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Adherence to NCCN Guidelines for Genetic Testing in Breast Cancer Patients: Who Are We Missing?

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ABSTRACT

Background. Genetic predisposition accounts for 5–10% of all breast cancers (BC) diagnosed. NCCN guidelines help providers identify appropriate candidates for counseling and testing. Concerns about underutilization of genetic testing have spurred interest in broader peri-diagnostic testing. We evaluated surgeon adherence to NCCN guidelines and studied patterns of testing in newly diagnosed BC patients.

Methods. A total of 397 patients were identified with newly diagnosed BC treated at our institution between 2016 and 2017 with no prior genetic testing. Eligibility for genetic testing based on NCCN criteria, referral, and patient compliance were recorded.

Results. In total, 212 of 397 (53%) met NCCN testing criteria. Fifty-nine of 212 (28%) patients went untested despite meeting one or more criteria. Fourteen of 59 (24%) of these were referred but did not comply. Most common criteria for meeting eligibility for testing both in the overall cohort and among missed patients were family history-based. Age $>$ 45 years old and non-Ashkenazi Jewish descent were predictive of missed referral ($p < 0.01$). We identified pathogenic mutations in 16 of 153 (10%) patients who did undergo testing (11 (7%) BRCA1 or 2 and 5 (3%) with other predisposition gene mutations) or 16 of 397 (4%) among the overall group.

Conclusions. Our data highlight the underutilization of genetic testing. Even in the setting of a full-service breast center with readily available genetic counseling, there is a substantial miss rate for identifying eligible patients, related to assessment of family history, patient age, and ethnicity, as well as patient compliance. Broader peri-diagnostic testing should be considered, and higher compliance rates with patients referred should be sought.

Breast cancer (BC) is the most common solid malignancy in women, and it represents the second most common cause of cancer-related deaths in females.[1,2] Findings show that 5–10% of women with a breast cancer diagnosis have actionable genetic mutations, which predisposes them to BC and may alter screening and treatment recommendations.[3–5] More than 50% of pathogenic germline variants occur in the BRCA1 and BRCA 2 genes.[6–8] Organizations, such as the National Comprehensive Cancer Network (NCCN), recommend screening women at high risk for harboring these mutations, especially in the BRCA1 and BRCA 2 loci. The NCCN's comprehensive guidelines for the diagnosis and treatment of all types of cancer added genetic testing criteria in 1998 to help providers to identify at-risk patients and trigger referral for counseling and testing when appropriate.[9] Criteria considered include a thorough overview of both personal history and family history variables. Over these past 20 years, criteria have progressively expanded to cast a wider net but debate over who exactly to recommend for testing remains.[10,11] Furthermore, additional predisposition genes have been characterized and identified thereby widening the panel of genes for which an individual with

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breast cancer can or should be tested, and in which pathogenic mutations may be identified, thereby increasing the yield of genetic testing.[9]

Despite widely available guidelines for genetic testing, a significant number of pathogenic mutations may remain undetected and carriers undiagnosed. These are thought to be largely women with moderate penetrance mutations, but even women with BRCA 1 or 2 mutations are being missed.[12] The reasons for this remain unclear; authors attribute missed testing to a variety of different factors, including barriers to access to genetic counselors, lack of insurance coverage, deficiencies in knowledge of referring providers, and/or patient compliance.[13]

The purpose of this study was to analyze patterns of referral for genetic evaluation and testing in newly diagnosed BC cases. We sought to evaluate surgeon adherence to NCCN guidelines and hypothesized that missed genetic testing likely stemmed from a combination of both provider oversight and patient compliance factors. We further sought to identify possible factors predictive of missed genetic referral or testing in order to improve uptake and referral for eligible patients.

METHODS

We conducted a review of a prospectively collected database of all newly diagnosed female BC patients at a single institution from January 2016 to April 2017. This study was approved by the Institutional Review Board. All patients had a new diagnosis of invasive breast cancer or ductal carcinoma in situ. We excluded those patients who presented with prior genetic testing and had results available for review. A retrospective chart review was then conducted, and each participant's medical and family histories were examined. We considered eligibility based on NCCN testing criteria concurrent with the study period (Version 2.2015), referral to genetic counseling, patient compliance with provider recommendations and genetic testing results, when available. A patient was considered referred to genetic counseling if either a discussion was documented between the physician and the patient or if a consultation note was identified from a genetic counselor. A patient was considered referred but not counseled (noncompliant) if the conversation was documented between physician and patient but no genetic consultation notes or test results were found. Those patients who underwent testing were identified by a positive or negative actionable mutation test result, as noted in the electronic chart. Of note, some patients underwent genetic testing ordered and sent by the surgeon without pre-test genetic counseling, with post-testing referral to the genetic counselor when results were positive, or warranted further discussion. Patient demographics and disease variables were summarized using mean (SD) for continuous variables and N (%) for categorical variables. Univariate analyses were performed by Student's *t* test for continuous variables and Chi square test, or Fisher's exact test when appropriate for categorical variables, to compare between tested and untested groups among those who met the test criteria. Frequency and percentage of testing criteria met for those untested was also recorded. Statistical analysis was conducted using SPSS 25.0 (IBM Corp, Armonk, NY), and all tests were performed at the significance level of 0.05. We recorded specific pathogenic mutation test results as positive and did not consider variants of uncertain significance (VUS) as positive test results.

RESULTS

During the study period, 459 newly diagnosed BC patients were identified. We excluded 62 (13.5%) who presented with prior genetic testing and documented results. Thus, a total of 397 patients who presented with a new diagnosis of BC and no prior genetic testing were identified. Study population demographics are summarized in Table 1. Of these, 212 (53%) met one or more NCCN testing criteria (Table 2). Two of the three most common NCCN criteria met among these 212 patients were family history-based (BC diagnosis at any age with ≥ 2 close relatives with BC at any age, and BC diagnosis at any age of an ethnicity with a high mutation frequency, such as Ashkenazi Jewish). Of the 212 patients who met NCCN testing criteria, 59 (27.8%) went untested despite meeting one or more of these factors. Fourteen of 59 (24%) of these "missed" patients were noncompliant with the surgeon's documented recommendation and ultimately chose not to pursue testing, whether because results would not affect their surgical decision (2, 14%) or for other unspecified reasons (12, 86%). Hence, there was a "true miss" rate of 21% (45/212) for genetic referral on the surgeon's part. These 45 "truly missed" patients met a total of 61 criteria (some patients met multiple criteria). Out of these, 54 of 61 (88.5%) occurrences pertained to family history-based factors (Table 3). Interestingly, only 4 of 45 (8.9%) patients qualified for genetic testing based on non-breast/ovarian cancer indications. These four patients had family histories of prostate and/or pancreatic cancer in the setting of a personal diagnosis of breast cancer, which may have been more difficult to discern. The remaining majority of patients missed for testing all had family or personal histories related to breast or ovarian cancer that met criteria.

Sixteen of 153 (10%) patients were found to have pathogenic mutations, with 11 (7%) BRCA 1 or 2 mutations identified, and 5 (2%) additional pathogenic

TABLE 1 Demographics and other patient characteristics ($N = 397$)

	Did not meet testing criteria	Met testing criteria ($n = 212$)		
		Testing performed	Testing missed	p value[a]
N	185	153 (72.2%)	59 (27.8%)	
Age at diagnosis (year)				< 0.01
≤ 45		100 (65.4%)	7 (11.9%)	
> 45		53 (34.6%)	52 (88.1%)	
Ashkenazi Jewish ancestry				< 0.05
Yes		50 (32.7%)	9 (15.3%)	
No		103 (67.3%)	50 (84.7%)	

[a]p values were obtained from Chi square tests or Fisher's exact tests to compare between patients who were tested and not tested among those meeting testing criteria

TABLE 2 National Comprehensive Cancer Center (NCCN) indications for hereditary breast and/or ovarian cancer syndrome testing

Personal history-based factors
Dx at age 45 years or younger
Dx at age 60 years or younger of triple-negative BC phenotype
Dx at age 50 years or younger with an additional breast cancer primary, either contralateral or clearly separate ipsilateral primary tumors
Personal history of ovarian cancer
Family history-based factors
Individual from a family with a known BRCA1/BRCA2 mutation
Dx at age 50 years or younger with:
≥ 1 close relatives with BC at any age[a]
An unknown family history
Either ≥ 1 close relatives with pancreatic cancer or ≥ 1 close relatives with prostate cancer (Gleason score ≥ 7)
Dx at *any* age with:
≥ 1 close relatives with BC at 50 years or younger
≥ 2 close relatives with BC at any age
≥ 1 close relatives with ovarian cancer (including fallopian tube and primary peritoneal cancers) at any age
≥ 2 close relatives with pancreatic cancer and/or prostate cancer (Gleason score ≥ 7) at any age
A close male blood relative with BC
For an individual of an ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish)

Version 2.2015

Dx diagnosis, *BC* breast cancer

[a]Close relatives include 1st-, 2nd- and 3rd-degree relatives on same side of family

mutations found in other high-risk genes (CDH1, CHEK2, MSH2, and ATM). Age > 45 years old ($p < 0.01$) and non-Ashkenazi Jewish descent ($p < 0.05$) were significantly predictive of missed referral for genetic testing.

Finally, some patients in the cohort underwent testing despite not meeting NCCN criteria (7/397, 1.7%), opting to forego insurance and pay for genetic testing out of pocket. Of these, 1 of 7 (14%) or 1 of 397 (< 1%) overall tested positive for a BRCA2 mutation.

DISCUSSION

More than 20 years after the identification of BRCA 1 and 2 and the initiation of incorporating clinical genetic testing into practice, genetic testing has not reached full scale implementation in 2020.[10,11,14,15] Despite increased availability, markedly decreasing costs and more widespread knowledge among both providers and patients, testing is still believed to be underutilized for BC patients.[16] Childers et al. estimated that of the 3.8 million breast and ovarian cancer survivors in the United States, only 14.1% have been actually tested, leaving more than 1 million untested patients.[15] Logistical barriers to testing

TABLE 3 Testing criteria met for 'truly missed' patients (61 total criteria in 45 patients[a])

Rank	Criteria	Frequency	%
1	Dx of BC any age with ≥ 2 relatives with BC any age[b]	17	27.8
2	Dx of BC any age with ≥ 1 relatives with BC 50 years or younger	15	24.6
3	Dx of BC any age with ≥ 1 relative with ovarian cancer	9	14.8
4	Dx of BC any age for individual of ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jew)	6	9.8
5	Dx of BC age 45 years or younger	4	6.6
6	Dx of triple negative BC at age 60 years or younger	3	4.9
6	Dx of BC age 50 years or younger with ≥ 1 relative dx with BC any age	3	4.9
7	Dx of BC any age with ≥ 2 or more relative pancreatic/prostate cancer at any age	2	3.3
7	Dx of BC age 50 years or younger with ≥ 1 relative with pancreatic/prostate cancer at any age	2	3.3

Dx diagnosis; *BC* breast cancer

[a]"Truly missed" patients defined as untested patients who were not referred by surgeon; some met multiple criteria

[b]Close relatives include 1st-, 2nd- and 3rd-degree relatives on same side of family

certainly exist and have been described (insurance coverage, limited nationwide availability of genetic counselors, etc.),[13] but concerns exist regarding enduring gaps in the initial steps of simply identifying patients at risk—a process that should be effortless in triggering referral to counseling and testing when appropriate. Brown et al. reported that 55% of young onset BC patients are not even discussing potential genetic testing with a medical provider,[17] and Stuckey et al. [18] reported that only 34% of women 50 years or younger were actually being referred for genetic counseling. A recent survey of oncology providers found that more than 80% of responders reported less than 50% of their patients with BC had ever had germline BRCA mutation testing.[19] Concerns about the underutilization of genetic testing have thus spurred talk about broader peri-diagnostic testing.[20]

Our data demonstrate that even in the setting of a full-service breast center with readily available genetic counseling and real-time testing for BC patients, there is a substantial miss rate for identifying eligible patients. The disproportionately high percentage of missed family history-based criteria (over personal history factors) in our study suggests that more thorough evaluation and documentation of close relatives' history must be sought, including second- and third-degree relatives with breast and ovarian cancers, as well as non-breast/ovarian cancer histories. In our study, interestingly, the majority of missed patients (41/45, 91.1%) were eligible for testing based on easily discernible breast and ovarian cancer family histories, as opposed to the less common cancer histories of prostate and pancreas—underscoring the importance of taking a thorough family history and of understanding the nuance of family history, age of diagnosis, and their implications for meeting genetic testing criteria. Kishan et al.[21] also found that many patients meeting testing indications only do so under family history-based criteria, and so more thorough, upfront family history documentation should increase the ability to identify and refer these patients appropriately.

The main purpose of genetic testing guidelines is to identify and select out patients with the highest probability of harboring actionable mutations, thereby justifying the increased cost of testing. The question of whether to broaden criteria continues to be debated, with some advocating eliminating adherence to guidelines altogether in favor of a more inclusive, all-comers testing approach. In 2019, the American Society of Breast Surgeons (ASBrS) released a consensus statement outlining testing recommendations to help medical professionals assess hereditary risk for BC patients. In it, they advocated that gene panel testing "should be made available to all patients with a personal history of breast cancer".[22] This recommendation was largely based on a study published by Beitsch et al., which argued that nearly half of patients with BC with pathogenic/likely pathogenic clinically actionable mutations are being missed by current testing guidelines. The multicenter, prospective study enrolled more than 1000 patients and recorded data for 959 patients, almost half of which (49.95%) met NCCN testing criteria. The authors found no statistically significant difference in positive test results yielding pathogenic/likely pathogenic mutations among patients who met NCCN guidelines (9.39%) and those who did not (7.9%), $p = 0.4241$.[23] They concluded that a testing-all approach would almost double the number of patients identified as carrying a clinically actionable mutation.

A similar effect of doubling genetic testing and concomitant yield was seen in a Canadian study investigating the impact of Angelina Jolie's story on referral and testing patterns.[24] In this 2016 study, referral and testing increased 90% in the 6 months following Angelina Jolie's public disclosure of undergoing bilateral risk-reducing mastectomy for BRCA 1 positivity compared with the period before her announcement. While it might be tempting to explain this uptick as an increase in frivolous referrals, and not necessarily those at risk, in fact the number of patients who qualified for testing similarly increased by 105%, and the number of gene mutation carriers identified increased in parallel by 110%. These findings highlight patient awareness, self-identification, and initiation as an integral component of optimizing genetic testing.

Another group for which population-based testing has been advocated includes those of Ashkenazi Jewish heritage where approximately 2% of the population will be found to test positive, regardless of family history.[25–27] Risk reduction strategies and screening could be more widely implemented in those discovered to be BRCA-positive, and these initiatives are being considered in Israel based on its significant Ashkenazi Jewish population.[21,28,29]

Some authors have made comparable broader population-based testing arguments in the past[20,30] but had restricted themselves to BRCA 1 and BRCA 2 testing only, whereas Beitsch et al. [22] argue for expanded panel testing for all patients with a personal history of BC. Such approaches have failed to gain traction nationally, mostly out of concerns for the inherent logistical challenges and implementation burden as well as increased healthcare costs that expanded testing would entail. The genetic counseling infrastructure would likely be overwhelmed as many more patients would require consultations to discuss results, including a projected increase in the identification of variants of uncertain significance (VUS). Until broader population testing approaches gain more support, we believe the greatest yield in identifying mutation carriers will come from adherence to NCCN guidelines, improving family history assessment, documentation and interpretation strategies, as well as ensuring patient compliance. In addition, peri-diagnostic testing should be made available to those with a personal diagnosis of breast cancer and in particular those patients of Ashkenazi Jewish heritage. It is important to note that the current landscape provides avenues for direct-to-consumer testing, circumventing both physician and genetic counselor, which provides no infrastructure for genetic testing result discussion or consultation. With the belief that this is not the optimal solution to implement broader-scale genetic testing based on patient demand, and based on our results that indicate that a substantial number of those meeting criteria are missed, we have increased offering and availability of genetic counseling/testing using a platform that facilitates availability of these services to all those desiring to be tested, regardless of ability to pay or insurance reimbursement.

Our study has several important limitations. This was a single institution, retrospective study, and therefore further studies examining other populations in a prospective setting are warranted. Due to the retrospective nature of the study, not all information was available from the electronic records at time of analysis. For example, we were unable to determine more precisely which genetic testing was performed (BRCA 1 and 2 only vs. multigene panels, and if so which genes were included). Additionally, the NCCN criteria that we used have been revised since the study was conducted. Only minor changes have been introduced since, however, and all of the criteria used at that time are still incorporated in the most recent guidelines. Our results should still apply to the current, most updated criteria.

In summary, our data reinforce the concern that genetic testing is currently underutilized for newly diagnosed BC patients, likely due to a combination of both provider and patient factors; factors that cannot be overcome merely by availability and adjacency to genetic counseling and testing services. The miss rate for identifying potential mutation carriers may be due to a combination of complex family history assessment and patient compliance with physician recommendations, issues that should be kept in mind when considering which patients to refer for testing. In addition, patients older than > 45 years and those of non-Ashkenazi Jewish background are at significantly higher risk for being missed for genetics referral. Broader genetic testing and methods to ensure patient adherence to provider recommendations should be considered.

DISCLOSURES The authors declare no conflicts of interest.

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