Genome-wide association studies (GWASs) have identified single-nucleotide variations (SNVs), which are common genetic variants that confer little individual risk but, considered additively, are associated with the risk of developing cancers. Polygenic risk scores (PRSs) use SNV panels to calculate cancer risk. The potential promise of PRSs is to refine risk estimates currently based on clinical factors and monogenic germline testing to ultimately improve health care delivery and patient outcomes. Noting that most breast cancer PRSs are derived largely from patients of European ancestry, Liu and colleagues\(^1\) investigate how 7 breast cancer PRSs performed in eMERGE network institution patients of European, African, or Latinx ancestry. The authors evaluated the association of breast cancer by percentiles of PRS adjusting for age, breast cancer family history, study site, and first 3 ancestry informative principal components; they additionally presented discrimination of models using the area under the receiver operating characteristic curve (AUC). Findings were largely concordant with other studies: PRSs associate with breast cancer risk; the strength of the association is greatest in the extremes of the score distribution; and the effect size is larger for estrogen receptor (ER)-positive than for ER-negative breast cancer. Importantly, the authors found that the PRSs based on patients with European ancestry generalize well to patient groups of European and Latinx ancestry, and less well to the patient group with African ancestry.

This study advances the goals of precision medicine, which aims to leverage scientific breakthroughs such as GWAS to personalize care. This work simultaneously highlights pervasive race-based inequities in health care. A major criticism of PRSs is that they are disproportionately applicable to patients with European ancestry and are insufficiently vetted and developed in other populations. If an instrument exists that has clinical utility in informing effective cancer risk mitigation strategies, then we must strive to ensure that it is available and applicable to all.

Taking a step back, the fundamental issue then becomes: do PRSs have clinical utility? The answer to this question begins with at least 2 considerations: first, do PRSs for breast cancer provide meaningful risk estimates; second, in what contexts are we applying these scores?

Regarding the first question, PRS frequencies are often depicted as bell curves of those with and without the disease. Most PRSs lie near the mean—they confer an overall neutral effect in breast cancer risk estimates. A minority of individuals have scores in the extremes of the PRS distribution where the breast cancer risk association is largest. A small percentage of individuals will be classified by PRS alone as having an absolute breast cancer lifetime risk of 20%, the usual threshold in the US to initiate breast magnetic resonance imaging (MRI). Discriminatory capacities of PRSs are often presented as AUCs. Consistent with the literature, AUCs presented for PRSs in the 3 groups (eTable 4 in the article Supplement) range from 0.48 to 0.61. Although the threshold for meaningful discrimination depends on the specific context, an AUC < 0.7 is generally not considered to reflect substantial discrimination. These AUCs are acceptable because PRSs do not inform risk in isolation. This brings us to the second, and perhaps larger, issue central to PRS clinical utility: context.

PRSs can be applied in 3 overarching clinical scenarios: (1) individuals deemed to be at population risk for breast cancer based on clinical factors and monogenic germline testing; (2) those at elevated risk based on personal or family history, but with no pathogenic variants (PV) in breast cancer susceptibility genes; and (3) those with PVS in breast cancer susceptibility genes.
In the first scenario, for a patient otherwise at population risk for breast cancer, a high PRS might reclassify overall risk and affect management; this likely pertains to a small proportion of patients, given that the majority of PRSs are within 2 standard deviations of the mean. If an ER-positive PRS is elevated, this may inform antiestrogen chemoprevention strategies. PRSs may modify the age at which screening should begin or factor into the recommendation for surveillance breast MRI. The WISDOM trial (NCT02620852) compares risk-based breast cancer screening with annual screening and includes use of a 96-variant SNV panel to inform elevated risk; this study may shed light on PRS clinical utility. If PRSs are to be applied to the general population, they must perform well in all ancestry groups to ensure equitable health care. Notably, Ambry Genetics previously reported AmbryScore, which combined a PRS with a clinical risk estimate, but removed their model from their testing menu effective May 20, 2021, in part because of limited data across ethnic populations.

For individuals in the second scenario (ie, at a clinically elevated risk but without a cancer susceptibility gene PV) PRSs are interpreted in the context of patients' personal and family histories. The CanRisk web tool is used widely in this setting and allows optional incorporation of a PRS score or raw variant genotyping information to estimate breast cancer risk. The Myriad riskScore (Myriad Genetics) presents a composite risk combining an 86-SNV panel PRS with the Tyrer-Cuzick clinical risk estimate; because a standalone PRS is not reported, the SNV-based and clinical risk estimates cannot be considered individually. If both PRS and clinical risk are high when considered as separate estimates, PRS is likely to confirm but not alter recommended risk mitigation strategies. If PRS is low and clinical risk is high, it is unlikely that either patient or clinician will feel comfortable scaling down on risk mitigation strategies given a concerning phenotype that contradicts the low PRS.

Finally, for individuals found to have a PV in a breast cancer risk predisposition gene, PRSs can provide more precise estimates of risk and inform management discussions. A 2021 report notes that PRSs may help reclassify more than 30% of CHEK2 and approximately 50% of ATM PV carriers as having a lifetime risk of breast cancer below 20%; these individuals may not, for example, need breast MRI surveillance, especially if phenotype is discordant with monogenic germline testing. PRSs may also be able to help modify the age at which an individual should begin breast MRI.

In any context, if management is affected by PRSs, clinical outcomes must be examined to inform clinical utility. And, in any context, PRSs must also be accessible to and validated in all ancestry groups to avoid worsening existent racial health care disparities. This may not be an easily attainable goal. The authors include almost 40,000 women in their study and yet were unable to include patients with Asian ancestry because of the small number of breast cancer cases. Ancestry groups may need to be parsed for PRSs to be valid, requiring larger sample sizes; for example, while some women of Latinx ethnicity have genetic ancestry that overlaps with women with European ancestry, Latinx women from the Caribbean may have considerable African ancestry. The authors’ approach of evaluating generalizability of existent PRSs to women with Latinx or African ancestry is commendable; GWASs conducted in larger minority populations are also needed to identify novel risk variants specific to racial/ethnic minority groups.

Currently, National Comprehensive Cancer Network guidelines advise against the clinical use of PRSs due to limitations in interpretation and encourage further research. Essential objectives of this research must be to examine if, when, and in whom PRSs are useful. Studies will need to not only consider discriminatory capacity, equity, and clinical utility, but also psychosocial impact and cost-effectiveness, each in context. Polygenic risk scores may well personalize cancer risk management and improve patient outcomes, but we will need to further investigate these critical issues before determining whether they can fully deliver.
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