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# Breast Cancer Genetic Testing Guidelines Exclude Almost Half of High Risk Patients

## Criteria Fail to Keep Pace with Modern Science

***Abstract: Are Genetic Testing Guidelines Still Relevant?***

***Abstract: HBOC Patients Who Do Not Meet Medicare Criteria for Genetic Testing Have Similar Rates of Clinically Actionable Findings as Those Who Do Meet Criteria***

Orlando, May 3, 2018--Current restrictive genetic testing guidelines exclude many patients who harbor high-risk breast cancer mutations, according to two new studies presented this week at the annual meeting of the American Society of Breast Surgeons. One study found that whether or not patients met National Comprehensive Cancer Network (NCCN) testing guidelines, they had a similar number of pathogenic mutations related to breast or other cancers. In a second study, Medicare patients who did not meet guidelines for BRCA1/2 testing also had similar rates of these genetic variants as those who qualified. In addition, study findings were consistent for other breast cancer-related mutations.

Strongly emphasizing the need for revised testing criteria, both authors note that guidelines pre-date today's more sophisticated BRCA1/2 and multi-gene testing. They caution that most insurance providers model their coverage after these guidelines, usually recommending testing for BRCA1/2 only, and that many patients with inherited breast cancer risks are being missed.

Peter Beitsch, MD of TME Breast Care Network reported on early data from the organization's Universal Genetic Testing Registry for breast cancer patients who had no prior genetic testing. Participants underwent an 80-gene panel test for genetic variants that have a known association to breast and/or other cancers. The target accrual is 1,000 patients with 500 who meet and 500 who do not meet NCCN testing guidelines. Current accrual is 923 with 713 having testing and CRF's completed. The patients

who met criteria had a 10.2% pathogenic/likely pathogenic variant rate (36/353) and the patients who did not meet criteria had an 8.6% pathogenic/likely pathogenic variant rate (31/360).

Dr. Beitsch comments, "There is no statistically significant difference between the pathogenic variant rate between patients who meet and who do not meet NCCN guidelines. Furthermore, the cost of expanded panel genetic testing has decreased to the point that economically-based guidelines for testing are no longer relevant."

In a second study, genetic counselor Jennifer Axilbund, MS, CGC of Invitae examined 1,990 Medicare patients referred by physicians for BRCA1/2 and optionally other breast cancer-related genetic testing. Of these, 1,516 (76.2%) met BRCA1/2 testing guidelines, while 474 (23.8%) did not. An analysis of patients testing positive for BRCA1/2 variants found no statistical difference between Medicare qualifiers and non-qualifiers (3.3% vs. 2.3%). Similar results were found when testing for other breast cancer-related mutations (9.6% vs. 7.8%). Axilbund stresses that under Medicare criteria, "Almost half of all patients with actionable variant genes are missed."

Both researchers note that test criteria screen more effectively for carriers of highly penetrant BRCA1/2 mutations than for other genetic variants, and that this is expected. "These guidelines were created specifically to capture this group, and generally they do," says Axilbund. She notes that with the recent growth of genetic sequencing, however, the number of known breast- and overall cancer-related pathogenic variants increased dramatically, and test guidelines have not kept pace.

This broader genetic information can benefit patients and their families, who may share the same mutations, and allow more targeted breast cancer screening, surveillance and management. Dr. Beitsch notes, "Women do not need to be protected from their genetic health information. Genetic testing is the future of medicine, not just in patients with cancer but all patients."

**Expert Commentary:**

"These two studies highlight the importance of discussing genetic testing with patients diagnosed with breast cancer. With the advances in panel testing for predisposition genes the likelihood of identifying a pathogenic or likely pathogenic mutation are higher (around 8-10% in these studies). However, we must remember that not all mutations are medically actionable. When evaluating genetic testing, we should consider the likelihood of identification of a mutation, cost of testing and potential impact of the result on medical management."

Judy C. Boughey, MD
Breast Surgeon, Mayo Clinic and ASBrS Publications Committee Chair

**Abstract, Official Proceedings**

## Are Genetic Testing Guidelines Still Relevant?

**Presenter:** Peter Beitsch, MD

**Institution:** TME Breast Care Network

**Objective:** Pathogenic genetic mutations are estimated to occur in 10-15% of all breast cancer patients, with BRCA 1/2 accounting for 40-50% of pathogenic/likely pathogenic (P/LP) mutations. However, it is estimated that <30% of breast cancer patients harboring a BRCA 1/2 mutation have been identified, with the percentage being much less for the ~20 other breast cancer-associated genes. Our failure to identify patients with P/LP mutations is multifactorial and includes physician education, insurance road blocks, and most importantly, confusing and restrictive testing guidelines. We created a community-based registry to determine the incidence of P/LP mutations in patients with breast cancer who meet and do not meet the NCCN 2017 genetic testing criteria.

**Methods:** An IRB-approved multicenter prospective registry was initiated with 18 community and academic breast physicians experienced in cancer genetic testing and counseling. Eligibility criteria included patients with a breast cancer diagnosis who had not previously had genetic testing. Patients were consented and underwent an 80-gene panel test (InVitae Multi-Cancer Panel). Recruitment goals were 500 patients who met NCCN genetic testing criteria and 500 who did not, with the objective of identifying if there was a statistically significant difference in P/LP mutation rate between these 2 patient cohorts. The non-inferiority study was powered to detect a difference in positive/LP mutation rate of 4 percentage points with statistical significance ($p<0.05$, Fisher's exact test). HIPAA-compliant electronic case report forms collected information on patient diagnosis, test results, and physician recommendations made after test results were received. IRB approval and oversight was provided by WIRB (Puyallup, WA) or via a local IRB.

**Results:** Six hundred two patients have been registered as of November 6th, 2017, data from 364 patients have been reviewed (48% met NCCN criteria, and 52% did not), and we have genetic mutation data on 235 patients to date. Median age for the enrolled patients is 62. Median age for patients who met NCCN criteria is 60; those who did not, have a median age of 64.5. There were 60.8% of patients recently diagnosed with breast cancer. Of these, 46.6% met NCCN criteria; 53.3% did not. Of those not recently diagnosed, 49.7% met NCCN criteria; 50.3% did not. Eleven percent of patients had a history of a prior non-breast cancer, 46.3% of those met NCCN criteria, and 53.7% did not. There were 12.4% of patients who met NCCN criteria and had test results with a P/LP mutation, while 11.5% of patients who did not meet criteria had a pathogenic mutation. The difference of positive cases among the 2 groups is not statistically significant ($p= 0.84$). The spectrum of mutated genes varied between the 2 groups, with some overlap.

**Conclusions:** Patients who did not meet NCCN genetic testing guidelines had a similar percentage of pathogenic/likely pathogenic mutations compared to patients who met NCCN guidelines. Expanded panel testing yields more pathogenic hereditary mutations than BRCA 1/2 or breast cancer panels with 5-7 genes. More than 42% of patients with P/LP mutations may be missed if NCCN guidelines are

required for genetic testing. Current guidelines are detrimental to identifying patients with P/LP mutations and should be abandoned.

**Table 1. Genetic Testing Mutation Rate in Non-NCCN/NCCN Breast Cancer Populations**

| NCCN criteria designation<br><br>(**235** with reported test results/mutation data) | #/% who have P/LP mutations | % who do not have P/LP mutations |
|---|---|---|
| Patients who meet current guidelines | **14/113** (**12.4%**) | **99/113 (87.6%)** |
| Patients who do not meet guidelines | **14/122 (11.5%)** | **108/122 (88.5%)** |

**Abstract, Official Proceedings**

## HBOC Patients Who Do Not Meet Medicare Criteria for Genetic Testing Have Similar Rates of Clinically Actionable Findings as Those Who Do Meet Criteria

**Presenter:** Jennifer Axilbund, MS, CGC

**Institution:** Invitae

**Objective:** Over 275,000 patients are diagnosed with breast or ovarian cancer every year. An estimated 5-10% are due to hereditary causes, such as hereditary breast and ovarian cancer syndrome (HBOC). Medicare, the third party payer that covers 44 million patients in the U.S., has implemented a set of clinical criteria to determine coverage of testing the BRCA1 and BRCA2 genes. Other insurance providers' policies often mimic Medicare. Current Medicare BRCA1/2 genetic testing criteria require a personal diagnosis of cancer, and often need additional family history of cancer. However, the efficacy of these widely utilized clinical testing criteria has not been established. Additionally, current criteria were developed to identify carriers of BRCA1/2 variants and have not been evaluated in the panel testing era. In a series of patients insured by Medicare undergoing genetic testing, we evaluate the efficacy of Medicare genetic testing criteria in identifying patients with hereditary risk.

**Methods:** We studied a consecutive series of Medicare patients where the testing indication was a personal and/or family history of breast and/or gynecological cancer, and the order included at least the BRCA1 and BRCA2 genes. Ordering clinicians completed a brief checklist indicating whether patients did or did not meet Medicare criteria for BRCA1/2 genetic testing. Genetic test outcomes were compared between the in-criteria and out-of-criteria groups for different sets of genes. Positive outcomes were pathogenic (P) or likely pathogenic (LP) variants; uncertain results were identification of one or more variant of uncertain significance (VUS); and negative outcomes were findings of only benign or likely benign variants. Patients in families with known P/LP variants were excluded from the primary analysis.

**Results:** Among all 1990 unique patients in this cohort, 1516 (76.2%) met Medicare testing criteria and 474 (23.8%) did not meet criteria. When only results from BRCA1 and BRCA2 are considered, the positive rate of the in-criteria group is 1.43 fold as that of the out-of-criteria group (3.3% vs. 2.3%), a difference that is not statistically significant (p=0.35). When all the genes ordered for each patient are considered, the positive rates between the two groups are also similar (9.6% vs. 7.8%, p = 0.27). Rates of VUS did not differ substantially between the two groups. The in-criteria group on average ordered slightly fewer genes than out-of-criteria group (average panel size 18.6 genes vs. 22.5 genes), but the difference was not significant (Z = 0.21).

**Conclusions:** The rate of LP/P variants was similar among patients who did and did not meet Medicare criteria for BRCA1/2 genetic testing. The current criteria specifically reflect the historically severe presentation of high-penetrant BRCA1/2 variants, and do not adequately capture the range of clinical presentations commonly seen. Additionally, carriers of clinically actionable variants in genes other than BRCA1/2 are just as likely to fall outside of current criteria. Almost half of Medicare patients with actionable variants will be missed if testing is restricted to those meeting current criteria. This is likely to be true for other insurance providers who follow Medicare genetic testing criteria.

**Table 1. Results**

| Outcome | In-Criteria: BRCA1/2 Alone | Out-of-Criteria: BRCA1/2 Alone | In-Criteria: Larger HBOC Panels Ordered | Out-of-Criteria: Larger HBOC Panels Ordered |
|---|---|---|---|---|
| **Positive** | 3.3% | 2.3% | 9.6% | 7.8% |
| **Uncertain** | 2.8% | 3.8% | 18.7% | 20.9% |
| **Negative** | 93.9% | 93.9% | 71.8% | 71.3% |