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Evaluating the NCCN Clinical Criteria for Hereditary Breast and Ovarian Cancer Syndrome Genetic Testing

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EVALUATING THE NCCN CLINICAL CRITERIA FOR HEREDITARY BREAST AND
OVARIAN CANCER SYNDROME GENETIC TESTING

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A

THESIS

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by

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Hereditary Breast and Ovarian Cancer (HBOC) syndrome predisposes females with a *BRCA1* or *BRCA2* mutation to an up to 85% lifetime risk for breast cancer and an up to 40% lifetime risk for ovarian cancer. It is crucial for individuals with HBOC to be identified to allow for proper screening, management, and identification of at-risk family members in order to reduce mortality. The National Comprehensive Cancer Network (NCCN) has established clinical guidelines for when to recommend *BRCA1/2* testing. A retrospective chart review of 1123 M.D. Anderson Cancer Center breast cancer patients was performed in order to evaluate the positive predictive values (PPVs) of 14 individual criterion for predicting a *BRCA1/2* mutation. Two criteria had PPVs significantly below 10%. Only 2 of 115 patients recommended for testing based solely on the criterion of “diagnosed with breast cancer ≤ 45 years of age” tested positive for a pathogenic mutation at a PPV of 1.6% (0.2-6%, 95% CI), which is significantly below the clinical utility cut-off of 10% ($p = 0.001$). Additionally, 0 out of 37 individuals who underwent testing based on the criterion, “diagnosed with breast cancer at any age with ≥ 2 close blood relatives with breast cancer at any age” tested positive (0-9%, 95% CI). Overall, an individual who meets more than one criterion has a PPV of 12% while those who meet only one criterion has a PPV of 3.52%, which is significantly below 10% ($p < .0001$) for predicting *BRCA1/2* positivity. This data can help provide more personalized risks and anticipatory guidance for patients in their decision to pursue genetic testing.

TABLE OF CONTENTS

Introduction.....	Page 1
Methods.....	Page 4
Results.....	Page 7
Discussion.....	Page 12
Bibliography.....	Page 18
Supplemental Data	Page 21
Vita.....	Page 23

LIST OF TABLES

Table 1. Study population demographics: comparison between <i>BRCA1/2</i> positive and <i>BRCA1/2</i> negative groups	Page 7
Table 2. Composition of positive <i>BRCA1/2</i> genetic testing results.....	Page 8
Table 3. Positive predictive values based on number of criteria fulfilled	Page 9
Table 4. Positive predictive values of individual NCCN criterion as sole basis for recommending testing	Page 11

INTRODUCTION

Hereditary Breast and Ovarian Cancer (HBOC) syndrome is a cancer susceptibility syndrome that predisposes individuals to significant elevated risks for breast and ovarian cancer over that of the general population. Females with HBOC have an up to 85% lifetime risk for breast cancer, an up to 40% lifetime risk for ovarian cancer, and are at an increased risk for a second primary breast cancer as well as other cancers such as pancreatic cancer (Antoniou, Pharoah, Narod, Risch, Eyfjord, Hopper, Loman, Olsson, Johannsson, Borg, Pasini, Radice, Manoukian, Eccles, Tang, Olah, Anton-Culver, Warner, Lubinski, Gronwald, Gorski, Tulinius, Thorlacius, Eerola, Nevanlinna, Syrjakoski, Kallioniemi, Thompson, Evans, Peto, Lalloo, Evans, & Easton, 2003; Chen & Parmigiani, 2007; Ford, Easton, Stratton, Narod, Goldgar, Devilee, Bishop, Weber, Lenoir, Chang-Claude, Sobol, Teare, Struewing, Arason, Scherneck, Peto, Rebbeck, Tonin, Neuhausen, Barkardottir, Eyfjord, Lynch, Ponder, Gayther, & Zelada-Hedman, 1998). Males with HBOC are at an increased risk for male breast cancer, pancreatic cancer, and prostate cancer. At approximately 234,190 new cases estimated for 2015 in the United States, breast cancer is one of the most common cancers (American Cancer Society, 2015). The prevalence of carrying a *BRCA1* or *BRCA2* mutation is estimated at 1 in 400 to 1 in 800 individuals in the general non-Ashkenazi Jewish population, and approximately 1%-6% of female breast cancers are associated with a *BRCA1* or *BRCA2* mutation (Frank & Critchfield, 2001; McClain, Palomaki, Nathanson, & Haddow, 2005; Petrucelli, Daly, & Feldman, 2010). It is imperative that these very high-risk individuals to be identified amongst the hundreds of thousands of breast cancer cases that have a more sporadic cause, without accumulating significant costs and harms associated with testing unsuitable candidates.

The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of 26 of the leading cancer centers in the United States devoted to research, education, and improvement of care for cancer patients (National Comprehensive Cancer Network, 2015). In 1996, the NCCN

began a program to develop comprehensive clinical practice guidelines for management of the most common tumors reflecting a process of consensus relying on evaluation of evidence and structured feedback (Winn, Botnick, & Dozier, 1996). These guidelines are revised twice a year to incorporate the most recent literature and developments in the field. One practice guideline was specifically developed for “Genetic/Familial High-Risk Assessment: Breast and Ovarian”. These guidelines describe the recommendations for detection and management of individuals at an increased risk for breast and/or ovarian cancer. Included in the guidelines are clinical criteria for when to recommend testing for the *BRCA1* and *BRCA2* genes.

As genetic information may have significant implications for the individual undergoing testing, it is important to consider the value of genetic testing for each individual. Benefits to genetic testing may include the potential for surveillance and risk-reducing surgeries which may significantly reduce cancer-associated mortality as well as relief from uncertainty (Nelson, Pappas, Zakher, Mitchell, Okinaka-Hu, & Fu, 2014) Costs associated with genetic testing may include anxiety from cancer risks, fear of genetic discrimination, and financial burden (Nelson, Pappas, Zakher, Mitchell, Okinaka-Hu, & Fu, 2014). HBOC is inherited in an autosomal dominant manner, meaning that each first degree relative of an individual with a mutation in *BRCA1* or *BRCA2* has a 50% chance of also having inherited the mutation. Identifying a deleterious mutation in the family also allows for at-risk relatives to undergo predictive testing and to determine if additional family members will need to undergo high-risk screening and management.

The purpose of this study was to evaluate the clinical utility of the NCCN criteria for when to recommend *BRCA1* and *BRCA2* genetic testing. A widely accepted threshold of clinical utility for the positive predictive value of genetic testing is 10%, at which point there is a balance between the benefits to genetic testing versus its costs (Roberts, Vogelstein, Parmigiani, Kinzler, Vogelstein, & Velculescu, 2012). Clinical molecular genetic testing for the *BRCA* genes has been

available to patients at MD Anderson since its launch in 1996, allowing for a retrospective data review of genetic testing results in our patient population. Even though each of the genetic testing criteria put forth in the NCCN guidelines is weighted equally in recommending referral to genetic testing, we expect some criteria to be more predictive than others. As the current guidelines only require one criterion to be fulfilled in order to recommend genetic testing, our study aims to evaluate the clinical utility of individual clinical criteria for recommending *BRCA1/2* testing in patients with breast cancer.

METHODS

The NCCN guidelines in effect during the study period was “Genetic/Familial High-Risk Assessment: Breast and Ovarian Version 2.2014” (National Comprehensive Cancer Network, 2014). This study specifically aims to clarify how these NCCN criteria apply to breast cancer patients in the absence of a known familial mutation. Therefore, the criterion recommending testing based on a known deleterious *BRCA1* or *BRCA2* mutation as well as the criteria recommending testing based on family history in the case of an unaffected proband were excluded.

A retrospective chart review of one-thousand-and-twenty-three M.D. Anderson Cancer Center patients with breast cancer was performed in order to evaluate the positive predictive values (PPVs) of fourteen individual criteria for predicting a *BRCA1/2* mutation. Chart review involved the electronic medical record as well as a review of pedigrees through the Progeny database. All 1123 patients had a personal history of breast cancer or DCIS and all have had *BRCA1/2* genetic testing with results available for review. These 1123 patients included male breast cancer patients who were seen for genetic counseling at MD Anderson between September 9, 1999 and June 30, 2014 for a larger sample size due to the rareness of male breast cancers. Female patients included those seen for genetic counseling at our institution during a 15-month span from March 31, 2013 to June 30, 2014. Data gathered included the patient’s age at genetic testing, age at first breast cancer diagnosis, presence or absence of known Ashkenazi Jewish ancestry, hormone receptor status, additional cancer sites and ages at diagnosis, whether they fulfill each of the 14 criteria being evaluated, and genetic testing results.

Of these 1123 patients, 26 had variants of unknown significance (VUS). These patients were excluded as it is uncertain whether they carry pathogenic mutations or benign variants, and therefore positive predictive values could not be calculated. An additional 25 patients were

excluded from this study as they underwent *BRCA1/2* testing without having met any NCCN criterion for HBOC genetic testing. All 25 patients tested negative. While genetic testing is a personal decision that any individual can pursue, we did not include them in our analysis as our study focused on patients who are recommended for testing based on NCCN criteria.

For the purposes of statistical analysis, the 1072 results were grouped into *BRCA 1/2 positive* and *BRCA1/2 negative*. *Positive* results included those which were reported as ‘deleterious’, ‘suspected deleterious’, and ‘see below’. A ‘see below’ result means that a deleterious mutation had been detected. However, the reporting laboratory commented that the cancer risks associated with the specific mutation may be lower than the generally quoted risk numbers for HBOC. We categorized these results as positive since they are foremost recognized damaging mutations, and still portend increased lifetime risks for breast cancer. *Negative* results included those which were reported as ‘likely benign’ and ‘no mutation detected’.

Statistical analyses were performed on these 1072 in order to define patient demographics, categorize additional primaries, and calculate positive predictive values for patients meeting each criterion. Specifically, we wanted to challenge each criterion individually by calculating the PPV of each criterion when it is the only basis for which the patient was recommended to have genetic testing. This study also seeks to evaluate the PPV of when patients fulfill more than one criterion.

Patient demographics and characteristics were calculated and compared between BRCA positive and BRCA negative patients with chi-squared test. Wilcoxon rank-sum test was used to compare the age of cancer diagnoses between BRCA positive and BRCA negative patients. Positive predictive values were calculated for the 14 NCCN criteria being evaluated as well as for meeting only one criterion versus meeting more than one criteria using chi-squared test. Chi-

squared tests were also used to calculate whether any single or combined groups of criterion had PPVs significantly below 10%.

RESULTS

Table 1. Study population demographics: comparison between *BRCA1/2* positive and *BRCA1/2* negative groups

<i>Variable</i>	<i>All Available</i>	<i>BRCA1/2 Positive</i>	<i>BRCA1/2 Negative</i>	<i>P-value</i>
Gender				
Female	991 (92.4%)	90 (90.9%)	901 (92.6%)	0.5442
Male	81 (7.6%)	9 (9.1%)	72 (7.3%)	
Mean age at genetic testing in years +/- SD (min, max)	51.1 +/- 12.1, (23, 89)	50 +/- 11.2, (26, 81)	51.2 +/- 12.2, (23, 89)	0.5322
Mean age at first breast cancer diagnosis in years +/- SD (min, max)	47.5 +/- 11 (23, 87)	44.9 +/- 8.7 (28, 80)	47.7 +/- 11.2 (23, 87)	0.0442
Tumor staining for ER				
Positive	688 (64.2%)	38 (38.4 %)	650 (66.8%)	<.0001
Negative	281 (26.2%)	45 (45.5%)	236 (24.2%)	
Low Positive	28 (2.6%)	3 (3%)	25 (2.6%)	
Unavailable or equivocal	75 (7%)	13 (13.1%)	62 (6.4%)	
Tumor staining for PR				
Positive	583 (54.4%)	28 (28.3%)	555 (57%)	<.0001
Negative	367 (34.2%)	55 (55.6%)	312 (32.1%)	
Low Positive	34 (3.2%)	2 (2%)	32 (3.3%)	
Unavailable or equivocal	88 (8.2%)	14 (14.1%)	74 (7.6%)	
Tumor staining for HER2/neu				
Positive	130 (12.1%)	5 (5.1%)	125 (12.9%)	0.0284
Negative	736 (68.7%)	72 (72.7%)	664 (68.2%)	
Unavailable or equivocal	206 (19.2%)	22 (22.2%)	184 (18.9%)	
Additional primaries				
Breast	113 (44.2%)	15 (51.7%)	98 (43.8%)	
Ovary*	24 (9.4%)	6 (20.7%)	15 (6.7%)	
Prostate	9 (3.5%)	0 (0%)	9 (4%)	
Pancreas	6 (2.3%)	2 (6.9%)	4 (1.8%)	
Other organ	104 (40.6%)	6 (20.7%)	98 (43.7%)	
P-values from Wilconxon rank-sum test comparing <i>BRCA1/2</i> positive and <i>BRCA1/2</i> negative groups; *includes fallopian tube and primary peritoneal cancers				

Our study population of 1072 breast cancer patients pursued genetic testing between the years 1998 and 2014. While some individuals chose to pursue genetic testing during their MD

Anderson genetic counseling visit, other individuals have had previous genetic testing results from outside institutions, accounting for the wide range of years at *BRCA1/2* genetic testing.

Tumors staining of ER, PR, and HER2/neu in breast tumors were obtained from the genetic counseling consultation notes. In the case of multiple breast primaries, the hormone receptor status of the breast cancer diagnosis that triggered the genetics evaluation was collected in this study. Hormone receptor tumor staining was categorized as the following: greater than 9% were considered positive, between 1 and 9% was considered low positive, and below 1% were considered negative. For the purposes of statistical analysis, low positive tumors were considered negative (Sanford, Song, Gutierrez-Barrera, Litton, Bedrosian, Albarracin, Valero, & Arun, 2014). We evaluated the difference in PPV when using these “stricter” versus “looser” definition of triple negative diagnosed at or under age 60 in our analysis. When using the “looser” definition which includes those individuals with ER and/or PR receptors with low positive signals (staining between 1-9%), 3 out of 39 individuals tested positive for a PPV of 7.1% (1-19%, 95% CI). When using the “stricter” definition with ER and PR staining at below 1% signal, 3 out of 34 individuals tested positive for a PPV of 8.1% (2-22%, 95% CI).

Table 2. Composition of positive *BRCA1/2* genetic testing results

<i>BRCA1</i>	<i>BRCA2</i>
54 deleterious	36 deleterious
1 suspected deleterious	3 suspected deleterious
1 see below	3 see below
1 deleterious, also <i>BRCA2</i> VUS	

The average age at time of *BRCA1/2* genetic testing was 51.1 years, with a range of 23 years to 89 years. The average age at first breast primary diagnosis was 47.5, with a range of 23

years to 87 years. The patients who tested *BRCA1/2* positive averaged an age of 44.9 years compared to patients who tested negative at 47.7 years ($p = 0.0442$). This is a statistically significant age difference between these two groups.

Estrogen (ER), progesterone (PR), and human epidermal growth factor receptor 2 (HER2/neu) hormone receptor statuses was collected and compared between those who tested positive and those who tested negative. Patients who were ER negative ($p < .0001$) and/or PR negative ($p < .0001$) and/or HER2/neu negative ($p = 0.0284$) were more likely to be *BRCA1/2* positive.

Positive predictive values were calculated for all patients who met only one of 14 NCCN criteria versus those who met two or more NCCN criteria. Approximately 31.8% of breast cancer patients in our study population were recommended for testing on the basis of a single criterion. The PPV of 12% for meeting two or more criteria was significantly higher than the PPV of 3.2% for when a patient only met one criterion ($p < .0001$). This PPV is significantly below 10% ($p < .0001$).

Table 3. Positive predictive values based on number of criteria fulfilled

<i>Number of criteria met</i>	<i>BRCA1/2 Negative</i>	<i>BRCA1/2 Positive</i>	<i>Total</i>	<i>PPV (95% CI)</i>	<i>P-value</i>
1	329	11	341	3.2% (1.6% - 5.7%)	<0.0001
≥2	644	88	731	12.0% (9.8% -14.6%)	0.08
Total	973	99	1072		

Chi-squared test comparing against 10% PPV

Positive predictive values were calculated for each of the 14 criteria when each was the sole criterion the patient met. One criterion had a PPV significantly below 10% by chi-square

test. One hundred and fifteen patients were recommended for genetic testing based on fulfilling only the criterion of ‘diagnosed with breast cancer ≤ 45 years of age’. Of these 115 patients, only 2 patients tested positive for a mutation in *BRCA1* or *BRCA2* for a PPV of 1.7%, which is significantly below the clinical utility cut-off of 10% for PPV ($p = 0.001$).

Additionally, the positive predictive value of the criterion, “diagnosed with breast cancer at any age with ≥ 2 close blood relatives with breast cancer at any age” was calculated to be 0% (95% confidence interval of 0%-9.0%) as none of the 37 patients who were tested based solely on this criteria ended up testing positive for a mutation in *BRCA1/2*.

Out of the 1072 *BRCA1* and *BRCA2* genetic testing results that were analyzed, 22 (2.05%) patients had targeted analysis for three common Ashkenazi Jewish mutations, 7 (0.65%) patients had only sequencing analysis, 105 (9.79%) patients had only sequencing plus analysis for 5 common rearrangements in *BRCA*, and 938 (87.5%) patients had comprehensive sequencing and rearrangement analysis. We do not expect this variation in the type of genetic testing to significantly impact our study outcomes as the 22 patients who underwent targeted analysis for three common Ashkenazi Jewish mutations did not go on to have sequencing or rearrangement analysis due to not having met additional criteria other than reported Ashkenazi Jewish ancestry.

Certain patients who tested negative for a *BRCA1/2* mutation carried mutations in other hereditary cancer syndrome genes. Three patients tested positive for mutations in *TP53*, and one had a VUS in *TP53*. One patient had a VUS in *PTEN*. One patient was positive for *PTEN*. One patient was positive for a *MSH2* pathogenic mutation.

Table 4. Positive predictive values of individual NCCN criterion as sole basis for recommending testing

<i>NCCN Criterion</i>	<i>BRCA1/2 Negative</i>	<i>BRCA1/2 Positive</i>	<i>PPV (95% Confidence Interval)</i>	<i>P-value compared to 10% PPV</i>
• Diagnosed with breast cancer $\leq 45y$	113	2	1.7% (0.2%, 6%)	0.001
• Diagnosed with breast cancer $\leq 50y$ with a second breast primary at any age	3	0	0% (0%, 71%)	N/A
• Diagnosed with breast cancer $\leq 50y$ with ≥ 1 close blood relative with breast cancer at any age	19	0	0% (0%, 18%)	N/A
• Diagnosed with breast cancer $\leq 50y$ with unknown or limited family history	17	0	0% (0%, 20%)	N/A
• Diagnosed with breast cancer $\leq 60y$ with triple negative hormone receptor status	39	3	7.1% (1%, 19%)	0.7673
• Diagnosed with breast cancer at any age with ≥ 1 close blood relatives with breast cancer $\leq 50y$	20	0	0% (0%, 17%)	N/A
• Diagnosed with breast cancer at any age with ≥ 2 close blood relatives with breast cancer at any age	37	0	0% (0%, 9%)	N/A
• Diagnosed with breast cancer at any age with ≥ 1 close blood relative with epithelial ovarian cancer	27	2	6.9% (0.8%, 23%)	0.8699
• Diagnosed with breast cancer at any age with ≥ 1 close blood relative with ≥ 2 close blood relatives with pancreatic cancer and/or prostate cancer (Gleason score ≥ 7) at any age	3	0	0% (0%, 71%)	N/A
• Diagnosed at any age with a close male relative with breast cancer	4	0	0% (0%, 60%)	N/A
• Personal history of epithelial ovarian cancer	10	1	9.1% (0.2%, 41%)	1.0000
• Personal history of male breast cancer	28	2	6.7% (0.8%, 22%)	0.8227
• Diagnosed at any age as an individual of ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish)	9	1	10% (0.3%, 45%)	0.8025
• Personal history of pancreatic cancer or prostate cancer (Gleason score ≥ 7) at any age with ≥ 2 close blood relatives with breast and/or ovarian and/or pancreatic or prostate cancer (Gleason score ≥ 7) at any age	No patients fulfilled only this criterion			

Two-sided exact test comparing against 10% PPV

DISCUSSION

Conclusions

Out of 14 NCCN criteria evaluated from the “Genetic/Familial High-Risk Assessment: Breast and Ovarian Version 2.2014” guidelines for recommending genetic testing, 12 criteria did not have PPVs statistically significantly differing from 10% PPV, and 2 did had positive predictive values significantly below 10% for predicting a mutation in *BRCA1* and *BRCA2*. This data suggests that possible revisions may be necessary in future versions of these specific NCCN guidelines in order to improve clinical utility of when to recommend genetic testing for HBOC.

The current NCCN guidelines recommend *BRCA1/2* testing for any patient that meets one or more criterion. From our study, individuals who fulfilled only one criterion had a 3.2% (0.2-6%) chance to test positive for a *BRCA1/2* mutation. This PPV is significantly below that of the clinical utility cut-off of 10%. Interestingly, previous studies suggest that the incidence of *BRCA1/2* mutations in women with breast cancer up to age 70 is between 1% and 6% (Frank & Critchfield, 2001; McClain, Palomaki, Nathanson, & Haddow, 2005). This suggests that the population of individuals who meet only one NCCN criterion for testing may not be a population enriched in *BRCA1/2* mutations.

Patients who meet more than one criterion for testing are more likely to test positive for a *BRCA1/2* mutation, and may need to be counseled differently from those who fulfill only one criterion. In our study, individuals who met two or more criterion had a 12% (9.8-14.6%, 95% CI) likelihood of having a mutation in *BRCA1* or *BRCA2*. Meeting more than one criterion correlated with having a higher risk for HBOC.

A previous study estimates the mutation rate in women diagnosed with breast cancer by age 45 to be between 4% and 8% (McClain, Palomaki, Nathanson, & Haddow, 2005). In our study, there 115 patients who were recommended for testing solely based on having fulfilled the criterion of being diagnosed with breast cancer by age 45. There were 441 additional patients who were recommended for testing based on having fulfilled this criterion as well as one or more other criterion. In total, 56 out of the 556 patients who fulfilled this criterion tested positive for a *BRCA1/2* mutation for a yield of 10.1% overall. Of the 115 patients who were tested solely based on being diagnosed with breast cancer by age 45, the positive predictive value for a *BRCA1/2* mutation was 1.7% (0.2-6%, 95% CI). This suggests that testing individuals based on this criterion alone may in fact be testing individuals at or below the incidence of HBOC in the general breast cancer population, and that individuals with a *BRCA1/2* mutation will often fulfill at least one other criterion, which helps identify a population at higher risk within the young (≤ 45 years) breast cancer population. It would be worth investigating the clinical usefulness of this criterion in consideration of the costs and harms associated with genetic testing with low yield.

In 2014 Dr. Mary Claire King made a public declaration recommending testing of all women at age 30, regardless of personal and family histories, for *BRCA1/2* genetic testing based on an estimated population prevalence higher than the 1 in 400 to 1 in 800 that is generally quoted (King, 2014). While our study was not aimed to assess the effectiveness of this approach, it may still be useful to consider *BRCA1/2* testing at a population level. Based on our findings, it may be noted that portions of the currently accepted practice guidelines recommend genetic testing at a yield comparable to the prevalence of *BRCA1/2* mutations in the general population. Thus, it may be effective to discuss the option of *BRCA1/2* testing with all patients with breast cancer.

These considerations are especially important in the atmosphere of genetic testing for cancer predisposition syndromes in recent years. Genetic testing has become increasingly

accessible to patients due to the decrease in cost of sequencing technologies. Further, large panels of cancer predisposition genes are being marketed to non-specialized oncologists in many large cities. As there are fewer and fewer barriers to offering genetic testing, it is more important now than critically evaluate the purpose of existing guidelines when looking forward to the future of genetic testing. In the case of the *BRCA* genes, the time may soon come when reduced cost, decreased stigma, and variant reclassification sophistication may finally allow for successful population-based testing. However, the challenge of providing appropriate counseling to all interested patients regarding risks and limitations of existing knowledge still remains.

Limitations

Due to limitations in sample size, several of the criteria being evaluated did not meet clinical significance. Because many criteria overlap, there were several criteria for which it was rare to be the sole criterion for which patients were recommended for testing. Therefore, the number of individuals who were tested solely based on having met one criterion was only a fraction of all patients in the study. However, the current data supports the idea that these criteria vary in their predictive values. As there is clear value in understanding these predictive values, a large-scale analysis of the detection rates, specificity, and positive predictive values of guidelines for HBOC genetic testing may be beneficial to provide specific clinical guidance and expectations.

Furthermore, our study population was likely biased towards being a higher-risk sample as they are patients who have been referred to genetic counseling out of concern for a hereditary cancer syndrome. This does potentially skew the results of our study. However, due to our aim to identify criteria with mutation yields, our presumably higher-risk population in fact strengthens

our findings. In other words, if a criterion has a low yield in a high-risk population, it likely has an even lower yield in the general breast cancer population.

Our study population consisted of only participants with a personal history of breast cancer. Evaluation of the criteria, “personal history of pancreatic cancer or prostate cancer (Gleason score ≥ 7) at any age with ≥ 2 close blood relatives with breast and/or ovarian and/or pancreatic or prostate cancer (Gleason score ≥ 7) at any age” and “personal history of epithelial ovarian cancer”, were limited due to the nature of these criteria not requiring the patient to have a personal history of breast cancer.

While it was possible to verify details of the patients’ personal histories of cancer, family histories were collected by patient report. As is often the case in patient-reported family history, there can be reports of ambiguous or unknown types of cancer, such reports of “female cancers” or “unknown primaries”. Furthermore, we were not able to verify the exact pathology of family members’ reports of cancer such as epithelial versus mucinous ovarian cancer and the Gleason score of prostate cancers. However, as the NCCN guidelines are intended as clinical criteria, we feel that this information is often difficult to obtain in a clinical setting. Therefore, our study realistically represents typical information that would be available in a high-risk cancer genetics consultation.

While the majority of our patients did undergo *BRCA1* and *BRCA2* sequencing and rearrangement analysis, there were 112 patients who did not have comprehensive testing. It is likely that very few would have tested positive on follow-up rearrangement testing. Large rearrangements account for approximately 5.9%-9.9% (Judkins, Rosenthal, Arnell, Burbidge, Geary, Barrus, Schoenberger, Trost, Wenstrup, & Roa, 2012) of pathogenic mutations in HBOC, mostly in *BRCA1*. These are patients who are likely to have more concerning family histories due to the higher penetrance of cancers in *BRCA1*-associated HBOC. Furthermore, 105 of 112

patients without full rearrangement analysis still had 5-site rearrangement analysis, which accounts for the most common pathogenic rearrangements affecting *BRCA1*.

Future Directions

Triple negative breast cancers are historically defined as those with tumor staining of less than 1% for ER, PR, and HER2/neu. In this study, a looser definition was used when evaluating the criterion of being “diagnosed with breast cancer ≤ 60 y with triple negative hormone receptor status”. For the purposes of this study, we defined triple negative tumor staining levels less than 9%. This was due to recent data demonstrating similar *BRCA1/2* mutation prevalence rates in hormone receptor negative and low positive groups (Sanford, Song, Gutierrez-Barrera, Litton, Bedrosian, Albarracin, Valero, & Arun, 2014). However, more studies are needed to confirm this association. The sample number in our study was not large enough to detect a significant difference. However, this topic warrants additional investigation in order to further define “triple negative” in the context of association with HBOC syndrome.

Currently there exist risk-assessment models for prediction of future risks for breast cancer, as well as risk-prediction tools that use family history to predict the likelihood of detecting a *BRCA1/2* mutation, such as BRCAPRO. However, these risk prediction tools can be time-consuming and are typically not used during the face-to-face time with the patient in order to make a decision on testing. Being able to generate an empiric likelihood for testing positive based on which NCCN criteria they fulfill, however, could offer more concrete information to the patient during the session in order to aid decision-making regarding testing and for anticipatory guidance. In this consideration, it is important to balance the goals and costs associated with each risk-assessment tool. Goals may include the accuracy of the tool and ease of usage in clinic. Costs may include the time, expertise, or specialized equipment that may be required to run the tool.

While this is outside of the scope of the current study, it may be of interest to assess the predictive value of these tools in comparison with the NCCN criteria to predict *BRCA1* and *BRCA2* positivity. No clinical guideline is perfect. It is always important to evaluate each family with a fresh eye. With that said, the ultimate goal would be to have a system, whether by a set of guidelines or by an automated pedigree- and pathology- assessment tool, that would allow for the most accurate risk estimate for our patients without undue burden on the healthcare infrastructure.

There may be clinical value in conducting similar evaluations of current NCCN criteria for recommending testing for other hereditary cancer syndromes such as Li-Fraumeni syndrome, Cowden syndrome, Lynch syndrome, familial adenomatous polyposis, MUYTH-associated polyposis, and Peutz-Jeghers syndrome.

Lastly, the data from this study provides practical implications. The empiric risk numbers from this study can be utilized to provide patients with an approximate chance for testing positive according to the specific NCCN criteria they fulfill. For patients who only fulfill a single criterion, it would be appropriate to inform them of the relative low likelihood of testing positive. For those who fulfill multiple criteria, we are able to have a discussion with more time dedicated to the next steps in the case of a positive test. While this also was not a goal of our study, and not a large sample, we do feel reassured that, in this 15-month period, every breast cancer patient who pursued *BRCA1/2* testing despite not having been recommended to do so based on the NCCN guidelines all tested negative and are likely truly at low risk.

BIBLIOGRAPHY

- Antoniou, A., Pharoah, P. D., Narod, S., Risch, H. A., Eyfjord, J. E., Hopper, J. L., Loman, N., Olsson, H., Johannsson, O., Borg, A., Pasini, B., Radice, P., Manoukian, S., Eccles, D. M., Tang, N., Olah, E., Anton-Culver, H., Warner, E., Lubinski, J., Gronwald, J., Gorski, B., Tulinius, H., Thorlacius, S., Eerola, H., Nevanlinna, H., Syrjakoski, K., Kallioniemi, O. P., Thompson, D., Evans, C., Peto, J., Lalloo, F., Evans, D. G., & Easton, D. F. (2003). Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet*, *72*(5), 1117-1130. doi: 10.1086/375033
- Chen, S., & Parmigiani, G. (2007). Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol*, *25*(11), 1329-1333. doi: 10.1200/JCO.2006.09.1066
- Ford, D., Easton, D. F., Stratton, M., Narod, S., Goldgar, D., Devilee, P., Bishop, D. T., Weber, B., Lenoir, G., Chang-Claude, J., Sobol, H., Teare, M. D., Struewing, J., Arason, A., Scherneck, S., Peto, J., Rebbeck, T. R., Tonin, P., Neuhausen, S., Barkardottir, R., Eyfjord, J., Lynch, H., Ponder, B. A., Gayther, S. A., & Zelada-Hedman, M. (1998). Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. *Am J Hum Genet*, *62*(3), 676-689.
- Frank, T. S., & Critchfield, G. C. (2001). Identifying and managing hereditary risk of breast and ovarian cancer. *Clin Perinatol*, *28*(2), 395-406.
- Judkins, T., Rosenthal, E., Arnell, C., Burbidge, L. A., Geary, W., Barrus, T., Schoenberger, J., Trost, J., Wenstrup, R. J., & Roa, B. B. (2012). Clinical significance of large rearrangements in BRCA1 and BRCA2. *Cancer*, *118*(21), 5210-5216. doi: 10.1002/cncr.27556

- McClain, M. R., Palomaki, G. E., Nathanson, K. L., & Haddow, J. E. (2005). Adjusting the estimated proportion of breast cancer cases associated with BRCA1 and BRCA2 mutations: public health implications. *Genet Med*, 7(1), 28-33. doi: 10.109701.GIM.0000151155.36470.FF
- National Comprehensive Cancer Network. (2015). About NCCN. Retrieved April 3, 2015, from <http://www.nccn.org/about/default.aspx>
- Nelson, H. D., Pappas, M., Zakher, B., Mitchell, J. P., Okinaka-Hu, L., & Fu, R. (2014). Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: a systematic review to update the U.S. Preventive Services Task Force recommendation. *Ann Intern Med*, 160(4), 255-266. doi: 10.7326/M13-1684
- National Comprehensive Cancer Network. (2014). Genetic/Familial High-Risk Assessment: Breast and Ovarian (Version 2.2014). *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines)*. Retrieved November 30, 2014, 2014, from http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf
- Petrucci, N., Daly, M. B., & Feldman, G. L. (2010). Hereditary breast and ovarian cancer due to mutations in BRCA1 and BRCA2. *Genet Med*, 12(5), 245-259. doi: 10.1097/GIM.0b013e3181d38f2f
- Roberts, N. J., Vogelstein, J. T., Parmigiani, G., Kinzler, K. W., Vogelstein, B., & Velculescu, V. E. (2012). The predictive capacity of personal genome sequencing. *Sci Transl Med*, 4(133), 133ra158. doi: 10.1126/scitranslmed.3003380
- Sanford, R. A., Song, J., Gutierrez-Barrera, A. M., Litton, J. K., Bedrosian, I., Albarracin, C. T., Valero, V., & Arun, B. (2014). Incidence of germline BRCA mutation in patients with ER-low positive/PR negative/HER-2 neu negative tumors. *ASCO Meeting Abstracts*, 32(26_suppl), 2.
- American Cancer Society. (2015). Cancer Facts & Figures 2015. *American Cancer Society*.

Winn, R. J., Botnick, W., & Dozier, N. (1996). The NCCN Guidelines Development Program.
Oncology (Williston Park), 10(11 Suppl), 23-28.

SUPPLEMENTAL DATA

The subset of current NCCN criteria being evaluated includes (from ‘Genetic/familial high-risk assessment: breast and ovarian. Version 1.2014’, © National Comprehensive Cancer Network, Inc 2011, All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN Guidelines®, NCCN COMPENDIUM® and NCCN TEMPLATES® are trademarks owned by the National Comprehensive Cancer Network, Inc.)

Hereditary Breast and/or Ovarian Cancer syndrome testing criteria

- Personal history of breast cancer + ≤ 1 of the following :
 - Diagnosed ≤ 45 y
 - Diagnosed ≤ 50 y with:
 - An additional primary
 - ≥ 1 close blood relative with breast cancer at any age
 - An unknown or limited family history
 - Diagnosed ≤ 60 y with a:
 - Triple negative breast cancer (hormone receptors: ER -, PR-, HER2/neu-)
 - Diagnosed at any age with:
 - ≥ 2 close blood relatives with breast cancer at any age
 - ≥ 1 close blood relative with epithelial ovarian cancer
 - ≥ 2 close blood relatives with pancreatic cancer and/or prostate cancer (Gleason score ≥ 7) at any age
 - A close male blood relative with breast cancer
 - For an individual of ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish) no additional family history may be required

- Personal history of epithelial ovarian cancer
- Personal history of male breast cancer
- Personal history of pancreatic cancer or prostate cancer (Gleason score ≥ 7) at any age with ≥ 2 close blood relatives with breast and/or ovarian and/or pancreatic or prostate cancer (Gleason score ≥ 7) at any age
 - For pancreatic cancer, if Ashkenazi Jewish ancestry, only one additional affected relative is needed)

Individuals with unknown or limited family history/structure, such as fewer than 2 first- or second-degree female relatives having lived beyond age 45 in either lineage, may have an underestimated probability of familial mutation detection. The likelihood of mutation detection may be very low in families with a large number of unaffected female relatives. Clinical judgment should be used to determine the appropriateness of genetic testing. The maternal and paternal sides should be considered independently.

For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included

Two breast primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors either synchronously or asynchronously

Close blood relatives include first-, second-, and third-degree relatives on same side of family.

For the purposes of these guidelines, fallopian tube and primary peritoneal cancers are included.

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