A second-generation polygenic risk score (PRS) based on genetic ancestry improves breast cancer (BC) risk prediction for all ancestries

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OBJECTIVE:

- We previously described a multiple-ancestry PRS (MA-PRS 149) based on 56 ancestry-informative and 93 BC-associated SNPs.1

RESULTS:

- Women referred for hereditary cancer testing who were negative for pathogenic variants in BC-associated genes between 1/2021 - 9/2023 were divided into consecutive development and validation study cohorts.

- An optimal set of BC-associated SNPs and European-specific SNP risks were determined using backward elimination from summary statistics2 together with reference data3 to account for linkage disequilibrium.

- The distribution of MA-PRS 383 in unaffected women was comparable across different ancestries in the validation set (Figure 2).

- In bivariate analyses, MA-PRS 383 outperformed both MA-PRS 149 and Eur-PRS 383, a PRS obtained by applying European-specific SNP risks to all ancestries.

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- The combined MA-PRS 383/ Tyrer-Cuzick risk model, CRS-383, reclassified more women from low to high or high to low risk than the combined MA-PRS 149/ Tyrer-Cuzick risk model, CRS-149 (Figure 5).

- Reclassification rates were similar in different ancestries (Figure 5).

- Of the 20.4% reclassified by CRS-383 overall, 36.3% were downgraded from the high to the low/moderate risk category.

CONCLUSIONS:

- MA-PRS 383 was well-calibrated and substantially improved the predictive accuracy of the existing PRS in all tested ancestral populations.

- Incorporation of MA-PRS 383 into BC risk assessment may lead to more accurate identification of women who are most likely to benefit from screening and preventive interventions.