

# BRCA1/2 Testing Criteria Offer High Clinical Sensitivity for ATM, PALB2, and CHEK2 Carriers in a Multigene Panel Cohort

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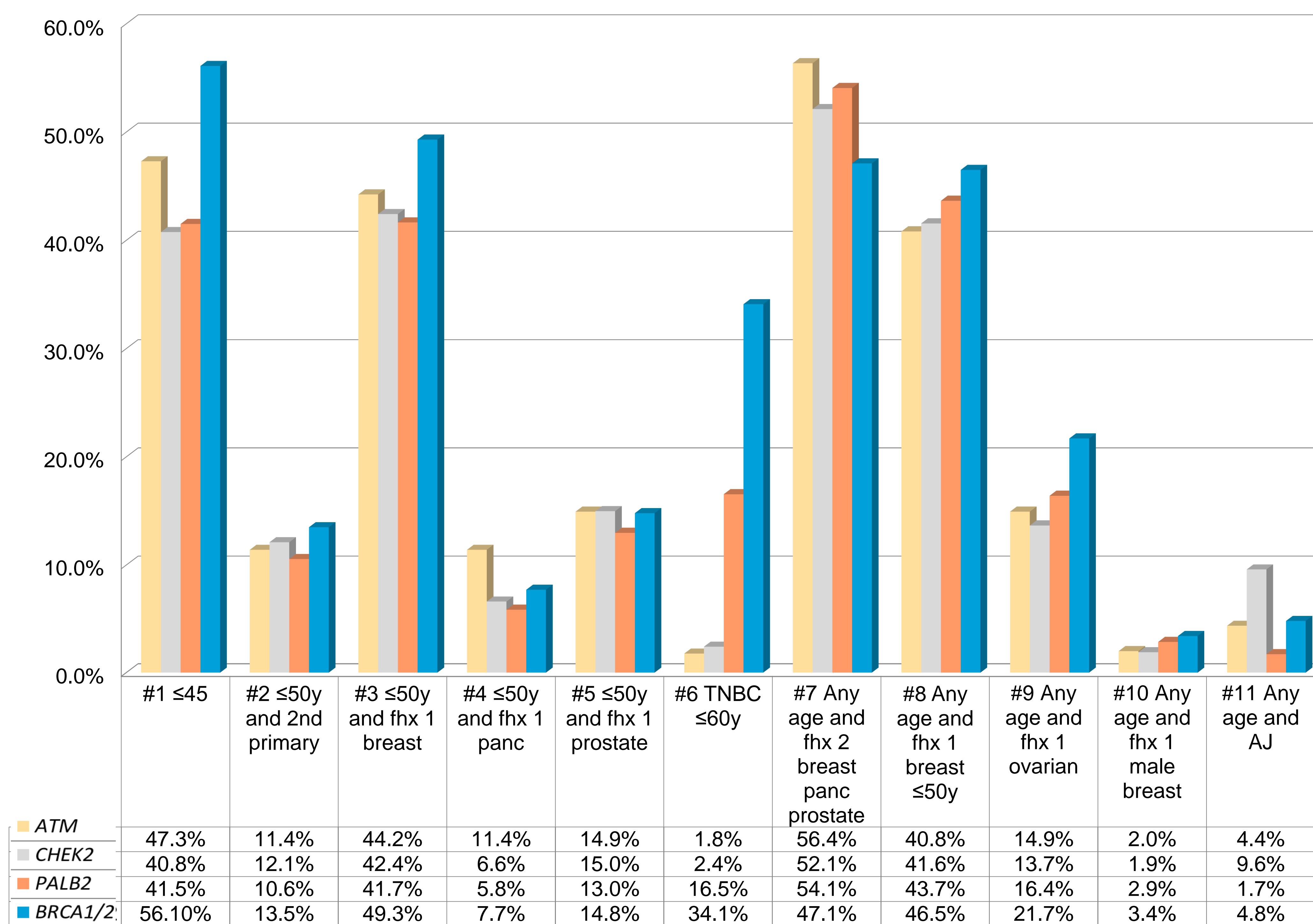
## BACKGROUND

- The National Comprehensive Cancer Network® (NCCN®) currently includes management recommendations for individuals with *ATM*, *CHEK2*, and *PALB2* mutations; however, there are no testing criteria specific to these genes to aid in decision making about how to identify at-risk individuals.
- Here we aim to assess the clinical sensitivity of existing NCCN *BRCA1/2* testing criteria when applied to *ATM*, *CHEK2*, and *PALB2*.

## METHODS

- 89,008 female breast cancer patients from June 2012 through December 2016 were tested at our clinical laboratory via multi-gene panel testing (MGPT) targeted for breast, ovarian, pancreatic, or prostate cancer (9 different panels; 5–49 genes).
- Based on the NCCN® 2.2017 guidelines, criteria pertaining to individuals with a personal history of breast cancer were assigned a number as described in table 1.
- Using personal and family histories obtained from test requisition forms and supporting clinical documents, individuals were assessed on whether they passed or failed each subset of the criteria. When applicable, differences in clinical sensitivities were compared between genes using the Chi square test.

**Figure 1. Comparison of Clinical Sensitivity by Criteria and Gene**



## RESULTS

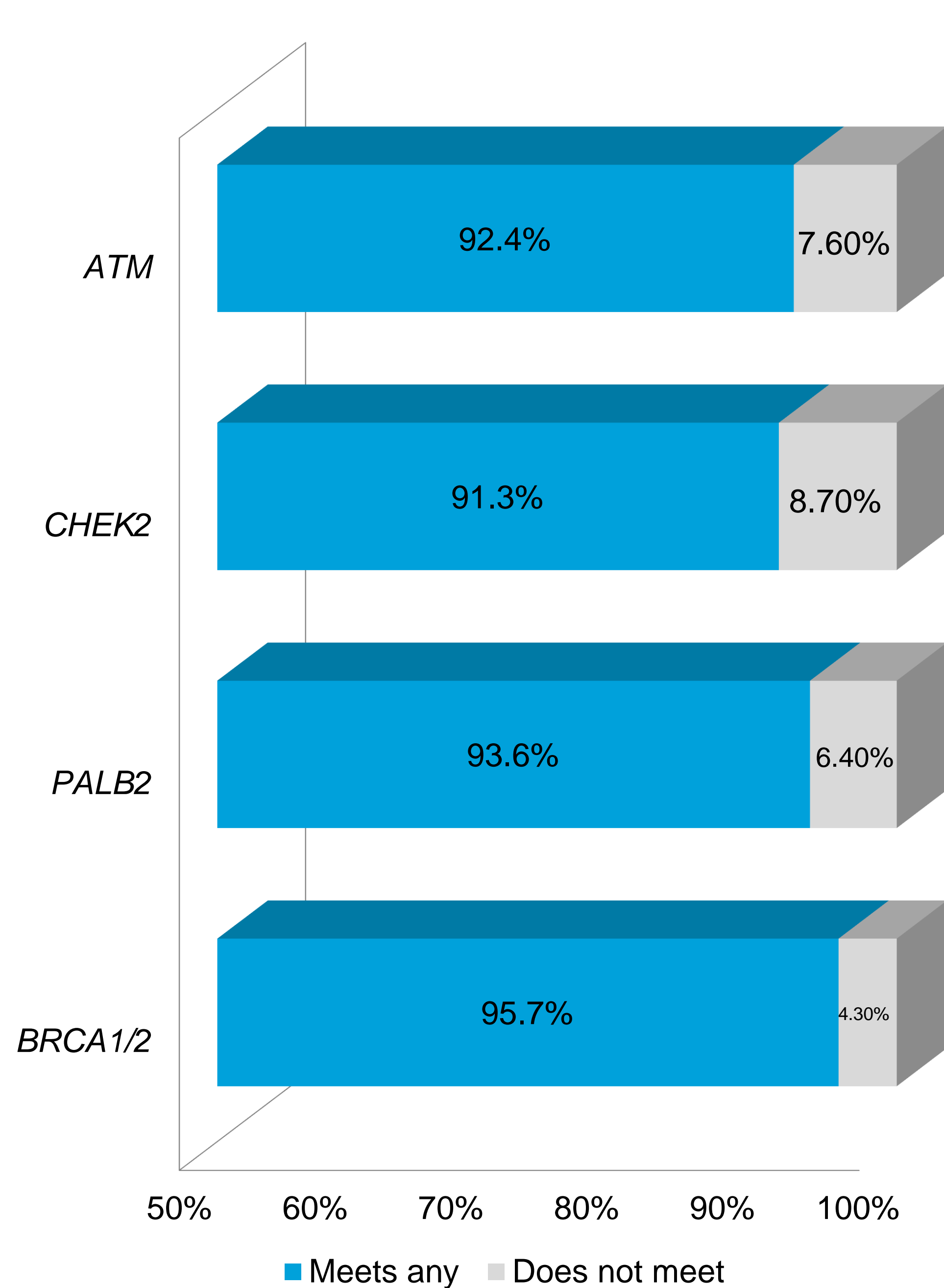
- A total of 3293 breast cancer probands had mutations in *ATM* (850), *CHEK2* (1742), or *PALB2* (701) without a co-occurring *BRCA1/2* mutation, and 3085 individuals had mutations in *BRCA1* (1517) or *BRCA2* (1568).
- The overall clinical sensitivity of the breast-specific criteria was 92.4% for *ATM* (785 of 850 positive individuals met at least one criteria), 91.3% (1590) for *CHEK2*, 93.6% (656) for *PALB2*, and 95.7% (2951) for *BRCA1/2* (Figure 2).
- Criteria #7 had the highest clinical sensitivity for *ATM* (56.4%), *CHEK2* (52.1%), and *PALB2* (54.1%), while criteria #1 had the highest sensitivity for *BRCA1* (63.4%) and *BRCA2* (49.0%) (Figure 1).
- Clinical sensitivity for *ATM*, *CHEK2*, and *PALB2* was within 5% of *BRCA1/2* in 5 of 11 criteria (#2, #4, #5, #10, and #11), within 2% of *BRCA1/2* in 2 of 11 criteria (#5 and #10). In contrast, criteria #1, #3, #6, #8, and #9, underperformed for *ATM*, *CHEK2*, and *PALB2*, with clinical sensitivity differing by greater than 5% (Table 1).
- Clinical sensitivity was significantly higher in *ATM* (p-value 1.92 E-06), *CHEK2* (p-value 0.0009), and *PALB2* (p-value 0.0009) compared to *BRCA1/2* in criteria #7.
- When averaged across criteria, clinical sensitivity was higher for *BRCA1* than *ATM* (p-value 3.42 E-09), *CHEK2* (p-value 6.18 E-11), *PALB2* (p-value 6.56 E-08), and *BRCA2* (p-value 2.63 E-15) (Table 2).

**Table 1. Breast-Specific Testing Criteria**

Criteria Description	Assigned Number
Breast cancer ≤45y	1
Breast cancer ≤50y and additional breast primary	2
Breast cancer ≤50y and ≥1 close relative with breast cancer at any age	3
Breast cancer ≤50y and ≥1 close relative with pancreatic cancer	4
Breast cancer ≤50y and ≥1 close relative with prostate cancer (Gleason score ≥7)*	5
<small>*updated to also include metastatic prostate cancer since these analyses</small>	
Triple negative breast cancer ≤60y	6
Breast cancer and ≥2 close relatives with breast cancer, pancreatic cancer, or prostate cancer (Gleason score ≥7) at any age	7
Breast cancer and ≥1 close relatives with breast cancer ≤50y	8
Breast cancer and ≥1 close relatives with ovarian cancer	9
Breast cancer and a close male relative with breast cancer	10
Breast cancer and Ashkenazi Jewish ancestry	11

- Sensitivity for *ATM/CHEK2/PALB2* is ≥5% higher than *BRCA1/2*
- Sensitivity for *ATM/CHEK2/PALB2* is ±5% of *BRCA1/2*
- Sensitivity for *ATM/CHEK2/PALB2* is >5% lower than *BRCA1/2*

**Figure 2. Percentage of Positives Meeting At Least One Criterion**



**Table 2. Clinical Sensitivity Is Superior for BRCA1 Compared to All Other Genes**

Gene	Total Mutation Carriers	Avg meeting each criteria	OR	95% CI	p-value
ATM	850	193			
BRCA1	3086	441	1.8	1.5-2.1	3.42E-09
CHEK2	1742	377			
BRCA1	3086	441	1.7	1.4-1.9	6.18E-11
PALB2	701	158			
BRCA1	3086	441	1.8	1.4-2.1	6.56E-08
BRCA2	1578	372			
BRCA1	3086	441	1.9	1.6-2.2	2.63E-15

Average clinical sensitivity of established guidelines is higher for *BRCA1* than all other genes including *BRCA2*.

## TAKE-HOME POINTS

- NCCN® testing criteria designed for *BRCA1/2* demonstrated high clinical sensitivity in a breast cancer cohort when applied to *ATM*, *CHEK2*, and *PALB2*.
- While this was somewhat expected based on cohort ascertainment and overlapping phenotypes, this study is a necessary first step in exploring the appropriateness of applying *BRCA1/2* testing guidelines to moderate penetrance breast cancer genes.
- Individuals with mutations in *ATM*, *CHEK2*, and *PALB2* were best captured by criteria without an age limit; limit may reflect the difference in age-related penetrance compared to *BRCA1/2*.
- Further investigation of *BRCA2*, *ATM*, *CHEK2*, and *PALB2* mutation carriers not meeting *BRCA1/2* testing criteria will help identify further opportunities to improve sensitivity without significantly compromising specificity.

## REFERENCES

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast and Ovarian v2.2017© National Comprehensive Cancer Network, Inc. 2017. All rights reserved. Accessed 07/20/2017. To view the most recent and complete version of the guideline, go online to NCCN.org.

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