

Improving a Polygenic Risk Score (PRS) for Breast Cancer (BC) Risk Assessment in Diverse Ancestries

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Background

- Previously, we described a multiple-ancestry PRS (MA-149) based on 56 ancestry-informative and 93 BC-associated single-nucleotide polymorphisms (SNPs).¹
 - MA-149 achieved accuracy for diverse populations by applying ancestry-specific risks to the fraction of each SNP attributable to African, East Asian, and European reference populations.
- Integrating MA-149 with the Tyrer-Cuzick (TC) model improved predictive accuracy by roughly 2-fold over TC alone.

Objective: We aimed to further improve the predictive accuracy of MA-149 by expanding the set of BC SNPs and refining ancestry-specific risks.

Methods

- We developed a novel stepwise regression methodology accounting for linkage disequilibrium to select an optimal set of BC SNPs.
- Women who were referred for hereditary cancer testing from January 2021 through September 2023 and who were negative for pathogenic variants in BC-associated genes were divided into 3 consecutive cohorts, to refine reference ancestry-specific risks and develop and validate a new PRS (**Figure 1**).
- Odds ratios (OR) from multivariable regression are reported per standard deviation (SD).

Figure 1. Study design: Refinement of reference ancestry-specific SNP risks, development of a 385-SNP PRS, and independent validation of the PRS

Reference Ancestry SNP Risks	PRS Development Cohort	Independent Validation Cohort
Black/African: N=58,191 East Asian: N=27,160	N=184,322	N=146,110
<ul style="list-style-type: none">European SNP risks were obtained from summary statistics²Meta-analyses combining clinical cohorts with literature³⁻⁷ led to ancestry-specific SNP risks based on up to 77,625 Black/African and 150,201 East Asian women	<ul style="list-style-type: none">Ancestry-specific SNPs were combined into a single multiple-ancestry PRS (MA-385) based on the development cohortThis cohort was used to define a combined risk score (CRS) combining the MA-PRS with the TC model	<ul style="list-style-type: none">The new PRS (MA-385) was independently validated in a diverse cohort.Predictive accuracy and calibration of MA-385 were evaluated overall and in different ancestry subpopulations

Results

- Characteristics of the validation cohort are detailed in Table 1.

Table 1. Characteristics of women included in the validation cohort

Self-reported ancestry	N or n	BC affected n (%)	Age Mean (SD)	First degree relative with BC n (%)	MA-149 Mean (SD)*	MA-385 Mean (SD)*
Full Cohort	146,110	28,519 (19.5)	47.5 (14.5)	43,337 (29.7)	-0.03 (0.34)	-0.00 (0.45)
Ashkenazi Jewish	1,514	206 (13.6)	50.4 (14.6)	502 (33.2)	0.09 (0.37)	0.04 (0.47)
Black/African	17,529	3,426 (19.5)	46.4 (13.8)	5,405 (30.8)	-0.02 (0.18)	-0.01 (0.29)
East Asian	2,868	745 (26.0)	47.9 (12.9)	849 (29.6)	-0.00 (0.24)	0.05 (0.42)
Hispanic	12,384	2,071 (16.7)	44.0 (13.3)	3,222 (26.0)	-0.10 (0.33)	-0.05 (0.45)
Mixed	7,664	698 (9.1)	42.0 (13.0)	2,150 (28.1)	-0.03 (0.32)	0.00 (0.43)
South Asian	937	213 (22.7)	44.3 (12.3)	268 (28.6)	0.01 (0.29)	0.04 (0.43)
White	91,516	17,679 (19.3)	48.3 (14.7)	27,705 (30.3)	-0.03 (0.37)	0.00 (0.48)

*Among unaffected women.

- An expanded set of 385 SNPs (56 ancestry-informative, 329 BC-associated) was selected for the new PRS (MA-385).
- For each ancestry, MA-385 improved on clinical factors and outperformed MA-149 (**Figure 2**).
 - In non-Europeans, MA-385 was a better BC risk predictor (OR, 1.47; 95% CI, 1.43–1.52) than MA-149 (OR, 1.40; 95% CI, 1.35–1.45).
 - Associations were strongest in Ashkenazi Jewish and Hispanic women.
- MA-385 identified more women at >2-fold higher BC risk than MA-149 (6.3% vs 2.0%, respectively).
- In goodness-of-fit tests, MA-385 was well-calibrated in both Europeans and non-Europeans (Figure 3A), while a similar PRS based on European weights was miscalibrated for non-Europeans, particularly for women of Black/African ancestry (**Figure 3B**).
- Within each ancestry, the combined MA-385 + TC risk model, CRS-385, reclassified more patients (high to low, or low to high risk) than the combined MA-149 + TC risk model, CRS-149 (**Figure 4**).

Figure 2. Risk prediction by MA-385 outperforms MA-149 across all ancestries

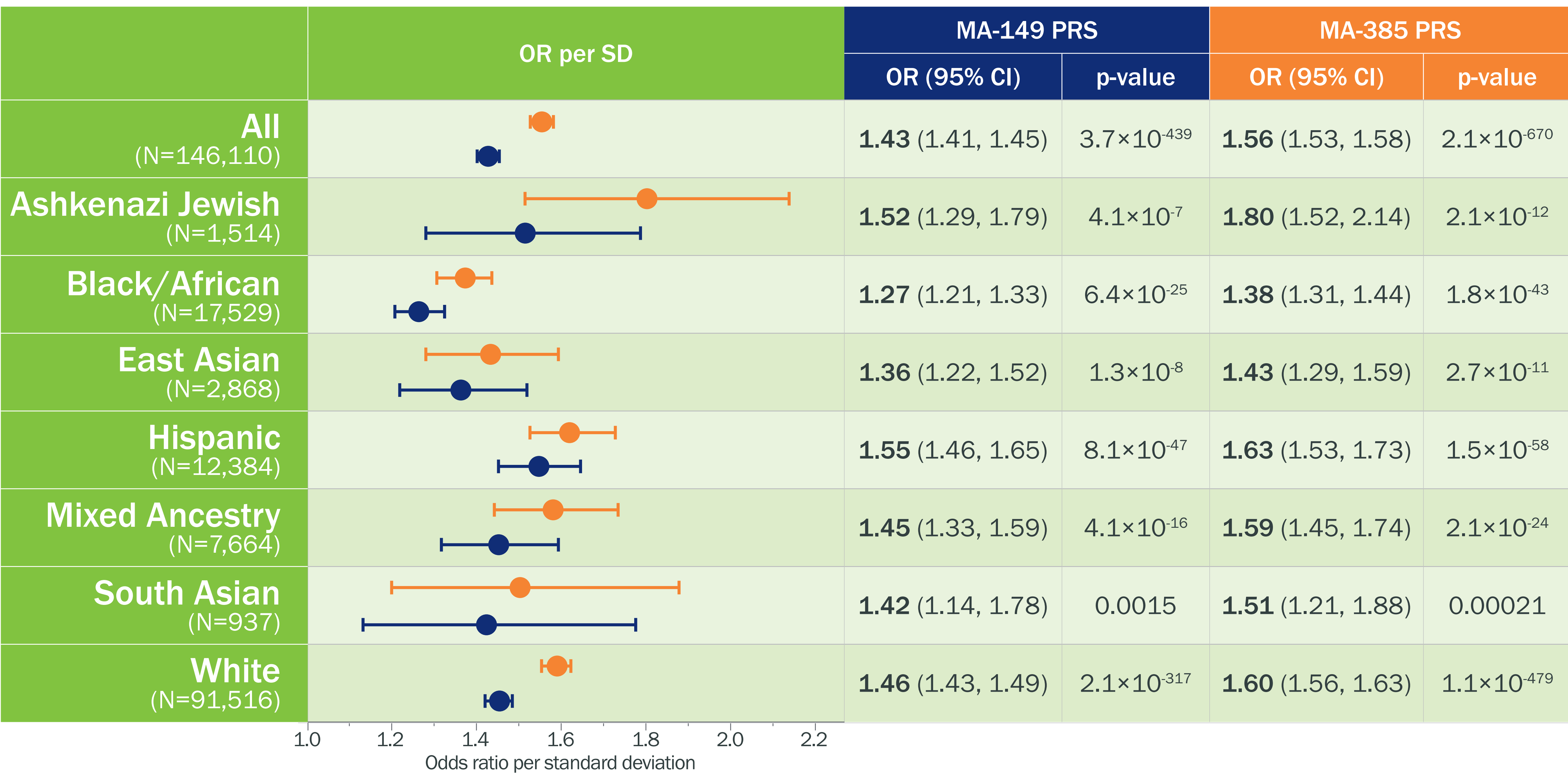


Figure 3. Calibration plots: **A)** MA-385 is well-calibrated in both European and non-European women; **B)** European PRS is inaccurate for Black/African women.

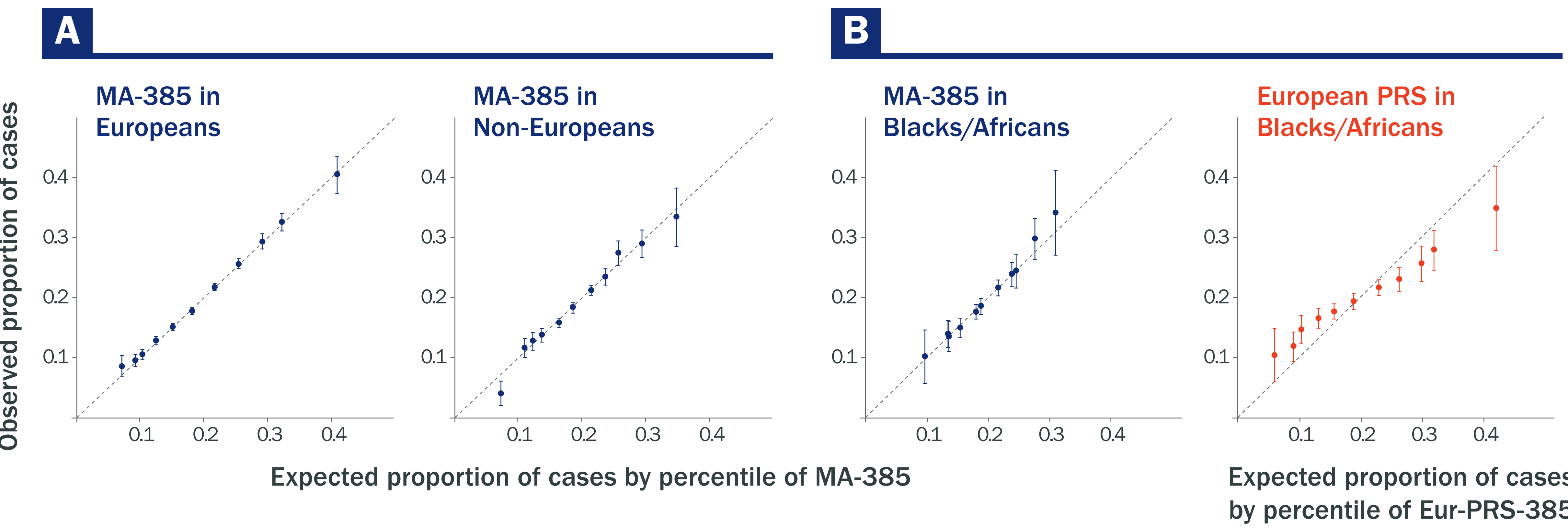
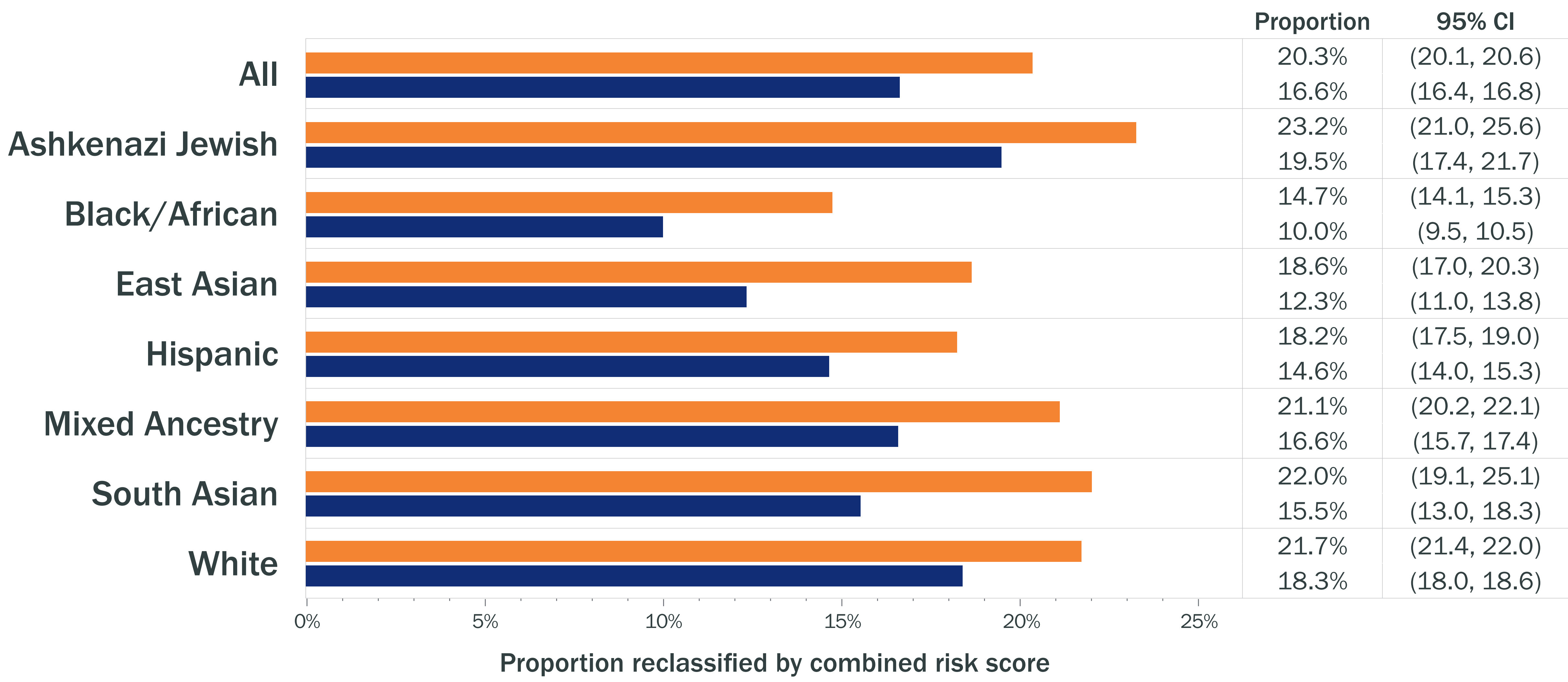


Figure 4. Patients reclassified by risk model



Conclusions

- MA-385 was well-calibrated, improved upon clinical factors, and outperformed existing PRS in all tested ancestries.
- Incorporation of MA-385 into risk assessment could improve the early detection and prevention of BC.

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Abbreviations: BC, breast cancer; CI, confidence interval; NH, non-Hispanic; OR, odds ratio; PRS, polygenic risk score; SD, standard deviation.

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