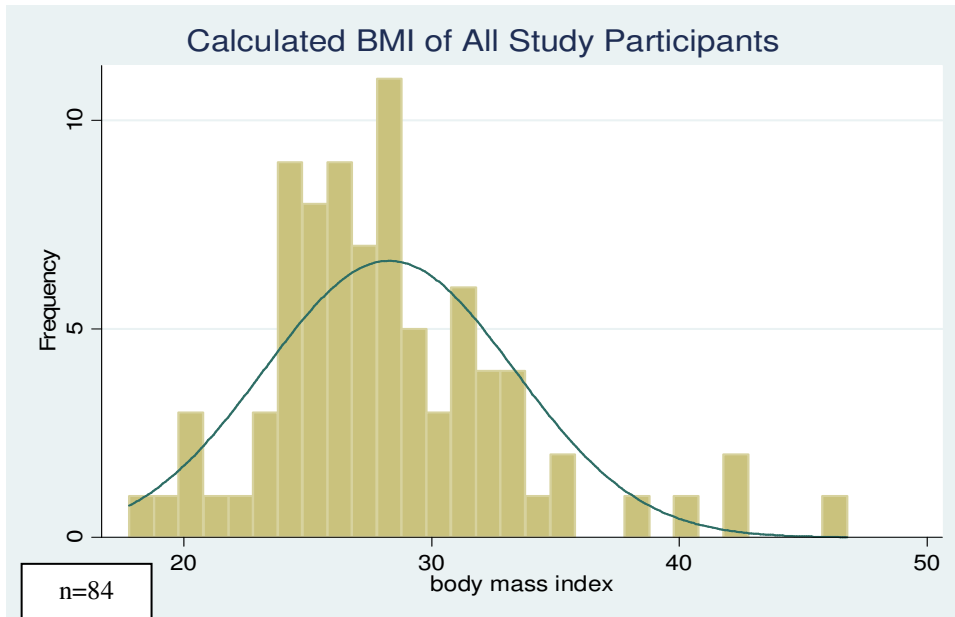


Figure 4 shows the calculated body mass index, or BMI, of study participants calculated for the 84 males who had both a recorded height and weight. BMI measurement takes into account an individual's height and weight and is calculated by the following formula: $\text{weight (kg)} / [\text{height (m)}]^2$. It is seen that BMI is not normally distributed within our cohort as it is skewed to the right. The median BMI is 27.75 with an IQR of 25.20 to 30.98. The p value from the skewness test was 0.001.

Figure 5: BMI for Males with Recorded Height and Weight



***BRCA* Testing**

Figure 6 displays the type of testing ordered across all three indications. For each study participant it is important to understand that more than one test may have been ordered. In total our cohort of 152 male, 174 *BRCA* tests were ordered. The most commonly ordered tested was comprehensive testing, which accounted for 47% or 81 of the total 174 tests ordered. It is seen that the least ordered test for our cohort was BART, as it accounted for only 8% of all of the tests ordered.

Figure 6: Type of *BRCA* Testing Ordered

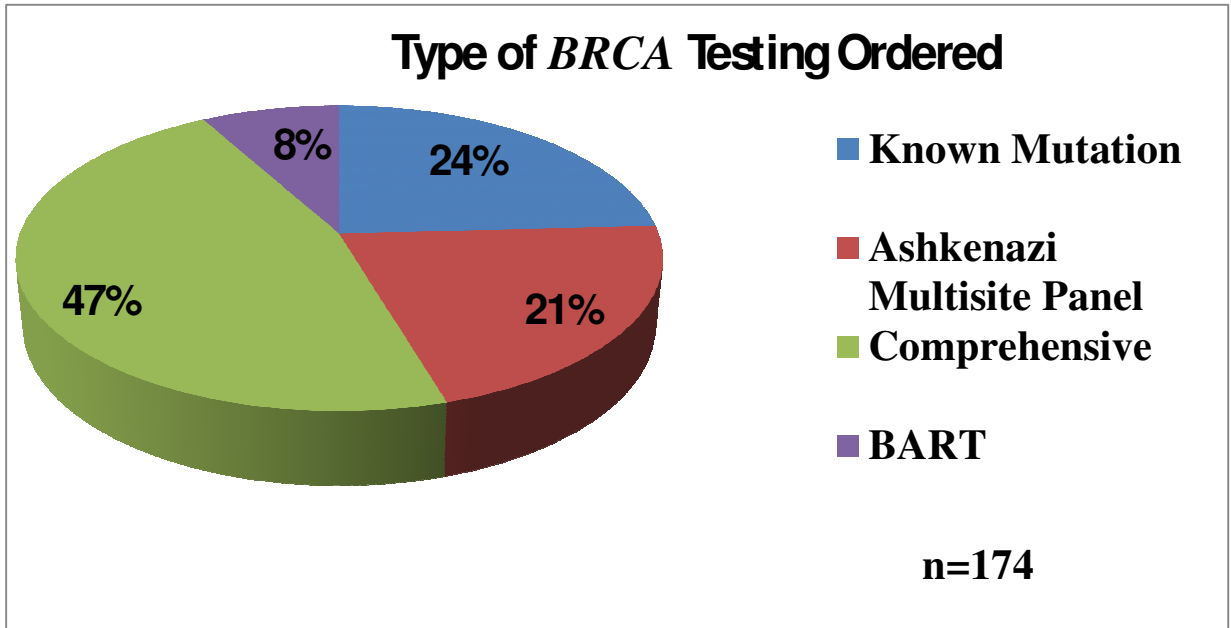
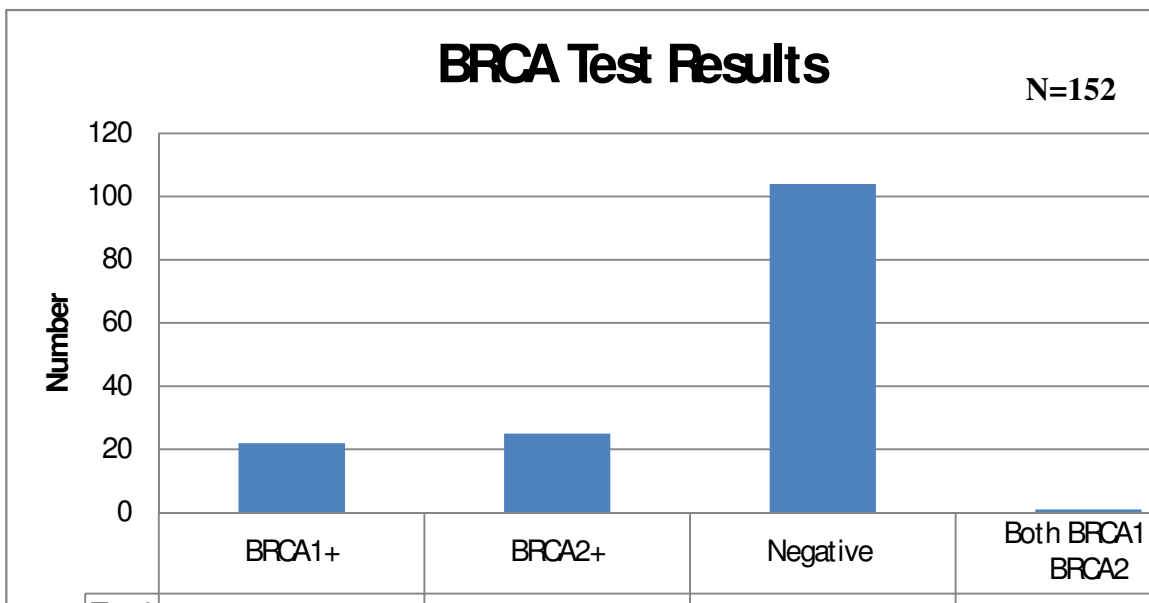


Figure 7 displays the overall *BRCA* test results of our cohort of 152 males. The majority of males were found to be negative 104 (68.42%). In total 25 males (16.45%) were found to be *BRCA2* positive and 22 males (14.47%) were found to be *BRCA1* positive, with one male (0.65%) being found to have both a *BRCA1* and *BRCA2* mutation.

Figure 7: Overall *BRCA* Test Results



The *BRCA* test results subdivided by indication are shown in a graph in figure 8. The majority of individuals who were found to be *BRCA1* positive (17) presented to clinic for a KFM, which accounted for 77.28% of all of the males who were *BRCA1* positive. Similarly 17 males were found to be *BRCA2+* who presented to clinic for a KFM, which accounted for 68% of all *BRCA2+* males. The majority of males tested due to a personal history suggestive of a *BRCA* mutation (77) were found to be negative, which represented 74.04% of all *BRCA* negative males. One study participant presented to clinic for a KFM and was found to have both a *BRCA1* and *BRCA2* which represented 0.65% of the total cohort.

Figure 8: *BRCA* Test Results Stratified by Indication

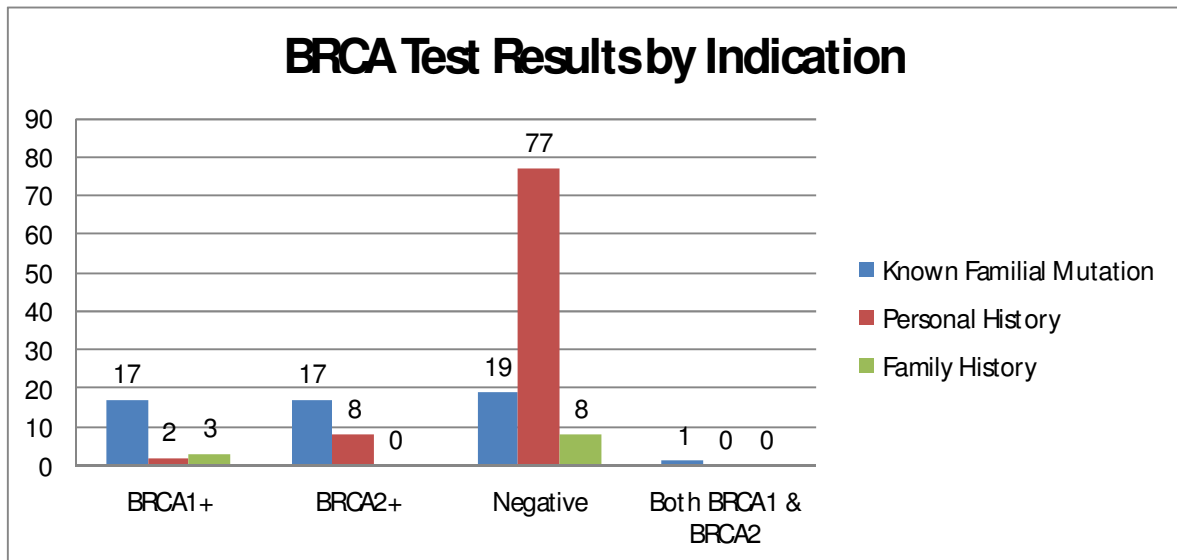


Table 7 summarizes both the type of *BRCA* testing ordered as well as the result of the testing ordered for each specific indication. For each study participant it is important to

understand that more than one test may have been ordered. The majority of study participants who were seen for a KFM had single site testing performed, (n=42, 77.78%). The second most commonly ordered test for males seen for this indication was the multisite panel (n=12), which would be ordered for anyone whose familial mutation was one of the three Ashkenazi Jewish founder mutations. The majority of individuals 74 (85.06%) seen for genetic counseling due to a personal cancer history suggestive of *BRCA* had comprehensive testing ordered. Similarly the majority of males, 6 (54.55%) who were seen due to a family history suggestive of a *BRCA* mutation had comprehensive testing performed.

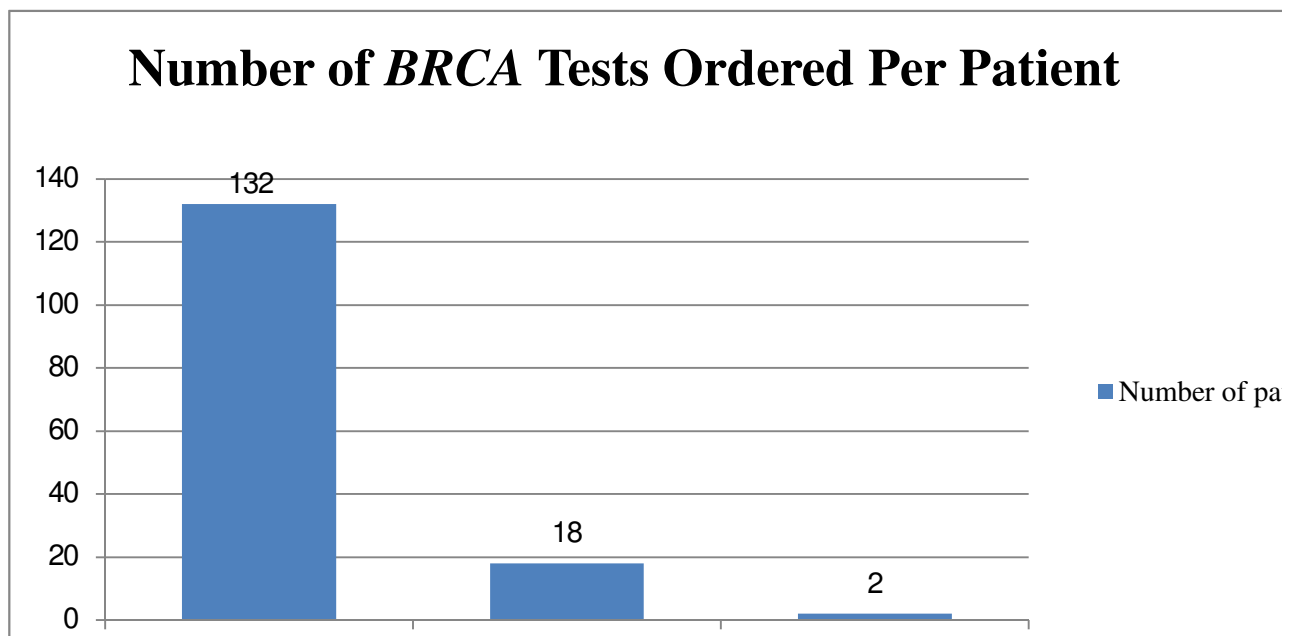
Table 7: *BRCA* Testing Ordered by Indication with Testing Results

<i>BRCA</i> Testing	Known Familial Mutation (n=54)	Personal History (n=87)	Family History (n=11)
Single site (n)	42 (77.78%)	0	0
BRCA1+	13 (30.95%)		
BRCA2+	14 (33.33%)		
BRCA1+ & BRCA2+	1 (1.85%)		
Negative	14 (33.33%)		
Multisite/ Ashkenazi Panel (n)	12 (22.22%)	20 (22.99%)	5 (45.45%)
BRCA1 +	4 (33.33%)	1 (%)	1 (20.00%)
BRCA2+	3 (25.00%)	1 (%)	0
Negative	5 (41.67%)	18 (%)	4 (66.67%)
Comprehensive (n)	2 (3.70%)	73 (83.91%)	6 (54.55%)
BRCA1+	0	1 (1.39%)	2 (40.00%)
BRCA2+	0	7 (9.59%)	0
Negative	2 (100%)	65 (89.02%)	4 (60.00%)
BART (n)	1 (1.85%)	11 (12.64%)	2 (18.18%)
BRCA1+	0	0	0
BRCA2+	0	0	0
Negative	1 (100%)	11 (100%)	2 (100%)

Figure 9 displays the number of *BRCA* tests ordered per patient. The majority of our cohort, (86.84%, n=132) had one test ordered. A much smaller number, 18 males (11.84%),

had two tests ordered after receiving negative tests results from the first test ordered. The most *BRCA* tests ordered for any one individual in our cohort was 3. In the case that a male started with either single site or multisite testing then reflexed to comprehensive and then additionally reflexed to BART testing. There were only 2 males (1.32%) that had 3 *BRCA* tests ordered.

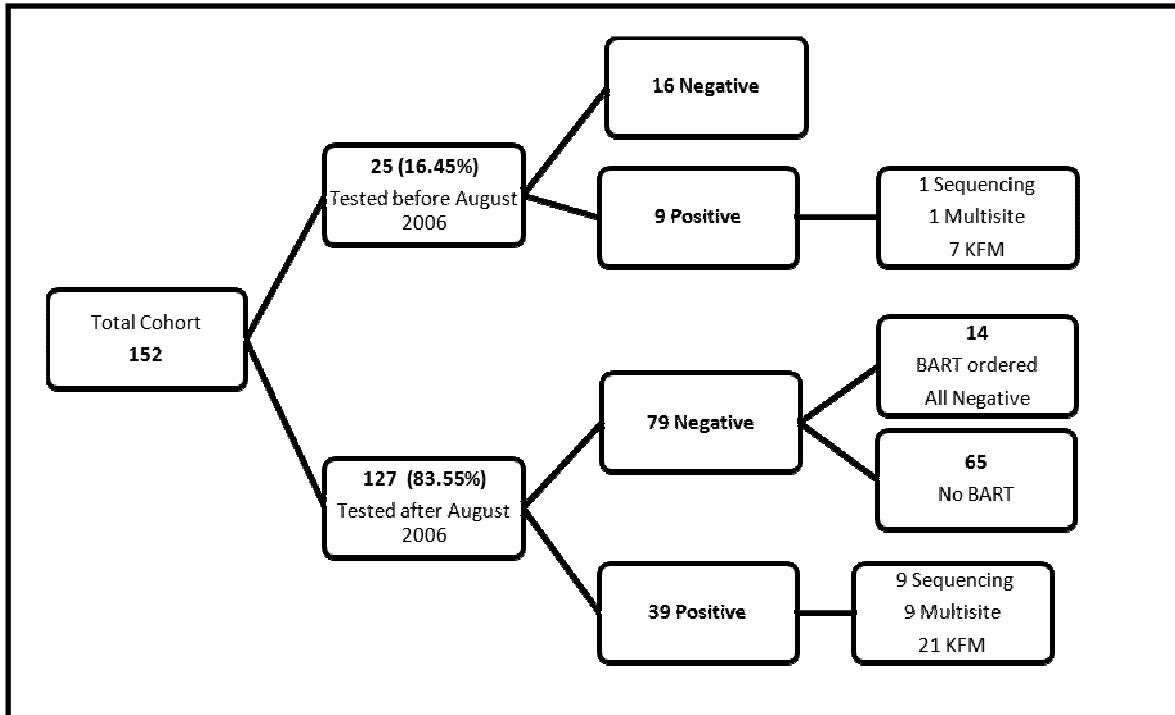
Figure 9: Overall Number of *BRCA* Tests Ordered per Patient



BART testing has been clinically offered by Myriad as additional reflex testing for negative test results since August 2006. In our study cohort, 25 males were tested before BART testing was created which accounts of 16.45% of our total study cohort. Out of these 25 males, 9 had positive test results and 16 had negative test results. Therefore 16 males were not offered BART testing as it did not yet exist. Of the 127 males who were tested after August 2006, there were 39 males found to be positive and 79 were found to be

negative test results. Of the males who were negative, only 14 decided to proceed with BART testing and all 14 received negative test results. The results of males offered BART within our cohort as well as how many BART tests were ordered are summarized in figure 10.

Figure 10: Flowchart of BART Tests Offered and Ordered



BRCAPro Scores

Table 8 summarizes the median calculated BRCAPro scores by the three different indications. The median and IQR values are reported since the BRCAPro scores were found to be skewed with a p-value <0.00005. The column denoted as “Overall” represents the entire cohort, not subdivided by indication, and has a median of 3.85 with an IQR from 0.3 to 47.8. The indication with the highest median BRCAPro score of 49.4 was the known

familial mutation subgroup. The indication with the lowest median BRCAPro score of 0.6 was a personal history of a *BRCA* associated cancer diagnosis.

Table 8: BRCAPro Calculated Scores by Indication

BRCAPro Score	Known Familial Mutation (n=54)	Personal History (n=87)	Family History (n=11)	Overall (n=152)
Median	49.4	0.6	0.9	3.85
IQR	39.5 - 50.0	0.1 - 3.9	0.4 - 9.1	0.3 - 47.8
Range	0.2 - 100	0 - 88.6	0.2 - 32.6	0 - 100

Table 9 summarizes the calculated BRCAPro scores for males diagnosed with breast cancer, pancreatic cancer, or prostate cancer who were seen due to their cancer diagnosis. It is seen that the highest median BRCAPro score of 3.6 was obtained for males diagnosed with breast cancer. The IQR for these males was 0.7 – 12.3 and a range from as low as 0 to as high as 88.6. The lowest median BRCAPro score of 0.2 was obtained for males diagnosed with pancreatic cancer with an IQR of 0 – 0.3 and a range from as low as 0 to as high as 20.2.

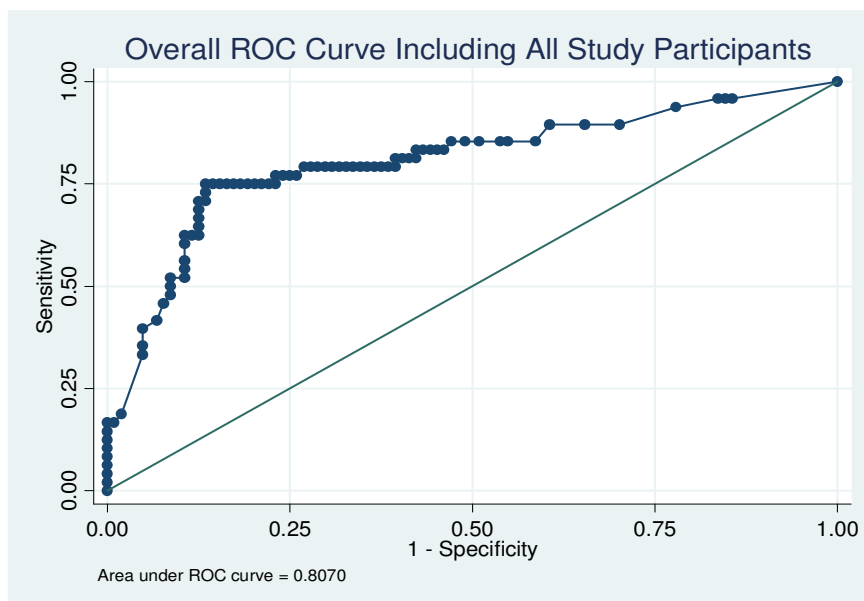
Table 9: BRCAPro Calculated Scores by Cancer Diagnosis

BRCAPro Number	Breast Cancer (n= 44)	Pancreatic Cancer (n= 16)	Prostate Cancer (n= 35)
Median	3.6	0.2	0.45
IQR	0.7 – 12.3	0 – 0.3	0.075 – 1.65
Range	0 – 88.6	0 – 20.2	0 – 88.6

ROC Curves

The overall maximum Youden's J of 0.165 was obtained at a BRCAPro threshold of 32 at which sensitivity is equal to 75% and specificity is equal to 87%. Positive predictive value (PPV) at a threshold of 32 is equal to 72% and negative predictive value (NPV) at this threshold is equal to 88%. When the BRCAPro threshold is lowered to 12, sensitivity increases to 77%, specificity decreases to 75%, PPV decreases to 59% and NPV remains the same at 88%. The value for specificity and PPV decrease when the BRCAPro score is lowered due to the fact that the number of false positives increases. This calculation included the entire cohort of 152 individuals and is represented in figure 11.

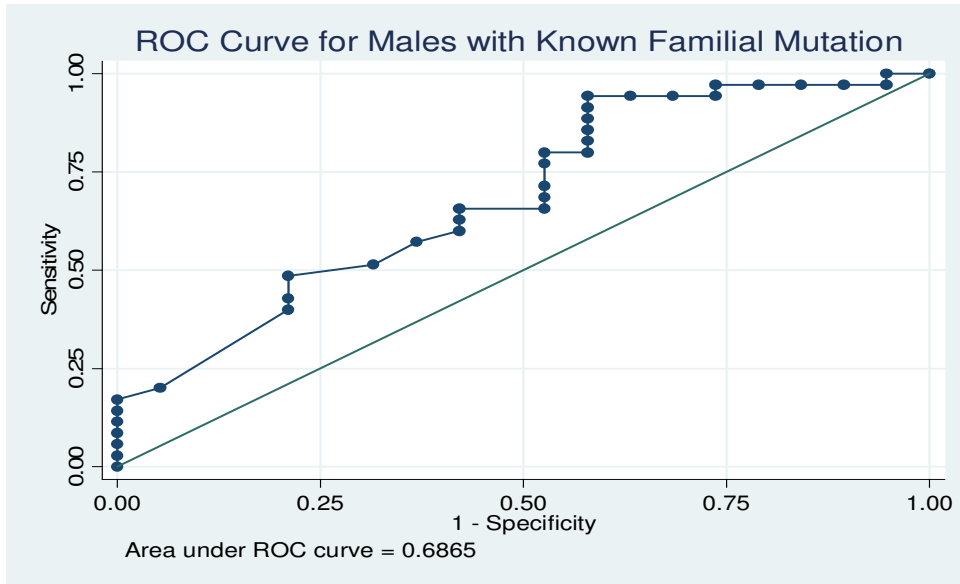
Figure 11: Overall ROC Curve Including All Study Participants



For males with a KFM a maximum Youden's J of 0.369 was obtained at a BRCAPro threshold of 32 at which sensitivity is equal to 94% and specificity is equal to 42%. PPV at

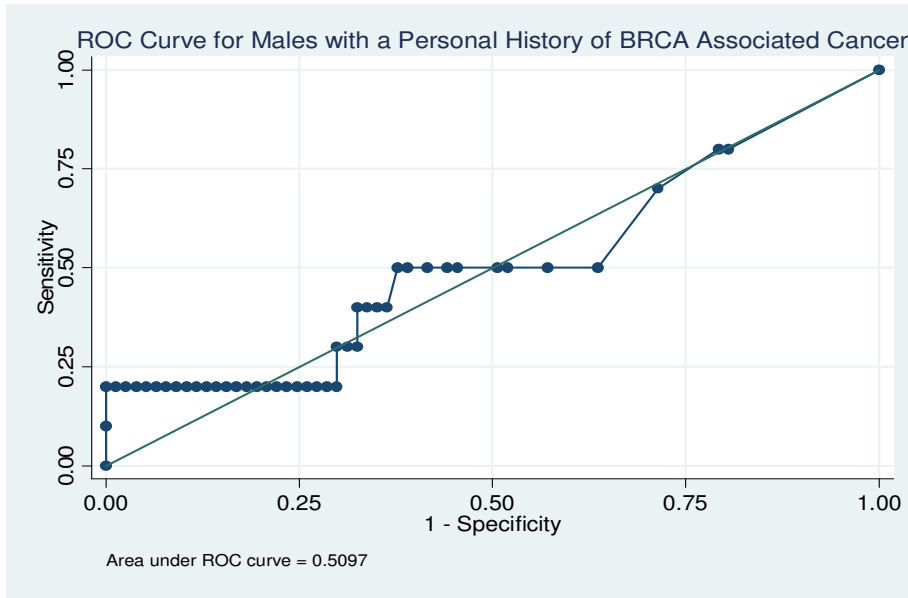
a threshold of 32 is equal to 75% and NPV at this threshold is equal to 80%. The ROC curve for males seen for a KFM is seen in figure 12.

Figure 12: ROC Curve for Males with a Known Familial Mutation undergoing Predictive *BRCA* Testing



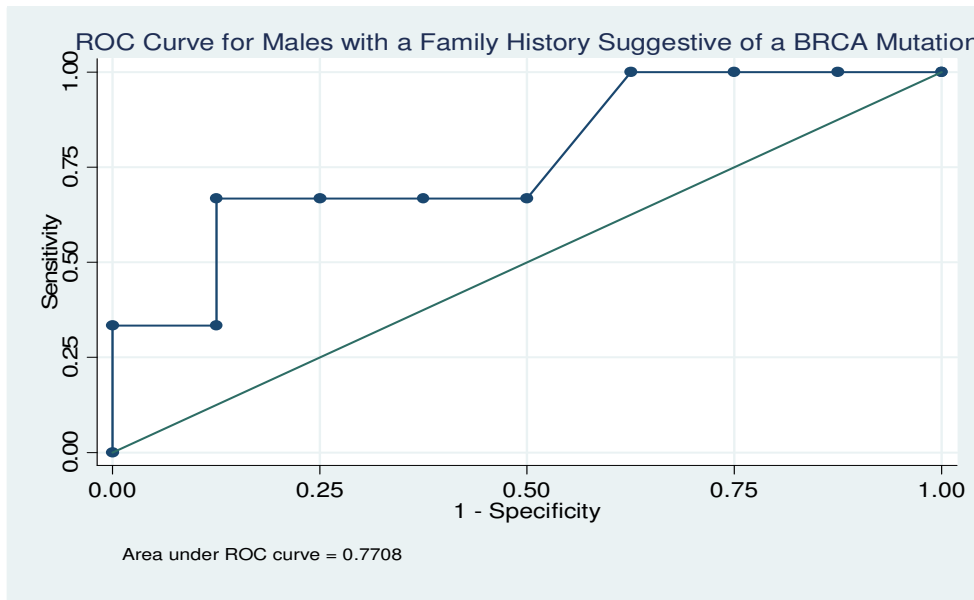
For males with a personal history suggestive of a *BRCA* mutation the area under the ROC curve (AUC) was calculated as .50. Therefore the discriminatory value of the BRCAPro model for males with an indication of personal history suggestive of a *BRCA* mutation, or males seen with a personal diagnosis of either breast, prostate, or pancreatic cancer is no different than random chance. The ROC curve for males with this indication is found in figure 13.

Figure 13: ROC Curve for Males with a Personal History of a *BRCA* Associated Cancer



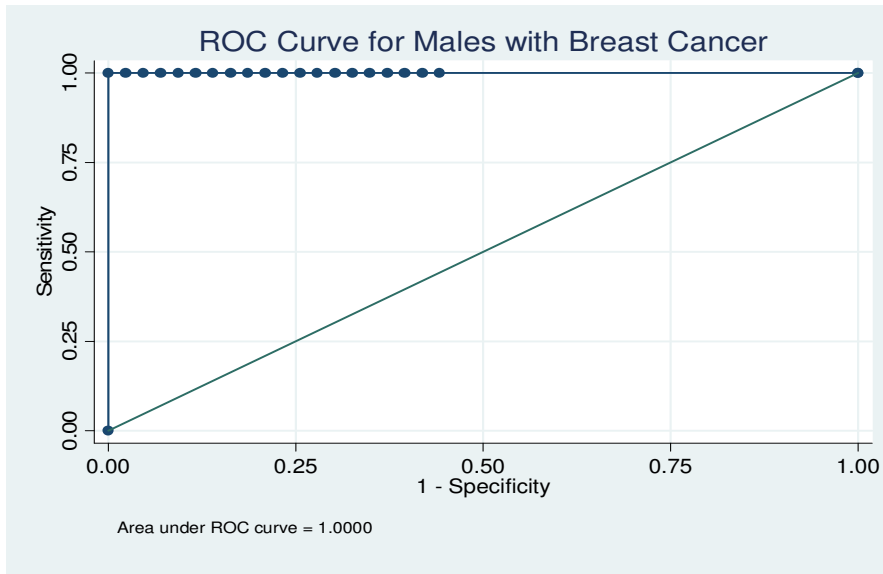
For males with a family history suggestive of a *BRCA* mutation a maximum Youden's J of 0.542 was obtained at a BRCAPro threshold of 2 at which sensitivity is equal to 67% and specificity is equal to 88%. PPV at a threshold of 2 is equal to 67% and NPV at this threshold is equal to 88%. This indication subgroup had a very small n, as only 11 males for seen for this indication. The ROC curve constructed for this sub section of our cohort is found in figure 14.

Figure 14: ROC Curve for Males with a Family History Suggestive of a *BRCA* Mutation



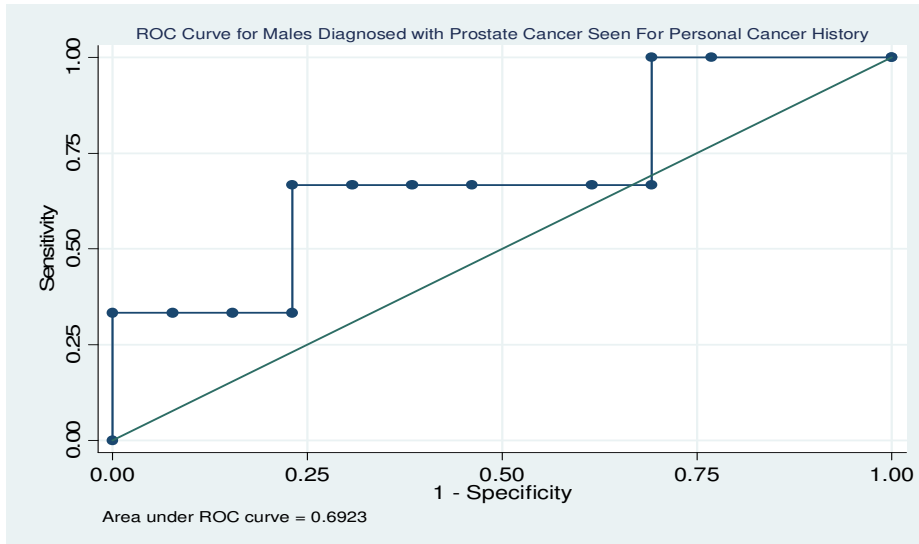
For males diagnosed with breast cancer it was found that a BRCAPro threshold of 56.2 predicts the presence of a *BRCA* mutation perfectly, since the only two individuals who tested positive were the only men with breast cancer and an indication of 2 who had a score higher than 56.2. The ROC curve for males diagnosed with breast cancer is found in figure 15.

Figure 15: ROC Curve for Males Diagnosed with Breast Cancer



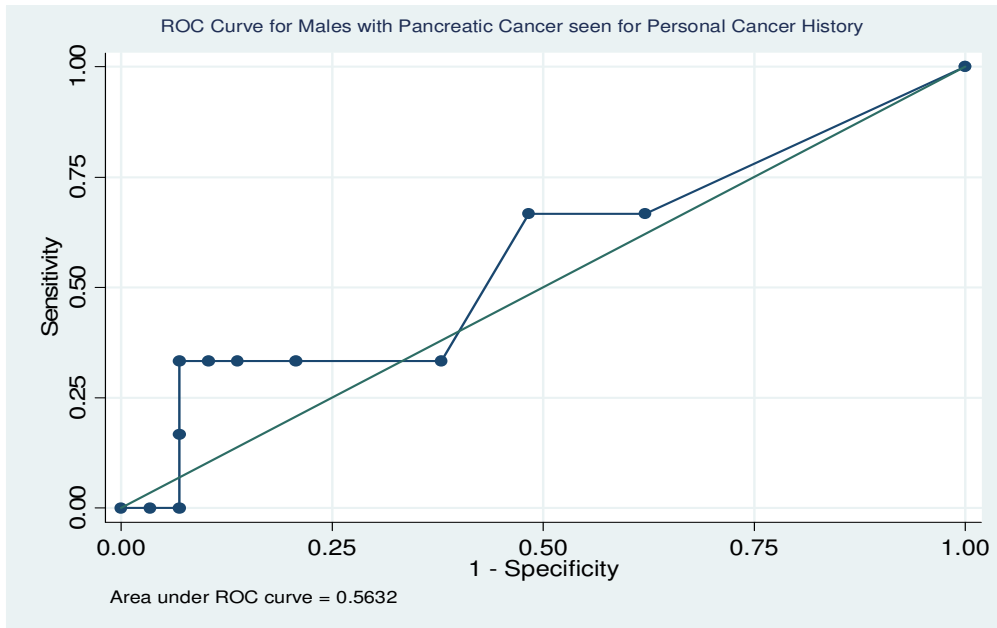
For males who were diagnosed with prostate cancer, a maximum Youden's J of 0.44 was obtained at a BRCAPro threshold of 1.0 at which sensitivity is equal to 67% and specificity is equal to 77%. PPV at a threshold of 1.0 is equal to 40% and NPV at this threshold is equal to 91%. The ROC curve for males diagnosed with prostate cancer is seen in figure 16.

Figure 16: ROC Curve for Males Diagnosed with Prostate Cancer



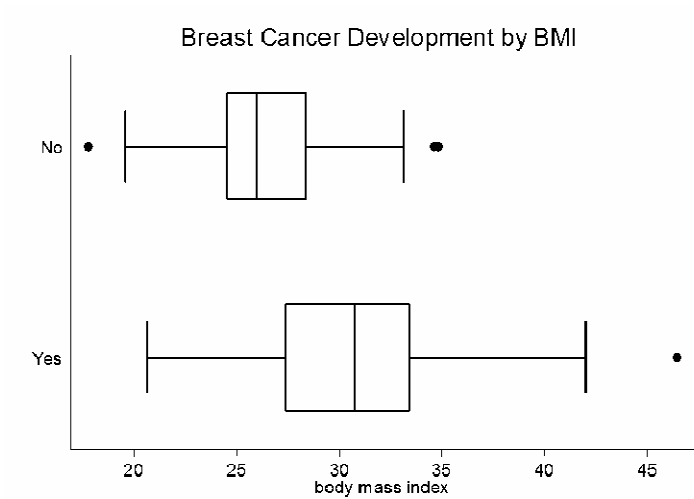
For males with pancreatic cancer a maximum Youden's J of 0.46 was obtained at a BRCAPro threshold of 0.3. The ROC curve for pancreatic cancer patients demonstrates that the BRCAPro5.1 model does not seem to be predictive for this particular patient population in identifying *BRCA* mutation carriers. The AUC calculated was 0.56 which demonstrates a discriminating ability that is not much different than random chance. The ROC curve for males diagnosed with pancreatic cancer is found in figure 17.

Figure 17: ROC Curve for Males Diagnosed with Pancreatic Cancer



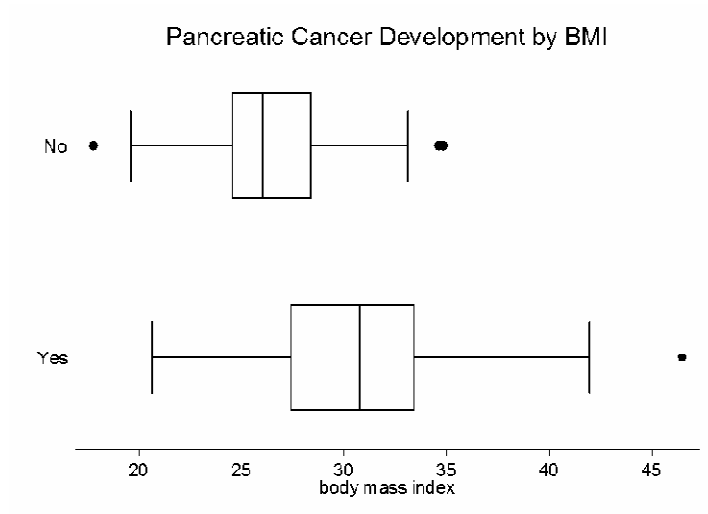
A ranksum statistical test was run on the two variables of breast cancer development and BMI. There was an association found due to a p value that was <0.00005 . The median BMI for males without breast cancer was 26.02 with an IQR of 24.57 to 28.40. The median BMI for males diagnosed with breast cancer was 30.78 with an IQR of 27.42 to 33.43. The box and whisker plot of this association is shown in figure 18.

Figure 18: Box and Whisker Plot of Breast Cancer Development by BMI



An association was found between development of pancreatic cancer and BMI, as a p-value of 0.0002 was obtained by running a ranksum test. The median BMI for males not diagnosed with pancreatic cancer was 29.21 with an IQR of 26.04 to 32.08. The median BMI for males diagnosed with pancreatic cancer was 25.95 with an IQR of 23.95 to 27.73. The box and whisker plot of this association is shown in figure 21.

Figure 19: Box and Whisker Plot of Pancreatic Cancer Development by BMI



DISCUSSION

This is the first study that seeks to evaluate the accuracy of the BRCAPro5.1 risk assessment model specifically in males. The aim of our study was to see how this particular model performed overall in our cohort of males seen for numerous different clinical indications for BRCA genetic testing. Additionally, other factors such as ethnicity, age of diagnosis, presence of gynecomastia, weight, height, etc., were obtained from the medical records of our study population and also tested for significance.

BMI

Males who had a higher BMI had a statistically significant increased risk of breast cancer ($p < 0.00005$). According to the World Health Organization, BMI calculations can be classified into four categories: underweight with a BMI < 18.5 , normal with a BMI between 18.5 to 24.9, overweight with a BMI of 25.0 to 29.9 and obese with a BMI over 30 [44]. Previous studies have shown that having a BMI ≥ 25.0 confers an increased risk for cancers specifically: endometrial cancer in women, postmenopausal breast cancer in women, renal cell carcinoma, colon cancer particularly in males and esophageal adenocarcinoma [45]. This finding is consistent with the current literature on increased BMI seen in males with breast cancer. One study published in 2002 reported a trend seen in 43 male breast cancer patients towards having a higher BMI, as the average BMI was reported to be 26.54 [46]. At this point in time the mechanisms for increased BMI in relation to male breast cancer are not fully understood however, it is hypothesized that having an increased surface area of breast tissue may predispose to the development of breast cancer in males. Another hypothesis is that obesity lowers IGFBP 1 & 2 and thus increases the availability of IGF-1.

Increased bioavailability of IGF-1 along with insulin have been thought to increase cell proliferation and decrease apoptosis, although this association has yet to be proven [47]. There is some debate as to which measure is most appropriate in order to investigate associations between weight and cancer development, as some feel other measures such as waist-to-hip ratio (WHR) measurement may be more appropriate in order to assess for body fat distribution which is not accounted for with BMI. Other limitations previously noted with BMI calculations is the fact that it performs with less accuracy in individuals >65 years old as well as in Asian individuals [44]. BMI was chosen as the most appropriate calculation for our study cohort, due to the fact that recorded heights and weights were able to be found within the electronic medical record, other measurements such as WHR were not recorded. Also very few males were noted to be of Asian ancestry within our study cohort.

In our cohort of males who developed pancreatic cancer, it was noted that their median BMI was actually lower in comparison to males who did not develop pancreatic cancer. The median BMI for males diagnosed with pancreatic cancer was 25.95 with an IQR of 23.95 to 27.73. The median BMI for males without pancreatic cancer was 29.21 with an IQR of 26.04 to 32.08. Previous studies have shown that there is an association between increased BMI to have an increased risk for pancreatic cancer in both males and females [45]. However, our cohort does not show this same association, which may be explained by several different factors. The height and weight measurements used to calculate BMI were taken from the patient's initial clinic visit, since a symptom of pancreatic cancer can be severe weight loss it can be postulated that patients with pancreatic cancer may have been under their typical weight at the time of their initial visit. Additionally, it was not noted whether patients in our cohort had a history of cigarette or tobacco use, which have been

found to be associated with the development of pancreatic cancer. Males who had a positive history of tobacco use may have lower recorded weights due to the increase in metabolism seen with tobacco use. Additionally as seen with male breast cancer and pancreatic cancer, some studies suggest that being overweight or obese as defined by one's BMI calculation is a risk factor in the development of prostate cancer. In our study cohort no significant difference was observed between the median BMI of males with prostate cancer compared to the median BMI of males without prostate cancer.

***BRCA* Mutation Results**

In our study cohort it was observed that more males were found to be *BRCA2* positive (25) than *BRCA1* (23) positive. There does not appear to be a significant difference between these two groups. The same number of *BRCA1* and *BRCA2* mutations, 17, were identified for males in our cohort who underwent testing for a KFM. Perhaps the finding of slightly more *BRCA2* mutation carriers can be attributed to the high number of males seen within our cohort who were diagnosed with pancreatic cancer, as it is characterized in the literature that *BRCA2* mutation carriers confer a higher lifetime risk for pancreatic cancer in comparison to *BRCA1* carriers [5]. Overall in our cohort, 8 males were found to have pancreatic cancer and a *BRCA2* mutation while 1 male was found to have pancreatic cancer and a *BRCA1* mutation, therefore when we take these males diagnosed with pancreatic cancer out, 21 males were found to be *BRCA1* mutation carriers and 17 males were found to be *BRCA2* mutation carriers.

BRCAPro5.1 Calculations

When looking at the median BRCAPro score calculated by indication, there was a large difference in the median generated for males with a KFM in comparison to males with an indication of either having a personal history of a *BRCA* related cancer diagnosis or for a suggestive family history. For males with a KFM, the median BRCAPro score was 49.4, which is expected as individuals undergoing predictive testing are commonly at a 50% risk to have inherited the particular familial mutation based purely on autosomal dominant inheritance and pedigree analysis. The BRCAPro risk assessment model can alter an individual's likelihood to test positive based on age of the individual at the time of testing and personal history of cancer diagnoses. An example from our cohort that illustrates the adjustment to a BRCAPro calculation based on age for males undergoing predictive testing is seen with an unaffected male who underwent predictive testing at the age of 58 with a BRCAPro score of 47.4 as compared to an unaffected male who had predictive testing at the age of 20 who was found to have a BRCAPro score of 50%, both individuals tested positive for their known familial mutations, which were both *BRCA1* mutations.

When looking at the median BRCAPro scores for males with either a personal history suggestive of a *BRCA* mutation or with an indication of a family history suggestive of a *BRCA* mutation, they appear low with the median scores being 0.6 and 0.9, respectively. The low scores may be explained by the fact that the only cancers calculated in the current BRCAPro5.1 model are breast and ovarian cancers. Therefore, males who are themselves diagnosed or who have family members who are diagnosed with other *BRCA* associated cancers such as prostate or pancreatic cancers are counted as an unaffected individual by the model. Although it is known that *BRCA* mutation carriers are at increased lifetime risks to

develop both prostate cancer in males and pancreatic cancer, it may prove to be difficult in assessing how these cancers best fit into the mathematical equation utilized in the BRCAPro model.

A statistically significance difference was noted in regard to the calculated BRCAPro scores across the three indications with a p-value of 0.0001. However no significant difference was noted in regard to ethnicity or the presence of Ashkenazi Jewish ancestry in regard to BRCAPro scores, which may be due to the small number of individuals in these categories. Within our cohort it was found that age of diagnosis was not statically significant ($p = 0.68$).

Overall Performance of the BRCAPro5.1 Model

When looking at the overall ROC curve constructed for the entire cohort the model performed quite well at an AUC of 0.8070 since an AUC of 1.00 is representative of a “perfect test” or one with a perfect discriminating ability in determining BRCA carriers from non-carriers. At a BRCAPro threshold of 32, obtained through calculating the maximum Youden’s J value, sensitivity of the BRCAPro model was equal to 75% and specificity was equal to 87%. The positive predictive value at the threshold of 32 was 72% while the negative predictive value was 88%. From these calculations it can be deduced that at our set threshold, BRCAPro had a better ability to determine males who were negative for *BRCA* mutations than positive.

The BRCAPro model can be used as not only a guide on how likely it is for a given individual to be a BRCA mutation carrier, but also under certain circumstances may in fact serve as a substitute for testing [41]. Thus when deciding at what level to set our threshold

for BRCAPro scores to calculate our ROC curves, it was decided to determine the optimal threshold by utilizing the maximum Youden's J calculation, since equal importance was placed on sensitivity and specificity. In the case of substituting BRCAPro scores for actual *BRCA* testing it can be argued that harm may be inflicted by calling either false negatives or false positives. It is a matter of opinion as to which of these outcomes is worse. Calling false negatives inaccurately assures individuals that they are not at an increased risk to develop *BRCA* associated cancers. If these individuals are not actively being screened for their increased cancer risks then there is potential for the development and advancement of cancers. The psychosocial impacts of calling false negatives must also be factored in when discussing potential harm caused to these individuals. On the converse side, calling false positives may also create certain unwarranted psychosocial harm. Additionally, false positives may inflict harm by means of an increased proportion of health care dollars being spent to ensure increased screening for these individuals who in actuality are not at increased risk.

ROC Curves Subdivided by Indication

The ROC curve constructed for males seen with a KFM had its maximum Youden's J at a BRCAPro threshold of 32, at which sensitivity is equal to 94% and specificity is equal to 42%. The AUC was calculated to be 0.68, which corresponds to a relatively poor discriminating ability, similarly the AUC calculated for males with a personal history suggestive of a *BRCA* mutation was found to be 0.50, which is the same discriminating ability as random chance. This finding may be explained by the fact that neither prostate or pancreatic cancers can be accounted for in the BRCAPro model, which could thus

significantly lower the BRCAPro calculations for males with personal histories of these cancers and/or family histories of these particular cancers.

The least common indication to seek genetic counseling in our cohort was that of having a family history suggestive of a BRCA mutation, as only 11 males were seen for this indication. The AUC calculated by the ROC curve was 0.77, and therefore there was a decent discriminating ability with the BRCAPro model for males with this indication. Thus, BRCAPro may be helpful for men with family histories of breast and/or ovarian cancer while not helpful for men with family histories abundant in prostate or pancreatic cancer diagnoses.

ROC Curves Subdivided by Cancer Development and Type

There were seven male probands included in the initial study that validated the use of the BRCAPro model in the clinical setting only three of which had male breast cancer [41]. All three were found to be *BRCA2* mutation carriers which may have skewed the results with the BRCAPro scores calculated for these three males all being found to be greater than 95. Which is similar to our finding that BRCAPro had a perfect discriminating ability in males with breast cancer at a BRCAPro calculation above 56.2 [41].

One previously published paper aimed to evaluate the use of the BRCAPro5.0 model in 102 Italian male breast cancer patients, and found at a set threshold of 10% the model had a sensitivity of 0.80, specificity of 0.78, positive predictive value of 0.29 and a negative predictive value of 0.97 [34]. This particular study utilized this threshold as this is the threshold value that the FHAT model uses [34]. Our study threshold used for our male breast cancer patients was obtained by calculating the Youden's J value. However when we

set our BRCAPro threshold to 10% we obtained a sensitivity of 100%, specificity of 76%, positive predictive value of 16% and negative predictive value of 100%. Therefore our findings were quite similar to those produced by the previous study conducted by Zanna et al, as both studies found the BRCAPro model to have higher sensitivity than specificity and very high negative predictive values with low positive predictive values.

The ROC curve constructed for males who were diagnosed with prostate cancer gave a calculated AUC of 0.69. The ROC curve constructed for males with pancreatic cancer seen for genetic counseling due to their personal cancer diagnosis had a AUC of 0.56. Again this finding may be due to the fact that males with a prostate cancer diagnosis are treated as unaffected individuals. In many cases prostate cancer may be a sporadic cancer due to advancing age, however early onset prostate cancer may in fact be more suggestive of a *BRCA* mutation. However, the current BRCAPro model has no way to account for such differences.

Study Limitations

This research project was a retrospective chart review, and there are several limitations noted. First and foremost, the overall study size is rather small with a total cohort of 152 males. Additionally all males in this study were patients at the same hospital and therefore the results may not translate to all other male patient populations seeking *BRCA* testing since demographic information may be different at different cancer centers.

Due to the nature of a retrospective chart review, some information was missing from the medical records for our study participants. For instance, height and weight of study participants were ascertained from the patient history database which is information taken

during their first clinical visit by a nurse. Many study participants were missing this information as 77 males were missing a recorded height and 74 males were missing a recorded weight. Other variables such as gynecomastia were researched in this study; however, it was only noted as being present if documented in the medical record. Therefore, there could have been more male patients with gynecomastia who were not denoted to have this condition if it was left out of their dictated medical notes.

An additional limitation of our study is the fact that family history is patient reported, which could potentially lead to misrepresentation of the family history as cancer diagnoses may be underestimated, overestimated, and/or simply incorrect. Study participants with a personal diagnosis of cancer were able to be verified through pathology reports from MD Anderson, although patients that present for a second opinion to MD Anderson may have pathology reports from an outside hospital or no pathology report present in their medical record.

One last limitation of this study can be attributed to the way clinical *BRCA* testing is currently conducted in the United States through Myriad Genetics Laboratories. The most comprehensive of testing to date includes both comprehensive sequencing as well as reflexing when a negative comprehensive test result is received to a large arrangement test that uses MLPA analysis known as BART®. In our study cohort only 14 (9.21%) males underwent BART® testing. Therefore the majority of our cohort did not receive the absolute most comprehensive testing available as of 2012. There are numerous reasons a study participant may not have BART® performed, whether it was that they were tested before August 2006 when the test first became clinically available or they did not wish to incur the additional cost of the test. For study participants who tested negative through either single

site analysis or multisite analysis, they would then need to reflex to comprehensive sequencing and then additionally BART® testing in the event the comprehensive sequencing was negative to be considered to have the most comprehensive testing to date. However, the residual risk to have a *BRCA* mutation after having either negative single site or negative multisite testing is very small and therefore many patients do not wish to continue further *BRCA* testing, especially with the relatively high cost of testing.

Implications and Future Research

Currently figures quoted in the medical literature provides a wide range of the likelihood a case of male breast cancer is attributable to a *BRCA* mutation from 4% to 40%. Although the overall sample size of males who had breast cancer without having a KFM is rather small in our cohort at 46, only 2 of these males had a *BRCA* mutation more specifically a *BRCA2* mutation, which is a significantly lower number than expected. Clearly more research and attention needs to be placed on determining what factors are causing male breast cancer, as the literature appears to overestimate the contribution that *BRCA* mutations have in regard to male breast cancer. There may in fact be specific genetic factors aside from *BRCA* mutations that play a role in the development of male breast cancer; therefore, research is needed to identify what these genetic factors are.

Conclusion

In conclusion, our study was able to find the ideal BRCAPro score threshold for both clinical indications and cancer subtype within our cohort. When lowering the BRCAPro score closer to the study populations overall median BRCAPro score (3.85) it was

demonstrated that the model performs inadequately. For males with an indication of having a personal cancer history, BRCAPro5.1 performed the same as random chance. Our study discovered that the BRCAPro5.1 model had perfect discriminating ability for males with breast cancer at a threshold of 56.2, as all of our male breast cancer patients with a *BRCA* mutation had a BRCAPro score well above this threshold. However, it is important to note that our sample size of male breast cancer patients was small, and this finding should not be applied to other male breast cancer cohorts. Additionally, adjusting the threshold to 10 demonstrates that BRCAPro is overestimating the likelihood that a man with breast cancer would test positive. The discriminating ability of the model for males with a personal or family history of pancreatic or prostate cancer was very poor. Directions for the future should include a large multicenter study combining patients diagnosed with male breast cancer to increase the overall sample size and further evaluate the validity of the findings from our study. Lastly, consideration should be given to determine a way to account for prostate and pancreatic cancers in future versions of the BRCAPro risk assessment model, which in turn might better evaluate the risk for males to test positive for *BRCA* mutations.

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