Family history was highly significant, but weakly correlated with the 149-SNP PRS ($r=0.08$; $n=100,688$). After accounting for family history and clinical factors in TC, the PRS component explained 7,909 (11.5%) of High TC. Predisposition to breast cancer has a substantial genetic component that can be used to inform risk prediction and personalized preventive measures.

We compared differences in classification of women with breast cancer (Table 1). The 149-SNP PRS incorporates 56 ancestry-informative variants with 93 BC-associated SNPs. It was significantly associated with BC risk after accounting for family cancer history. Here, we combine the 149-SNP PRS with version 7 of the clinical and family history-based Tyrer-Cuzick (TC) model.

As a Combined Risk Score (CRS), incorporating the 149-SNP PRS and the TC model, was developed based on a cohort of 145,786 women who were unaffected by breast cancer (Table 1). We examined associations between the 149-SNP PRS and each clinical risk factor in the TC model using linear regression. The development followed a previously described Fixed-Stratified method to avoid double-counting risk between confounded factors, in particular, between the 149-SNP PRS and family history. Consistent with previous studies, this study used an Ancestry-Inclusive approach.

A cohort of 68,803 unlinked women, independent from CRS development, was used to evaluate CRS calibration and risk stratification (Table 1). We tested CRS calibration against TC by comparing average RLR by CRS and TC. The equivalency of average RLR by CRS and TC is shown by the equivalency of average RLR by CRS and TC. The average absolute lifetime risks by CRS were similar to those from the TC model, with the exception of Hispanic carriers of a protective American SNP who were lower risk by CRS.

Adding PRS to TC significantly altered breast cancer risks for all ancestries, with 17.3% of patients classified differently by CRS vs TC alone (Table 2, Figure 3). Patients who were classified as high risk by TC, 29.1% were downgraded by CRS.

In this first breast cancer risk model based on a polygenic score, the 149-SNP PRS, which incorporates genetically determined ancestral composition and is validated for diverse ancestries.

Combining the 149-SNP PRS with TC substantially improved risk stratification over TC alone and may therefore lead to enhanced breast cancer risk reduction strategies such as increased surveillance and use of preventive medications.

REFERENCES