Evaluating the NCCN Clinical Criteria for Recommending *BRCA1* and *BRCA2* Genetic Testing in Patients With Breast Cancer

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Abstract

Background: Mutations in the *BRCA1* and *BRCA2* genes predispose individuals to a significantly elevated risk for breast and ovarian cancers. Identification of these individuals allows for proper screening, management, and testing of at-risk relatives. NCCN has established clinical criteria for recommending *BRCA1/2* testing. **Patients and Methods:** A retrospective chart review of 1,123 patients with breast cancer was performed to evaluate the positive predictive values (PPVs) of 14 individual criteria for predicting *BRCA1/2* mutations. **Results:** Two criteria had PPVs significantly below 10%. Only 2 of 115 patients who were recommended for testing based solely on the criterion of “diagnosed with breast cancer at ≤45 years of age” had pathogenic mutations at a PPV of 1.6% (95% CI, 0.2%–6.0%). Additionally, 0 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 (95% CI, 0%–9%). Overall, meeting >1 criterion has a PPV of 12%, whereas meeting only 1 criterion has a PPV of 3.2% (95% CI, 1.6%–5.7%), significantly below 10% ($P<.0001$) for predicting *BRCA1/2* positivity. **Conclusions:** Patients with breast cancer meeting >1 criterion constitute a population significantly enriched for *BRCA1/2* mutations, whereas those meeting only 1 criterion test positive at a rate similar to unselected patients with breast cancer. These data will inform ongoing discussions regarding how to best implement *BRCA1/2* genetic testing.

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Background

In the United States, 1 in 8 women will develop breast cancer in her lifetime. Although breast cancer is common, only 5% to 10% of these breast cancers are hereditary.¹ Hereditary breast and ovarian cancer syndrome (HBOC) associated with germline mutations in the *BRCA1* and *BRCA2* genes² is the most common hereditary breast cancer predisposition. In the general population, approximately 1 in 400 people (possibly up to 1/200 in select populations) have a *BRCA1/2* mutation.^{2–5} Although *BRCA1/2* mutations are rare, their identification is crucial because the associated 45% to

85% lifetime risk for breast cancer, 11% to 40% lifetime risk for ovarian cancer, and increased risks for pancreatic, male breast, and prostate cancers^{6–9} warrant specialized screening and prevention. In particular, risk-reducing bilateral salpingo-oophorectomy in women with *BRCA1/2* mutations meets the gold standard of demonstrated benefit via decreased cancer incidence and all-cause mortality.¹⁰

Throughout the past 20 years during which *BRCA1/2* genetic testing has been clinically available, the question of who should be offered genetic testing has been debated. Because most breast cancer is not

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attributable to *BRCA1/2* mutations, this debate has included the question of how to identify patients with breast cancer who are at higher risk of having a mutation based on analysis of personal and family history of cancer. Risk prediction models such as *BRCA*PRO and *BOADICEA*^{11,12} calculate the percentage likelihood of an individual testing positive for a *BRCA1/2* mutation. However, consensus regarding what percentage likelihood is high enough to warrant offering genetic testing has never been reached. The 1996 “Statement of the American Society of Clinical Oncology: Genetic Testing for Cancer Susceptibility” mentioned >10% as an example of a high estimated probability of mutation detection¹³; subsequent versions (including the current version)¹⁴ do not cite a specific numerical threshold. Absent clear consensus regarding the question of threshold, ≥10% mutation probability has been a commonly cited reference point. The American Congress of Obstetricians and Gynecologists (ACOG),¹⁵ health insurance companies such as Aetna,¹⁶ and researchers who have studied risk-prediction models^{11,12} have continued to include ≥10% probability as a consideration in determining who should undergo genetic testing.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Genetic/Familial High-Risk Assessment: Breast and Ovarian¹⁷ includes clinical criteria for when to recommend *BRCA1/2* genetic testing. These criteria do not use a pretest mutation probability threshold; rather, they list personal/family cancer history scenarios for which *BRCA1/2* genetic testing should be considered. These criteria are often used by insurers as a basis for determining when *BRCA1/2* genetic testing is a covered benefit. For example, the NCCN criteria are cited and incorporated into the Medicare *BRCA1* and *BRCA2* genetic testing local coverage determination¹⁸ and the Aetna clinical policy bulletin “*BRCA* Testing, Prophylactic Mastectomy, and Prophylactic Oophorectomy.”¹⁶

Given how widely adopted the NCCN *BRCA1/2* testing criteria are, it is important to understand how they perform. To our knowledge, the positive predictive value (PPV) of the NCCN criteria has not been previously studied. Therefore, our study goal was to assess the PPV of the NCCN criteria for recommending *BRCA1/2* genetic testing in patients with breast cancer.

Patients and Methods

After Institutional Review Board approval was obtained, a retrospective chart review was performed of 1,123 patients with breast cancer who were seen for genetic counseling at our institution between March 31, 2013, and June 30, 2014. Because of the rarity of male breast cancer, all male patients with breast cancer seen for genetic counseling were included (genetic testing dates ranged from September 9, 1999–June 30, 2014). All 1,123 study participants had a personal history of either invasive breast cancer or ductal carcinoma in situ and had complete 3-generation pedigrees available for review. All patients had undergone clinical genetic testing that included *BRCA1* and *BRCA2* and other high penetrance genes as indicated based on personal/family history. None of the study participants had undergone panel genetic testing.

Estrogen receptor (ER) and progesterone receptor (PR) immunohistochemistry results were categorized as follows: ≥10% staining was considered positive, 1% to 9% staining was considered low-positive, and <1% staining was considered negative, whereas *HER2/neu* receptor staining was categorized as positive, equivocal, or negative by immunohistochemistry and/or fluorescence in situ hybridization. For the purposes of statistical analysis and for genetic testing criteria, low-positive tumors were considered negative due to recent data demonstrating similar *BRCA1/2* mutation prevalence rates in hormone receptor-negative and low-positive groups.¹⁹ In the case of multiple breast primaries, the receptor status of the breast cancer diagnosis that triggered the genetic evaluation was collected.

Each participant’s medical and family histories were assessed to determine which of the NCCN *BRCA1/2* testing criteria (Version 1.2014) were met. Twenty-five participants were then excluded from the study because they underwent *BRCA1/2* testing without having met any NCCN criteria for HBOC genetic testing. Of note, all 25 tested negative. An additional 26 participants were excluded from the study due to having *BRCA1/2* variants of unknown significance. The 1,072 genetic testing results that remained eligible for analysis were grouped as follows: positive results included those which were reported as “deleterious” (55 in *BRCA1*; 36 in *BRCA2*), “suspected deleterious” (1 in *BRCA1*; 3 in *BRCA2*), and “see below” (1 in *BRCA1*; 3 in *BRCA2*).

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Variable	All Available	BRCA1/2-Positive	BRCA1/2-Negative	P Value ^a
All	1,072	99 (9.2%)	973 ^b (90.8%)	
Sex				
Female	991 (92.4%)	90 (90.9%)	901 (92.6%)	.5442
Male	81 (7.6%)	9 (9.1%)	72 (7.3%)	
Mean age at genetic testing in years $\pm$ SD (min, max)	51.1 $\pm$ 12.1 (23, 89)	50 $\pm$ 11.2 (26, 81)	51.2 $\pm$ 12.2 (23, 89)	.5322
Mean age at first breast cancer diagnosis in years $\pm$ SD (min, max)	47.5 $\pm$ 11.0 (23, 87)	44.9 $\pm$ 8.7 (28, 80)	47.7 $\pm$ 11.2 (23, 87)	.0442
Ancestry				
Ashkenazi Jewish ancestry	60 (5.6%)	12 (12.1%)	48 (4.9%)	.0030
Non-Ashkenazi Jewish	1,012 (94.4%)	87 (87.9%)	925 (95.1%)	
Tumor staining for ER				
Positive ($\geq 10\%$)	688 (64.2%)	38 (38.4 %)	650 (66.8%)	<.0001
Negative (<1%)	281 (26.2%)	45 (45.5%)	236 (24.2%)	
Low positive (1%–9%)	28 (2.6%)	3 (3.0%)	25 (2.6%)	
Unavailable	75 (7.0%)	13 (13.1%)	62 (6.4%)	
Tumor staining for PR				
Positive ($\geq 10\%$)	583 (54.4%)	28 (28.3%)	555 (57%)	<.0001
Negative (<1%)	367 (34.2%)	55 (55.6%)	312 (32.1%)	
Low positive (1%–9%)	34 (3.2%)	2 (2.0%)	32 (3.3%)	
Unavailable	88 (8.2%)	14 (14.1%)	74 (7.6%)	
Tumor staining for HER2/neu				
Positive	130 (12.1%)	5 (5.1%)	125 (12.9%)	.0284
Negative	736 (68.7%)	72 (72.7%)	664 (68.2%)	
Unavailable or equivocal	206 (19.2%)	22 (22.2%)	184 (18.9%)	
Triple-negative status				
Triple-negative	229 (21.3%)	41 (41.4%)	188 (19.3%)	<.0001
Not triple-negative	627 (58.5%)	34 (34.3%)	593 (60.9%)	
At least one marker unavailable or equivocal	216 (20.1%)	24 (24.2%)	192 (19.7%)	
Additional primary cancers				
None	812 (75.8%)	68 (68.7%)	744 (76.5%)	.008
Additional breast primary	113 (10.6%)	15 (15.2%)	98 (10.1%)	
Ovary ^c	24 (2.2%)	7 (7.0%)	17 (1.7%)	
Prostate	10 (0.9%)	1 (1.0%)	9 (0.9%)	
Pancreas	9 (0.8%)	2 (2.0%)	7 (0.7%)	
Other organs	104 (9.7%)	6 (6.1%)	98 (10.1%)	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

^aP values evaluating the association of each variable with BRCA status are from Wilcoxon rank sum test for continuous variables and chi-square test for categorical variables.

^bIncludes 5 patients with pathogenic mutations in other hereditary cancer syndrome genes (3 with *TP53*, 1 with *PTEN*, and 1 with *MSH2*).

^cIncludes fallopian tube and primary peritoneal cancers.

Negative results included those that were reported as “variant, favor polymorphism” (4 in *BRCA1*; 14 in *BRCA2*) and “no mutation detected” (n=955). Of the 1,072 *BRCA1/2* genetic testing results evaluated, 22 (2.05%) were only targeted analysis for 3

common Ashkenazi Jewish mutations, 7 (0.65%) were only sequencing analysis, 105 (9.79%) were only sequencing plus analysis for 5 common rearrangements in *BRCA1*, and 938 (87.5%) were comprehensive sequencing and rearrangement analysis.

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Table 2. PPVs Based on Number of Criteria Fulfilled

Number of Criteria Met	BRCA1/2-Negative	BRCA1/2-Positive	Total	PPV (95% CI)	P Value ^a
1	329	11	340	3.2% (1.6%–5.7%)	<.0001
≥2	644	88	732	12.0% (9.8%–14.6%)	.08
All patients	973	99	1,072	9.2% (7.6%–11.1%)	.44

Abbreviation: PPV, positive predictive value.

^aChi-square test comparing against 10% PPV. In addition, $P<.0001$ when comparing 1 criterion met vs ≥2 criteria met.

Study population demographics were compared between *BRCA1/2*-positive and *BRCA1/2*-negative participants using the chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables. Chi-square and Fisher exact tests were used to calculate whether any single or combined groups of criteria had PPVs significantly <10%.

Results

Study population demographics are summarized in Table 1. Overall, 9.2% of the study population tested positive for a *BRCA1* or *BRCA2* mutation. Patients who were *BRCA1/2*-positive were younger at breast cancer diagnosis than those who tested negative (44.9 vs 47.7 years; $P=.0442$). Patients with tumors that were ER-negative ($P\leq.0001$), PR-negative ($P\leq.0001$), and HER2/neu-negative ($P=.0284$) were more likely to be *BRCA1/2*-positive. Five individuals who tested negative for a *BRCA1/2* mutation carried a pathogenic mutation in another hereditary cancer syndrome gene (3 *TP53*, 1 *PTEN*, 1 *MSH2*).

PPVs were calculated for meeting any 1 NCCN criterion versus meeting ≥2 (Table 2). Within our study population, 340 patients (31.8%) met only 1 criterion, with a PPV of 3.2% (95% CI, 1.6%–5.7%). The PPV of meeting ≥2 criteria was significantly higher ($P<.0001$) at 12% (95% CI, 9.8%–14.6%).

In order to further characterize the 340 patients who met only 1 criterion, PPVs were calculated for each of the 14 criteria when each was the sole criterion the patient met (Table 3). Only 2 of 115 patients who met only the criterion “diagnosed with breast cancer ≤45 years of age” tested positive for a *BRCA1/2* mutation (PPV, 1.7%; 95% CI, 0.2%–6.0%). Additionally, 0 of 37 patients who met only the criterion “diagnosed with breast cancer at any age with ≥2 close blood relatives with breast cancer” tested positive for a *BRCA1/2* mutation (PPV,

0%; 95% CI, 0%–9.0%). No combinations of any 2 criteria yielded a significant difference when comparing against 10% PPV; most 2-criteria combinations yielded 0 *BRCA1/2*-positive results. Those that yielded ≥1 positive result are listed in Table 4.

Discussion

When patients with breast cancer fulfilled ≥2 NCCN criteria, the *BRCA1/2* mutation rate was 12%, thus confirming that genetic testing is clearly indicated for those who meet ≥2 NCCN criteria. When patients with breast cancer undergo *BRCA1/2* genetic testing based on meeting only 1 of the NCCN criteria, however, the yield of positive results is significantly <10%. In individuals who fulfilled any 1 NCCN criterion, the mutation yield was 3.2%. Among patients diagnosed at ≤45 years of age who did not meet any other testing criteria, the mutation yield was even lower at 1.7%. In addition, 0 of 37 patients who underwent testing solely based on having 2 relatives with breast cancer tested positive for a *BRCA1/2* mutation. This information can be used during pretest genetic counseling to help patients understand their likelihood of testing positive.

The NCCN Guidelines also provide a separate set of criteria titled, “Criteria for Further Genetic Risk Evaluation.” These criteria are looser than the *BRCA1/2* testing criteria, and are intended to help healthcare providers identify individuals for whom formal risk assessment should be undertaken. Given the relatively low yield of even the stricter testing criteria demonstrated by this study, the utility of these looser criteria is unclear and should be further evaluated.

A helpful point of reference in evaluating these yields is to compare them with the prevalence of *BRCA1/2* mutations in unselected patients with breast cancer. Previous studies suggest that the prev-

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Table 3. PPVs of Individual NCCN Criterion When Only That Criterion Was Met

NCCN Criterion	BRCA1/2-Negative	BRCA1/2-Positive	PPV (95% CI)	P Value vs 10% PPV ^a
Diagnosed with breast cancer at age ≤45 y	113	2	1.7% (0.2%, 6%)	.001
Diagnosed with breast cancer at age ≤50 y with a second breast primary at any age	3	0	0% (0%, 71%)	N/A
Diagnosed with breast cancer at age ≤50 y with ≥1 close blood relative with breast cancer at any age	19	0	0% (0%, 18%)	N/A
Diagnosed with breast cancer at age ≤50 y with unknown or limited family history	17	0	0% (0%, 20%)	N/A
Diagnosed with breast cancer at age ≤60 y with triple-negative hormone receptor status	39	3	7.1% (1%, 19%)	.7673
Diagnosed with breast cancer at any age with ≥1 close blood relatives with breast cancer at age ≤50 y	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%)	.8699
Diagnosed with breast cancer at any age with ≥2 close blood relatives with pancreatic 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%)	.8227
Diagnosed at any age as an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish)	9	1	10.0% (0.3%, 45%)	.8025
Personal history of pancreatic 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 with breast cancer fulfilled only this criterion			

Abbreviation: N/A, not applicable; PPV, positive predictive value.

^a2-sided exact test comparing against 10% PPV

absence of *BRCA1/2* mutations in patients diagnosed at <65 to 70 years of age (but otherwise unselected) is 1% to 6%.^{3,20,21} Therefore, the prevalence of *BRCA1/2* mutations in patients with breast cancer meeting only 1 NCCN criterion in our study population is similar to that in unselected patients diagnosed at <70 years of age.

The main purpose of genetic testing criteria such as those of the NCCN is to identify individuals for whom the likelihood of testing positive justifies the costs of undergoing genetic testing. During the past 20 years, the availability of genetic testing has increased, cost has decreased, rate of detection of variants of uncertain significance has also decreased, and the Genetic Information Nondiscrimination Act of 2008 became law. Therefore, a 10% pretest probability threshold is probably too restrictive. What should that threshold now be? Consensus has not been reached on this topic. Our study demonstrates that patients with breast cancer are currently being offered *BRCA1/2* genetic testing based on criteria that

have a 3.2% mutation yield. Because this is similar to the likelihood of an unselected patient with breast cancer diagnosed at <70 years of age testing positive, perhaps it is acceptable to consider genetic testing for all individuals with breast cancer, or for all individuals diagnosed with breast cancer at <70 years of age and for those diagnosed at >70 years of age who meet other testing criteria. This would also be comparable to the 2% to 3% likelihood of identifying Lynch syndrome in unselected patients with colorectal cancer, for whom universal Lynch syndrome screening has gathered wide support.²²

Offering genetic testing to all patients with breast cancer would significantly increase the size of the testing population, which would pose practical barriers. On the other hand, this would be a less drastic step than implementing general population screening for *BRCA1/2* mutations, as was recently proposed²³ (and challenged²⁴), which would vastly expand the target population and lower the yield even further. Given that mutations in other high-

Table 4. PPVs of Combinations of 2 Individual NCCN Criteria When Only Those 2 Criteria Were Met

Two Criteria Meta	<i>BRCA1/2</i> - Negative	<i>BRCA1/2</i> - Positive	PPV (95% CI) ^b
1. Ashkenazi Jewish ancestry	0	1	100% (2.5%–100%)
2. Diagnosed with triple-negative breast cancer at age ≤60 y			
1. Ashkenazi Jewish ancestry	0	1	100% (2.5%–100%)
2. ≥1 close blood relative with epithelial ovarian cancer			
1. Diagnosed with breast cancer at age ≤45 y	8	1	11.1% (0.3%–48.2%)
2. Diagnosed with breast cancer at age ≤50 y and have a second breast primary			
1. Diagnosed with breast cancer at age ≤45 y	62	3	4.6% (1.0%–12.9%)
2. Diagnosed with breast cancer at age ≤50 y with ≥1 close blood relative with breast cancer at any age			
1. Diagnosed with breast cancer at age ≤45 y	23	3	11.5% (2.4%–30.2%)
2. Diagnosed with breast cancer at age ≤50 y with unknown or limited family history			
1. Diagnosed with breast cancer at age ≤45 y	18	3	14.3% (3.0%–36.3%)
2. Diagnosed with triple-negative breast cancer at age ≤60 y			
1. Diagnosed with breast cancer at age ≤45 y	15	1	6.2% (0.2%–30.2%)
2. ≥1 close blood relative with epithelial ovarian cancer			
1. Diagnosed with breast cancer at age ≤45 y	0	1	100% (2.5%–100%)
2. Diagnosed with epithelial ovarian cancer at any age			
1. Diagnosed with breast cancer at age ≤50 y with ≥1 close blood relative with breast cancer at any age	11	1	8.3% (0.2%–38.5%)
2. Diagnosed with breast cancer at any age with 1 close blood relative diagnosed with breast cancer at age ≤50 y			
1. Diagnosed with breast cancer at age ≤50 y with ≥1 close blood relative with breast cancer at any age	7	1	12.5% (0.3%–52.7%)
2. ≥1 close blood relative with epithelial ovarian cancer			
1. Diagnosed with triple-negative breast cancer at age ≤60 y	6	2	25% (3.2%–65.1%)
2. ≥1 close blood relative with epithelial ovarian cancer			
1. Diagnosed with breast cancer at any age with 1 close blood relative diagnosed with breast cancer at age ≤50 y	46	4	8% (2.2%–19.2%)
2. Diagnosed with breast cancer at any age with ≥2 close blood relatives with breast cancer at any age			
1. Diagnosed with breast cancer at any age with ≥2 close blood relatives with breast cancer at any age	1	1	50% (1.3%–98.7%)
2. Diagnosed with epithelial ovarian cancer at any age			

Abbreviation: PPV, positive predictive value.

^aOnly combinations yielding ≥1 patient with *BRCA1/2*-positive breast cancer were included.^b95% CI calculated using the Clopper-Pearson exact test.

penetrance genes were also detected in the study population, a hereditary breast cancer panel genetic test could be the appropriate test to offer. Inclusion of moderate penetrance breast cancer genes could also be considered; although this would certainly lead to an overall increase in the number of mutations identified, it should also be acknowledged that significant questions regarding clinical utility remain to be answered.¹⁴ Further studies are needed to determine the utility, yield, and feasibility of universal

hereditary breast cancer genetic testing for patients with breast cancer.

Several limitations to the current study should be considered. This was a single-institution study, and therefore further studies examining other populations are warranted. The NCCN criteria have been revised since the study was conducted; however, because all of the criteria analyzed here are still in effect and only minor changes to the criteria for patients with breast cancer were made, our study results should still generally apply to the current criteria. The study

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population comprised patients with breast cancer referred for genetic counseling, and thus may be biased toward a higher likelihood of detecting *BRCA1/2* mutations compared with an unselected sample. However, this would tend to bias the results toward a higher yield of *BRCA1/2* mutations; the fact that the mutation yields were still relatively low actually strengthens our result. The intent of our study was to evaluate the NCCN criteria as they pertain to patients with breast cancer, and therefore the findings are not generalizable to individuals without a personal diagnosis of breast cancer. There were several criteria for which it was rare to be the sole criterion met, which limited our ability to assess the PPV of those individual criteria. As is often the case in patient-reported family history, reports of ambiguous or unknown types of cancer could not be clarified. Pathology was not verified beyond that of the patients' cancers. However, because the NCCN Guidelines are intended for clinical use, we feel that

this information is realistically representative of the typical level of information that would be available in a cancer genetics consultation. Although most patients underwent *BRCA1/2* full sequencing and rearrangement analysis, 134 patients did not. Given that this represents only 12.5% of the study population and that at least 90% of mutations still would have been detected via the testing method used, this is unlikely to significantly impact the study findings.

Conclusions

Patients with breast cancer meeting more than 1 NCCN criterion constitute a population significantly enriched for *BRCA1/2* mutations, whereas those meeting only 1 criterion test positive at a rate similar to unselected patients. These data will help health-care providers in pretest risk assessment and genetic counseling, and will inform ongoing discussions of how to best implement *BRCA1/2* genetic testing.

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