BRCA1/2 testing criteria offer high clinical sensitivity for *ATM*, *PALB2* and *CHEK2* carriers in a multigene panel cohort

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As evidence surrounding the growing number of breast cancer predisposition genes has accumulated, *ATM*, *CHEK2*, and *PALB2* have become undisputed susceptibility genes conferring a moderate risk for breast cancer. 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*.

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.

A total of 3293 breast cancer probands had mutations in *ATM* (850), *CHEK2* (1742), or *PALB2* (701) without 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*, 93.1% (656) for *PALB2*, and 95.7% (2951) for *BRCA1/2*. 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%). 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%. 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).

Overall, the NCCN *BRCA1/2* testing criteria demonstrated high clinical sensitivity 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. Of note, the observation that individuals with mutations in these genes were best captured by criteria without an age 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 for without significantly compromising specificity.

Criteria description	Assigned Number
Breast cancer <=45y	1
Breast cancer <=50y and an additional breast cancer primary	2
Breast cancer <=50y and >=1 close blood relative with breast cancer at any age	3
Breast cancer <=50y and >=1 close blood relative with pancreatic cancer	4
Breast cancer <=50y and >=1 close blood relative with prostate cancer (Gleason score >=7)*	5
Breast cancer <=50y and an unknown or limited family history	6
Breast cancer and >=2 close blood relatives with breast cancer, pancreatic cancer, or prostate cancer (Gleason score >=7)* at any age	7
Breast cancer and >=1 close blood relatives with breast cancer <=50y	8
Breast cancer and >=1 close blood relatives with ovarian cancer	9
Breast cancer and a close male blood relative with breast cancer	10
Breast cancer and of Ashkenazi Jewish ancestry	11