

Performance of current Hereditary Breast and Ovarian Cancer (HBOC) testing criteria for the detection of carriers of pathogenic variants in clinically significant breast cancer risk genes other than *BRCA1/2*

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BACKGROUND

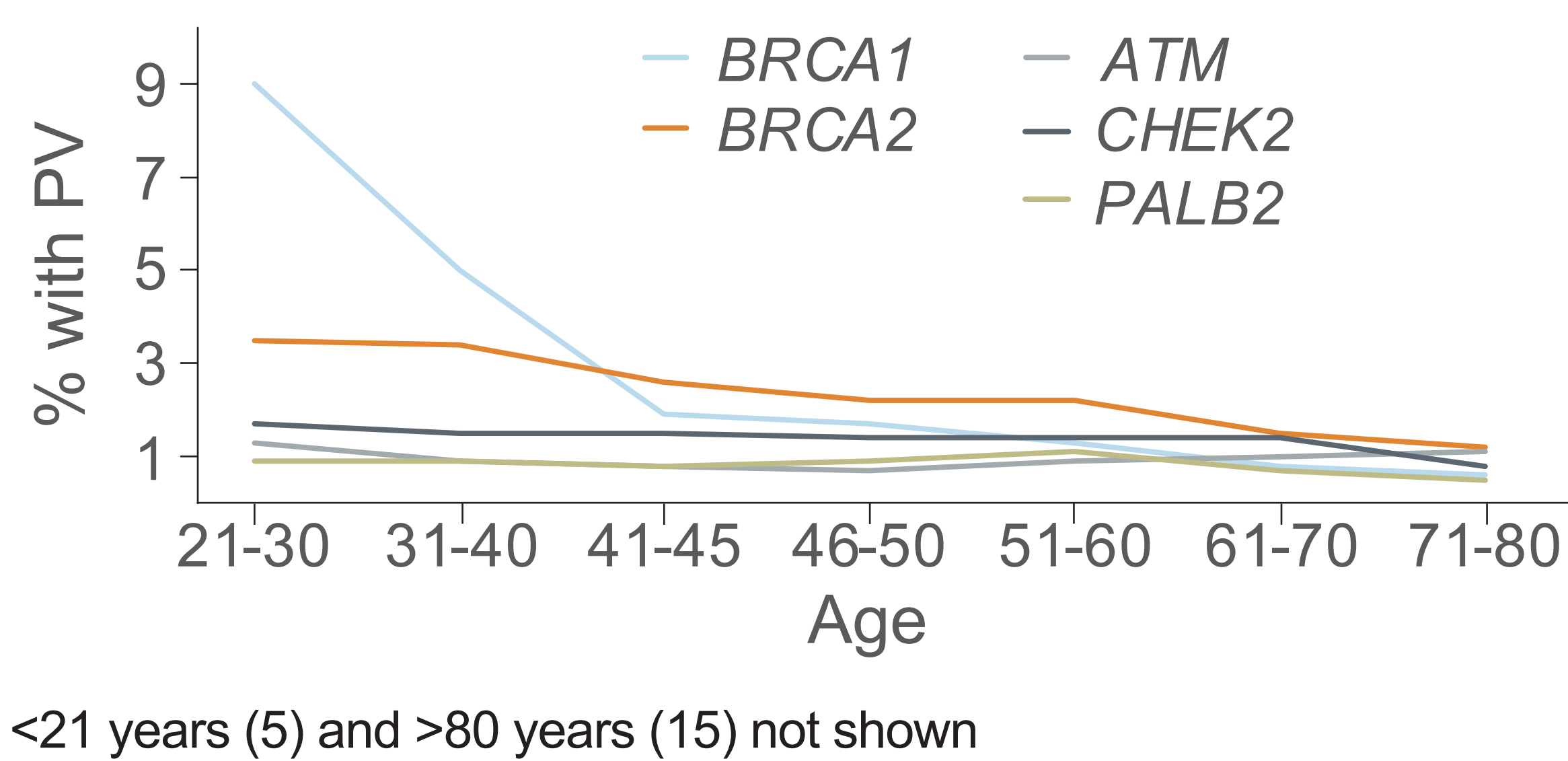
- Genetic testing for hereditary breast cancer risk now routinely includes genes other than *BRCA1/2*; therefore, it is important to evaluate the performance of existing NCCN HBOC testing criteria for the detection of pathogenic variants (PVs) in other clinically significant breast cancer risk genes.
- This study focused on *ATM*, *CHEK2*, and *PALB2*, as PVs in these genes are relatively common in women ascertained for suspicion of hereditary breast cancer risk, and there are clear medical management recommendations for carriers.

METHODS

- This cohort included 294,234 women who had testing for hereditary cancer using a 25-gene or 28-gene hereditary cancer panel ascertained for suspicion of HBOC by their healthcare providers between 09/20/2013 and 10/06/2017.
- Women were excluded from the analysis if their genetic testing identified >1 PV, if they were from a state with laws preventing the use of de-identified genetic data for research, or if the ordering provider indicated that the woman had been ascertained for suspicion of Lynch syndrome.
- Personal and family cancer history information was obtained from healthcare provider-completed test requisition forms.
- Prevalence estimates were calculated separately for each personal/family history group by gene or gene group, repeated for 3 clinical indications based on NCCN testing criteria for HBOC (V1.2018).
- Confidence intervals were calculated using the following equation:
 - Prevalence estimate $\pm 2 \times$ Standard Error.

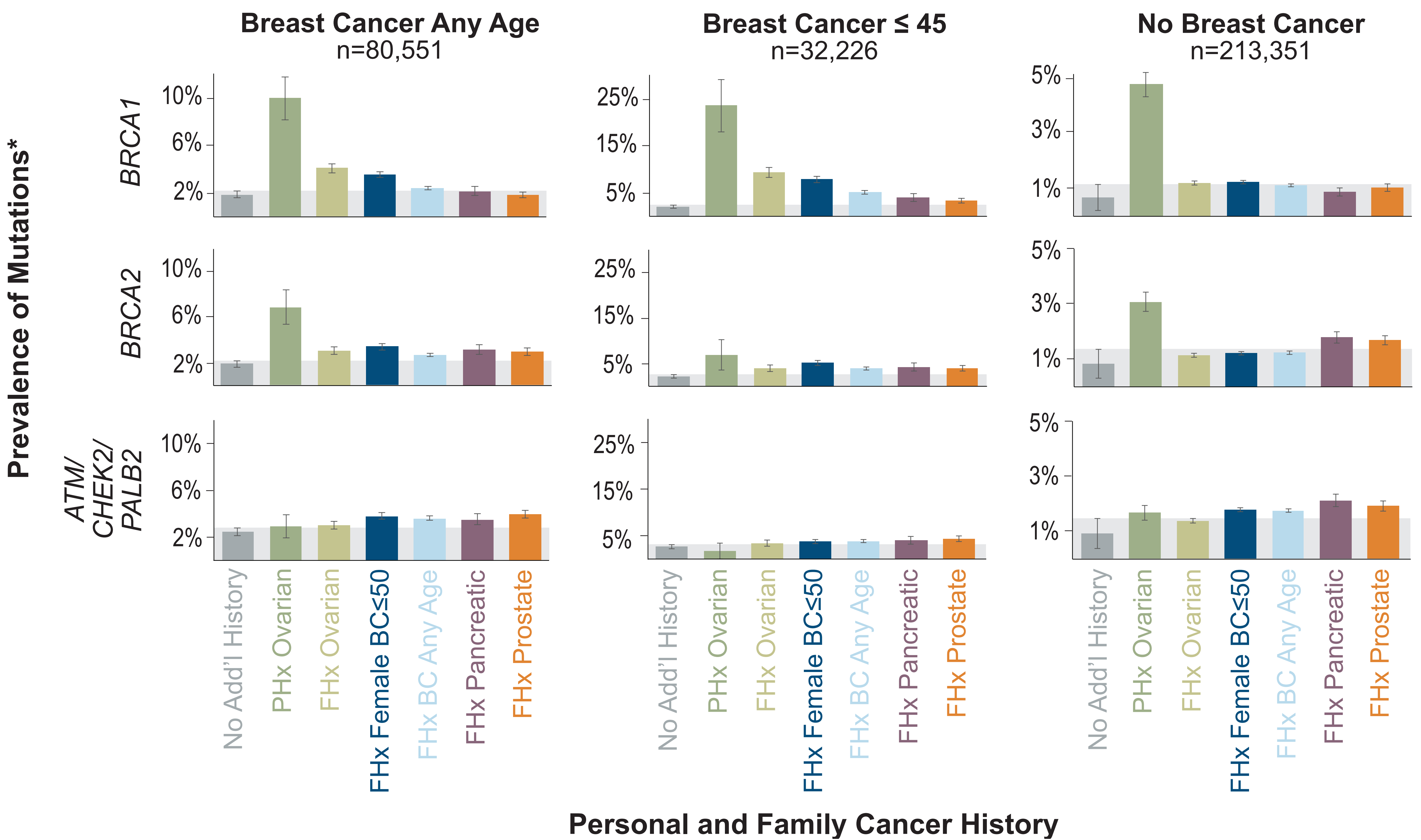
RESULTS

Figure 1. Percentage of women with a pathogenic variant by age of breast cancer



- The likelihood of finding a PV in *BRCA1/2* declines with age of breast cancer diagnosis, but age is largely unrelated to the likelihood of finding a PV in *ATM*, *CHEK2*, or *PALB2* (Figure 1).
- Relative to no additional cancer history, personal or family history of ovarian cancer significantly increases the likelihood of finding a PV in *BRCA1/2*, but not in *ATM*, *CHEK2*, or *PALB2* (Figure 2).
- A family history of breast cancer increases the likelihood of finding a PV in all 5 genes, but this effect is largely independent of the age at which relatives are diagnosed (Figure 2).
- A family history of pancreatic or prostate cancer increases the likelihood of finding a PV in most genes, most significantly in *BRCA2* (Figure 2).

Figure 2. Prevalence of pathogenic variants according to clinical indication



Add'l, Additional; PHx, Personal History; FHx, Family History; BC, Breast Cancer
Light gray shading represents upper limit of the 95% confidence interval for prevalence of pathogenic variants in patients with no add'l cancer history
*Percentages of tested women in each P/FHx category with a pathogenic variant (out of all women in that P/FHx category)

CONCLUSIONS

- Current testing criteria based on the clinical features of *BRCA1* and *BRCA2* may perform poorly in identifying women at risk for mutations in other clinically significant breast cancer risk-genes, particularly when focusing on young ages of breast cancer diagnosis in probands and their relatives.
- Revision of these criteria may be appropriate if these genes are routinely included in hereditary breast cancer risk assessment.

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