

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

Timothy Simmons, MStat<sup>1</sup>; Elisha Hughes, PhD<sup>1</sup>; Dmitry Pruss, PhD<sup>1</sup>; Matthew Kucera, MSc<sup>1</sup>; Benjamin Roa, PhD<sup>1</sup>; Thaddeus Judkins, MS<sup>1</sup>; Thomas P. Slavin, MD<sup>1</sup>; Victor Abkevich, PhD<sup>1</sup>; Ryan Hoff, MS<sup>1</sup>; Srikanth Jammulapati, MS<sup>1</sup>; Susanne Wagner, PhD<sup>1</sup>; Dale Muzzey, PhD<sup>1</sup>; Jerry S. Lanchbury, PhD<sup>1</sup>; Alexander Gutin, PhD<sup>1</sup>

<sup>1</sup>Myriad Genetics, Inc., Salt Lake City, UT, USA

San Antonio Breast Cancer Symposium, December 5–9, 2023. San Antonio, Texas, USA

PS10-07



## Background

- We previously described a multiple-ancestry PRS (MA-PRS 149) based on 56 ancestry-informative and 93 BC-associated SNPs.<sup>1</sup>
- Here, we aimed to improve the predictive accuracy of MA-PRS 149, particularly for non-Europeans, through the inclusion of additional BC-associated SNPs.

## Methods

- Women referred for hereditary cancer testing who were negative for pathogenic variants in BC-associated genes between January 2021 and September 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 statistics<sup>2</sup> together with reference data<sup>3</sup> to account for linkage disequilibrium.
- Ancestry-specific SNP risks were determined from meta-analyses of literature with clinical cohorts of 57,827 Black/African and 26,992 East Asian women.
- Ancestry-specific PRS were combined into a single MA-PRS based on the development cohort consisting of 157,740 women.
- The development cohort was used to define a comprehensive risk score (CRS) combining the MA-PRS with the Tyrer-Cuzick risk model.
- Clinical validation of MA-PRS was conducted in an independent validation cohort.

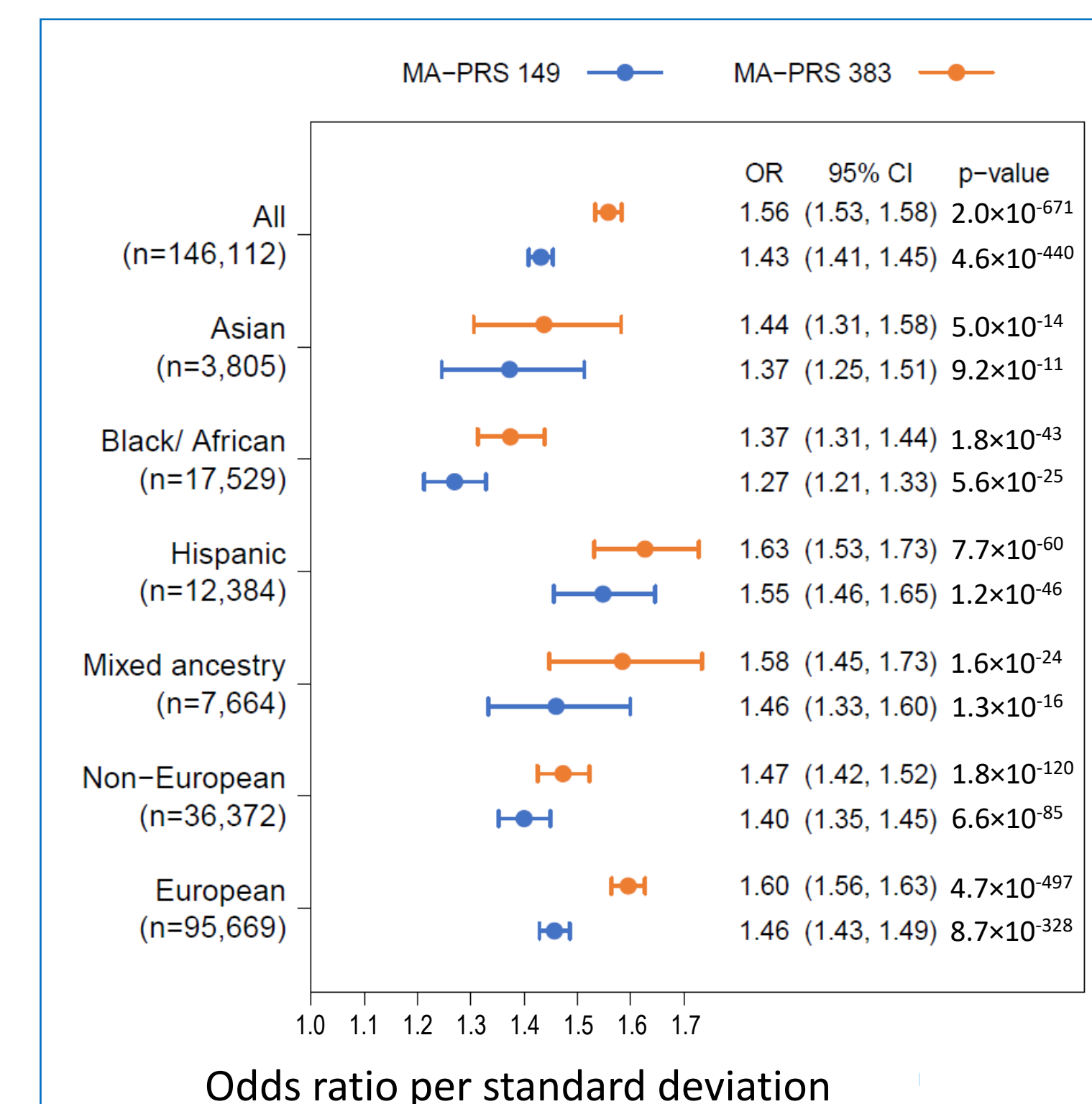
\*Included patients identifying as Black.

1. Hughes E, et al. *JCO Precis Oncol.* 2022. 2. Zhang H, et al. *Nat Genet.* 2020;52:572-581. 3. The 1000 Genomes Project Consortium. *Nature.* 2015;526:68-74.

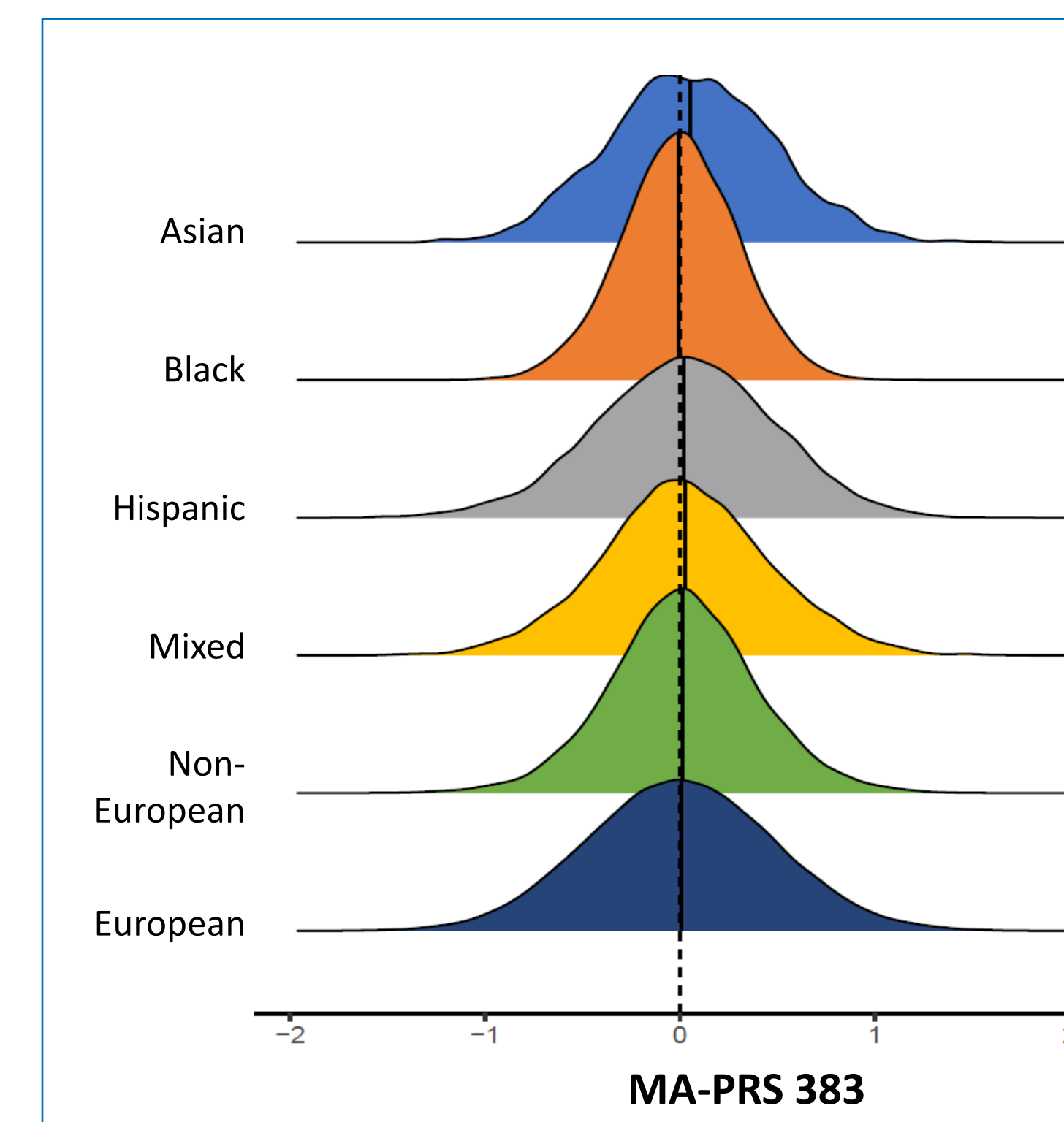
## Results

- An optimal set of 383 SNPs (56 ancestry-informative and 327 BC-associated) was included in the final PRS (MA-PRS 383).
- The validation cohort consisted of 146,112 women, 30.2% of whom reported non-European ancestries, and 29.7% of whom had been diagnosed with BC.
- MA-PRS 383 added significant predictive information to clinical factors within each ancestry (**Figure 1**).
- After adjusting for age, personal/family cancer history, and ancestry, the odds ratio per standard deviation (OR/SD) of MA-PRS 383 in the full cohort was 1.56 (95% CI 1.53, 1.58,  $p=2 \times 10^{-671}$ ) (**Figure 1**).
- The distribution of MA-PRS 383 in unaffected women was comparable across different ancestries in the validation set (**Figure 2**).

**Figure 1. MA-PRS 383 versus MA-PRS 149: Association with breast cancer risk after accounting for clinical factors**



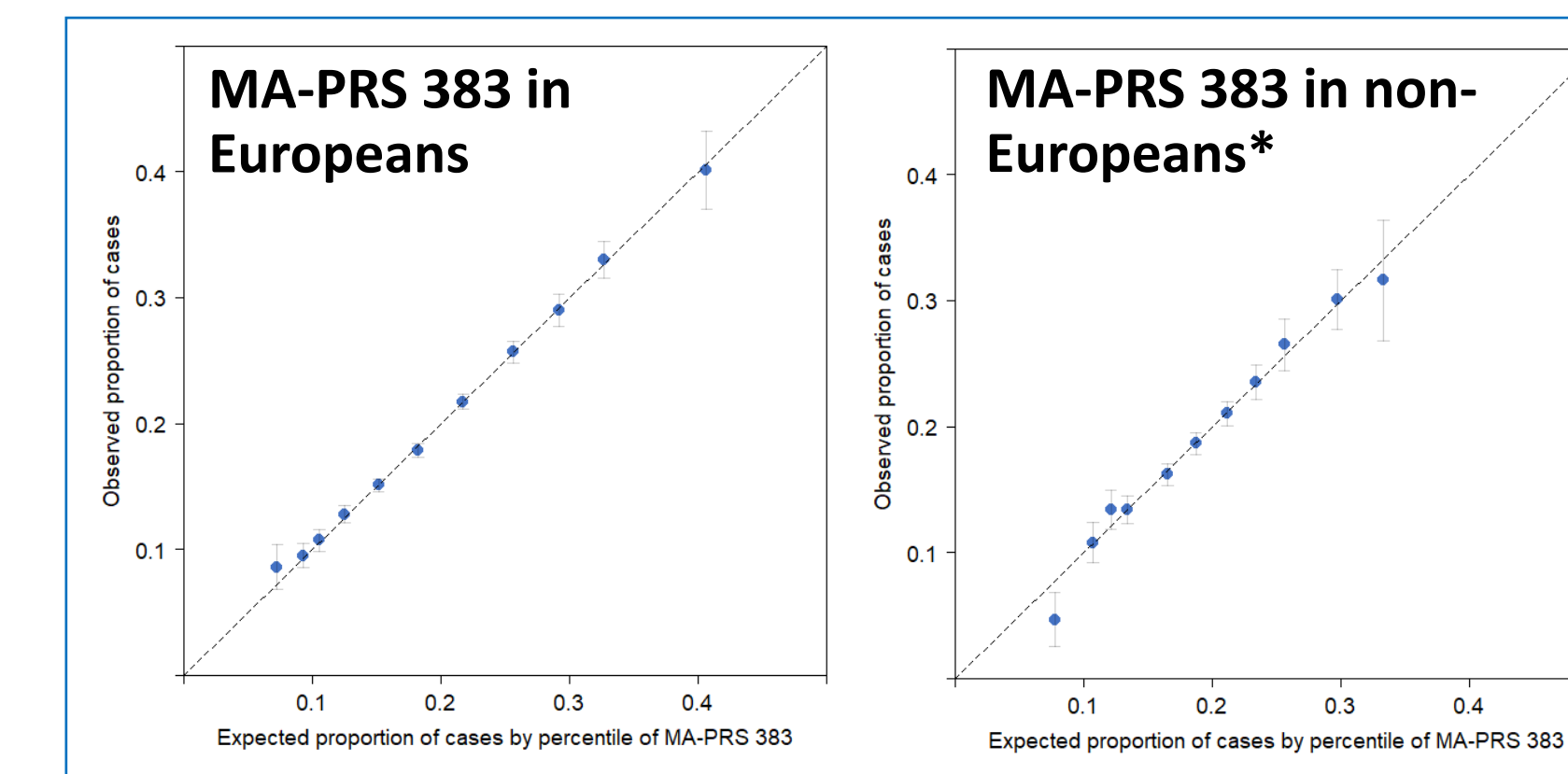
**Figure 2. Distribution of MA-PRS 383 in unaffected women of different ancestries (validation set)**



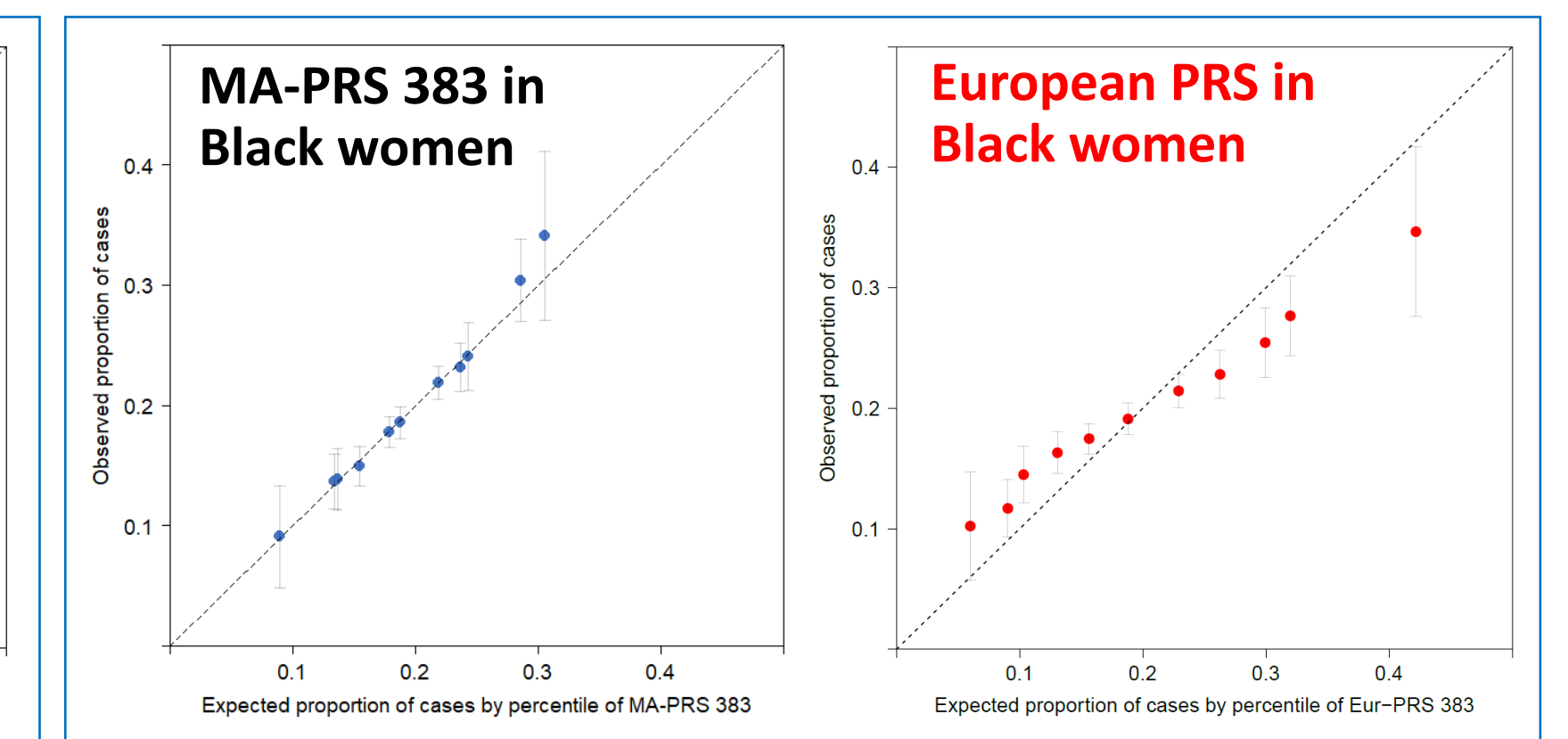
- In bivariate analyses, MA-PRS 383 outperformed both MA-PRS 149 and Eur-PRS 383, a PRS obtained by applying European-specific SNP risks to all ancestries.

- A comparison between the observed and expected proportions of cases within percentile-based bins of MA-PRS 383 showed that MA-PRS 383 was well-calibrated among both European and non-European women (**Figure 3**).
- A similar comparison showed that, while MA-PRS 383 was relatively well-calibrated among Black women, the European PRS was poorly-calibrated in this population (**Figure 4**).

**Figure 3. MA-PRS 383 calibration (observed vs expected)**

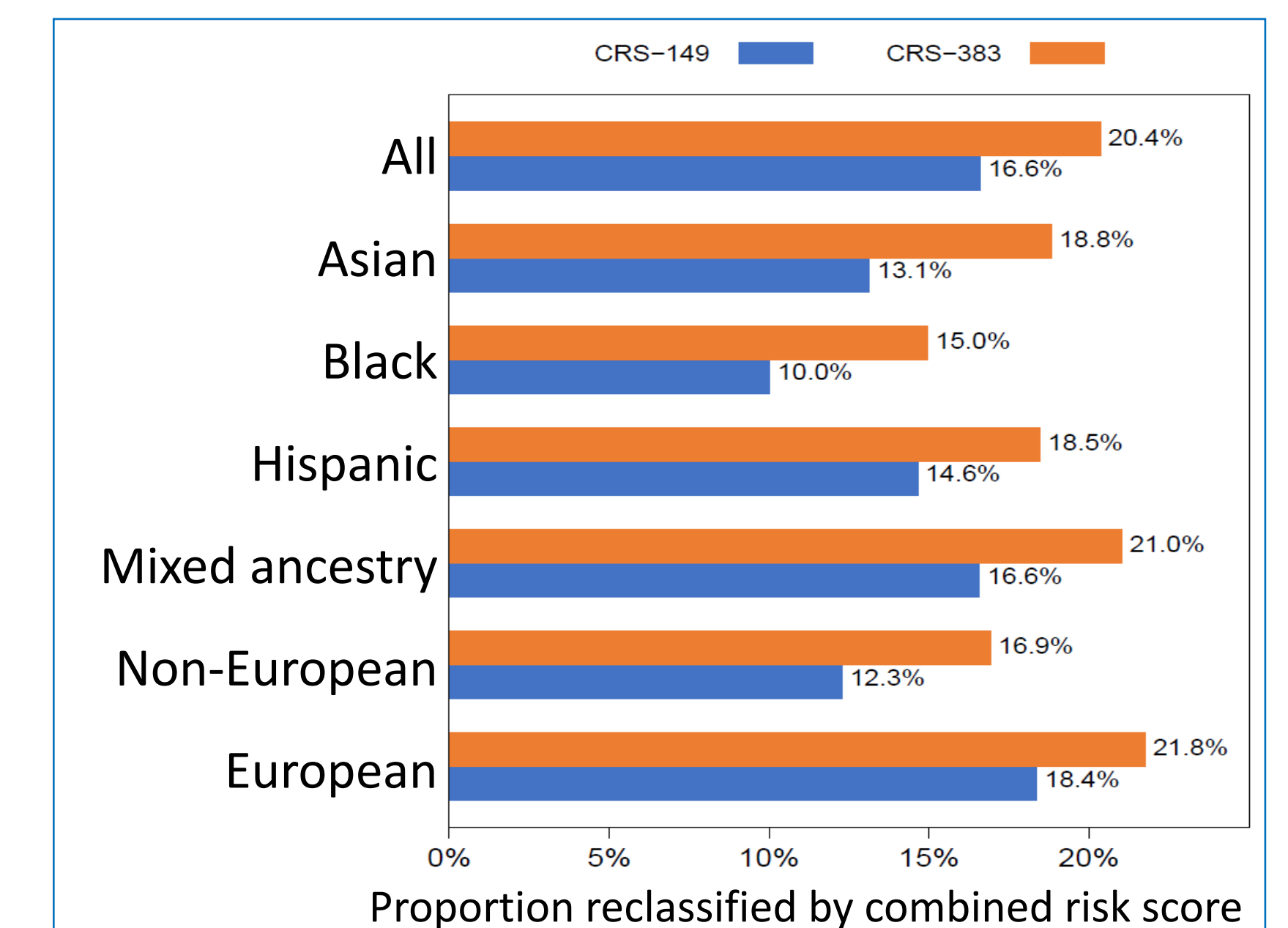


**Figure 4. MA-PRS 383 vs Eur-PRS 383 calibration in Black women**



- 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.

**Figure 5. Patients reclassified by risk model**



## 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.