

# Hereditary Cancer Risk: A Growing Body of Evidence Supporting Broader Testing

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## Background

Breast specialty physicians play an active role in cancer genetic risk assessment and testing. Traditionally, NCCN guidelines have been the primary reference for patient selection.

Although emerging research indicates that the rate of pathogenic mutations is higher than originally suspected in the general population<sup>1,2</sup>, few studies have examined the patients who present to breast practices: those perceived to be at higher risk or who have a diagnosis of breast cancer.

## Methods

An IRB-approved multicenter prospective data collection was performed that included 13 community-based breast physicians experienced in cancer genetic risk assessment and testing.

Consecutive patients were identified as test candidates based on perceived and actual risks for hereditary breast cancer. A single test price was used to eliminate cost as a variable in gene panel selection.

A total of 226 patients were tested and demographic data collected. Physicians reported whether patients met NCCN guidelines or not. The median age was 51 years. Patients met guidelines criteria as reported by their physician 65% of the time. The majority of patients (77%) were tested for >14 genes. A recent diagnosis of breast cancer was reported for 61.5% (139/226) of patients.

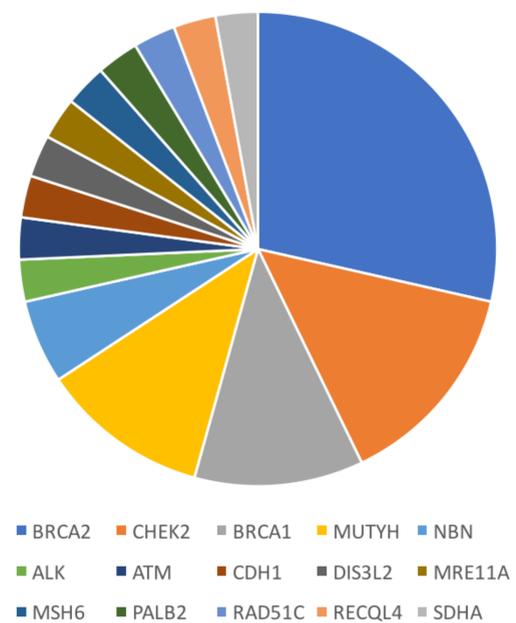
## Results

Among the 231 tested patients, 13.9% had a positive result for a pathogenic mutation. The most common positive findings were in BRCA1, BRCA2, CHEK2 and MUTYH.

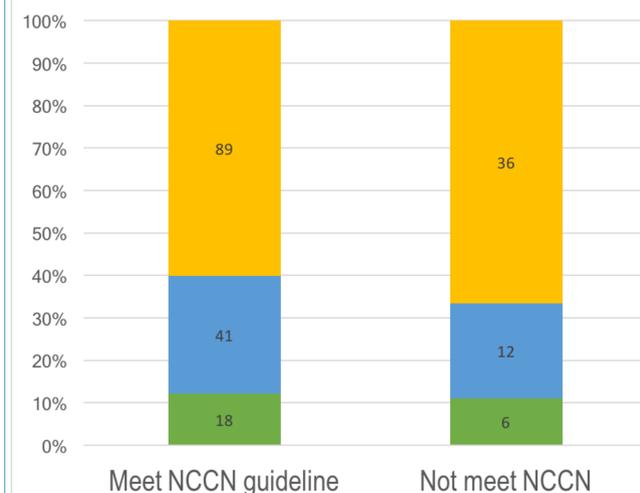
Among patients who met NCCN criteria for testing (148 patients), 12.2% had pathogenic mutations (50.0% of which were in BRCA1/2); whereas 11.1% of the patients who did not meet NCCN criteria (54 patients) had pathogenic mutations (28.6% of which were in BRCA1/2).

Patients under 50 had pathogenic mutations 13.5% (15/104); patients over 50, 12.3% (15/122) of the time. A higher percentage of patients younger than 50 had BRCA1/2 mutations (53.3% vs. 40.0%).

Pathogenic variants found in genes



## Results NCCN Guidelines



■ positive report ■ VUS report ■ negative report

### Met NCCN guidelines Positive findings

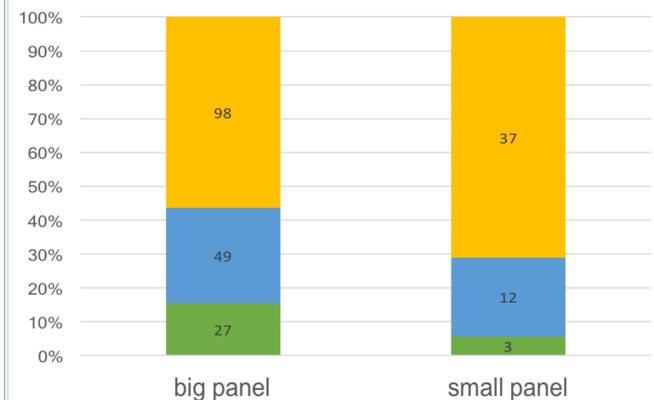
Genes	#	Genes	#
BRCA2	7	ATM	1
BRCA1	3	CDH1	1
CHEK2	2	MRE11A	1
MUTYH	2	RAD51c	1
NBN	2		

### Did not meet NCCN Positive findings

Genes	#
BRCA2	1
BRCA1	1
CHEK2	2
MUTYH	1
MSH6	1

## Panel Size and Test Outcome

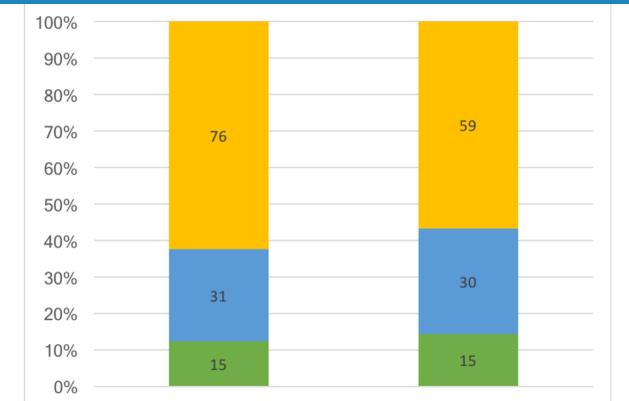
Large panels yield more positive findings without a significantly increased VUS rate.



■ positive report ■ VUS report ■ negative report

Larger panels yielded a higher VUS rate (28.2% vs. 23.1%) than the guidelines panel but also had a higher clinical yield (15.5% vs. 5.8%). The guideline panel included BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11, and TP53, ATM, CHEK2.

## Patient Age and Mutations



■ positive report ■ VUS report ■ negative report

## Conclusions

- Patients who did not meet NCCN genetic testing guidelines as reported by their physicians had a similar percentage of pathogenic mutations compared to patients who met guidelines.
- Expanded panel testing yields more pathogenic hereditary mutations that may be actionable.
- Patients grouped by age, under 50 and over 50, had different mutation distributions.
- Expanded panel testing accounts for the essentially equal number of patients with pathogenic mutations who did not meet the testing criteria. Non NCCN criteria patients had a lower incidence of the most common mutations (BRCA 1/2).
- These results support expanding evidence that equivalent rates of mutations may be found regardless of whether patients meet current testing criteria.
- As test costs continue to decrease, expanded testing will shift to larger groups of patients. A large multicenter study is under way to measure the benefits of universal testing in the breast cancer population.

## Discussion

- Due to the nature of the small sample size in the study, the positive rate observed here is not intended for prevalence calculation for large population.
- A large multi center study focused on mutation rates in vetted NCCN/Non NCCN patient populations is underway.

## References

1. Precision Medicine Meets Public Health: Population Screening for BRCA1 and BRCA2. Levy-Lahad, Lahad, and Mary-Claire King. J Natl Cancer Inst. 2015; 107 (1): dju420. First published online December 30, 2014. doi:10.1093/jnci/dju420.  
 2. Frequency of Germline Mutations in 25 Cancer Susceptibility Genes in a Sequential Series of Patients with Breast Cancer. Nadine Tung, Nancy U. Lin, John Kidd, Brian A. Allen, Nanda Singh, Richard J. Wenstrup, Anne-Renee Hartman, Eric P. Winer, Judy E. Garber. J Clin Oncol. 2016 May 1; 34(13): 1460-1468. Published online March 14, 2016. doi: 10.1200/JCO.2015.65.0747 PMCID