Clinical Implications and Utility of Polygenic Risk Scores in Women at Elevated Risk for Breast Cancer

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Introduction
Breast cancer remains one of the most common forms of malignancy in women worldwide, with 2.3 million women diagnosed globally in 2020.1 Only the minority of breast cancers are found to be linked to a single pathogenic gene variant, such as BRCA-1/2, although a much larger number of cancers may be familial. In recent years, population-based Genome Wide Association Studies (GWAS) have identified the impact of single nucleotide polymorphisms (SNPs) to explain up to 18% of familial breast cancers.2,3 SNPs are single base changes to the DNA and, while a single SNP may not greatly impact cancer risk, the combined effect of a cluster of SNPs could significantly increase the risk. The risk of this combined effect may be summarized using the polygenic risk score (PRS).
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The development of the PRS for predicting breast cancer has evolved over time, with early PRS accounting for statistical power from only about 70 SNPs whereas most recent studies have identified over 300 SNPs associated with breast cancer. Herein, we will discuss how the PRS may be implemented into routine clinical practice when counseling women at elevated risk for breast cancer.

**PRS use in High Risk in Women**

Women with a family history or other risk factors for breast cancer often benefit from enhanced screening and prevention strategies. A number of risk assessment tools and panels provide guidance on screening and prevention. As a prime example, the U.S. National Comprehensive Cancer Network (NCCN) recommends that women with lifetime risk of breast cancer >20% undergo annual screening MRI in addition to mammography.

Traditionally, we (the clinical community) have calculated breast cancer risk for patients using validated assessment tools, such as the Tyrer-Cuzick (IBIS) and Breast Cancer Risk Assessment Tool (BCRAT/Gail) models, which incorporate patient reported clinical data on family history; reproductive history; and mammographic breast density. While the discriminatory accuracy of these tools has been refined over time, there are still drawbacks with each of these models. For example, the BCRAT model incorporates only family history information for first degree relatives and does not consider how many unaffected relatives a patient may have. This particular model also does not include an individual’s breast density, which we know impacts risk.

While the IBIS model is more comprehensive, it also has limitations. For example, it has been established that IBIS will overestimate risk in women with a history of atypia, as well as in Hispanic women. These models are also population based and not personalized.

By combining both clinical and genomic information, the accuracy of risk assessment with both the BCRAT and IBIS models can be improved. In doing so, it is important that we adjust for shared risk contribution, where multiple risk factors may not be additive in their effect, particularly with regards to family history and polygenic risk. This was accounted for in one large validation study which combined an 86 SNP polygenic risk score with a calculated IBIS score.

Even after accounting for the confounding effect of family history, incorporation of PRS with clinical assessment models resulted in alterations to screening recommendations in 18% of women studied. Of those with estimated lifetime risk > 20% by IBIS model alone, 29% were downgraded to ≤ 20% lifetime risk by the combined IBIS and PRS estimation. Conversely, 12% of women with estimated risk ≤ 20% by IBIS were upgraded to > 20% by the combined score.

Accurate risk assessment is also critical when counseling women on breast cancer prevention strategies.

Historically, women with a 5-year risk of breast cancer calculated at >1.67% on the BCRAT model would qualify for use of prevention medications such as tamoxifen, raloxifene or the aromatase inhibitors. More recently, US. Preventive Services Task Force (USPSTF) and American Society of Clinical Oncology (ASCO) guideline updates have stated that optimal benefit to risk ratio with preventative medications is seen in those women whose 5-year estimated risk is ≥ 3%.

Despite the evidence showing benefit, uptake to available medications remains low. We have seen recently, however, that incorporation and counseling on the influence of individual PRS may improve adherence to prevention medication. In one particular trial, incorporation of PRS after clinical assessment with the IBIS model increased breast cancer risk estimates in 55.6% of women studied. After counseling about the result of their PRS and overall breast cancer risk, 41.9% of those

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**Figure 1:** PRS report demonstrating IBIS risk estimate decreasing (A) and increasing (B) after incorporation of PRS information.
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with increased risk estimates were more inclined to take prevention medication, and 46.7% of women with decreased risk estimates were less inclined to take medication.\(^5\)

Several studies have also been aimed to design PRS linked to subtypes of breast cancer, specifically Estrogen Receptor (ER)-positive versus ER-negative disease. For the most part, we have been better at predicting risk for ER-positive disease, as it occurs much more frequently, and therefore smaller sample sizes are needed.\(^1\) As GWAS evolves with larger cohorts, we will likely see more accurate PRS emerge for ER-negative disease. This would allow us to identify those women at risk for more aggressive disease, in whom preventative endocrine therapy may not be useful, and enhanced screening and other strategies become even more important.

These collective data suggest that the inclusion of information on PRS impacts decision-making and may improve the precision with which we individualize care for women at high risk and aid in decision making about preventive strategies.

**PRS Use in Hereditary Mutation Carriers**

For women who carry a pathogenic variant in genes known to increase breast cancer risk, the use of PRS may help to identify which patients would benefit the most from prophylactic measures such as surgery and better predict the optimal timing for such measures (versus continuing with intensive surveillance imaging).

Current NCCN guidelines recommend consideration and discussion of risk-reducing mastectomy for patients with highly penetrant genes, such as BRCA-1/2;\(^16\) however, there are some patients who may never develop breast cancer and could be managed with high-risk screening alone. In one study using data from 15,252 female BRCA1 carriers, those at the 90th percentile PRS had an estimated 19% breast cancer risk by age 40 years and 39% by age 50 years versus carriers in the 5th percentile who had only 5% risk by age 40 years and 21% by age 50 years.\(^15\) This knowledge of a more individualized risk prediction may impact a patient’s decision of when, and even if, to pursue risk reducing surgery.

**Genomic testing practices have evolved to include multigene panels, which test for an array of established moderate penetrance genes linked to breast cancer.**

Genomic testing practices have evolved to include multigene panels, which test for an array of established moderate penetrance genes linked to breast cancer. While the evidence for recommendations in managing patients with highly penetrant genes is fairly substantial, there is little clinical trial data to guide recommendations in patients with moderate penetrance genes, such as ATM or CHEK2. It has been shown that the penetrance of these genes may be influenced by many factors, including age and family history.\(^18,19\)

We are now learning that PRS can also help estimate individualized risk in these patients. In one study, incorporation of PRS into traditional risk prediction models identified more than 30% of CHEK2 carriers to have a lifetime risk below 20%, suggesting that these particular patients may not need supplemental MRI and can help prevent over-screening in this population.\(^20\)

**What Are the Ethnic Considerations When Using PRS**

To date, most studies on the use of PRS have been done in Caucasian women of European descent. Little is known about the use of PRS in women of underrepresented minorities. In general, the need to improve racial and ethnic diversity in all genomic research cohorts has been recognized, and this also holds true with the use of PRS and breast cancer.

Evaluation of validated PRS models previously developed in women of European ancestry, while still potentially helpful, has shown to have lower discriminatory accuracy in women of racial minorities, with the smallest effect size seen in women of African descent.\(^21\) While there have been some smaller GWAS which derived unique PRSs in women of African and Latinx ancestry specifically, these PRSs actually performed worse in their respective populations compared to the PRSs derived from women of European ancestry in one large validation study, likely due to much smaller cohort sizes and less SNPs identified.\(^21\) Some studies have suggested that certain SNPs which may increase breast cancer
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risk in one ethnicity may actually be protective in another. More research with larger sample sizes is needed to improve the use of PRSs in women of non-European descent.

**Future Clinical Implementation/ Counseling of High-Risk Women**

For patients with identified risk factors for breast cancer, validated models such as BCRAT and IBIS should be used to help determine an objective measure of risk. Patients should also be counseled about the growing body of data to support use of PRS for more accurate prediction and stratification.

Because the PRS is estimated independently from clinical breast cancer risk factors, hybrid clinical-PRS risk assessment models have been developed that account for confounding factors between the PRS and clinical risk scores. These hybrid models have demonstrated improved discriminatory accuracy compared to either the clinical score or the PRS alone.¹²

A personalized PRS report such as that displayed in Figure 1 may be used to help patients understand the influence of the PRS when combined with other clinical factors. In any case, breast cancer risk estimates that include the PRS should be reviewed and explained by a physician for a patient to understand the context of the score. The magnitude and direction of change in breast cancer risk estimates with the addition of PRS as compared to the risk calculator score need to be reviewed in detail. Shared decision-making can then be employed to guide patients to make appropriate informed decisions with respect to breast cancer screening and risk reduction options.

For carriers of known pathogenic hereditary breast cancer variants (including BRCA-1/2), the PRS can be combined with clinical risk estimates for the established gene variant using the CanRisk tool. "For carriers of known pathogenic hereditary breast cancer variants (including BRCA-1/2), the PRS can be combined with clinical risk estimates for the established gene variant using the CanRisk tool."

A report is generated with the CanRisk tool, as displayed in Figure 2, in which the polygenic burden is represented on a bell curve relative to that of the rest of the population. Absolute risk is then estimated in the report at 5-year increments, up to age 80 years. Again, this information can help stratify patients with these rare hereditary pathogenic variants and guide decisions as to if and when to consider risk reducing surgeries versus continued high-risk screening.

All patients who have had a calculated PRS need to be followed clinically over time with reassessment of risk as factors change. While the PRS estimate should remain constant over time (our genomes are fixed), other clinical variables such as biopsy results and affected relatives with breast cancer may change and influence recommended screening and prevention strategies. Ongoing discussion with one’s physician regarding factors, which should be updated along with recalculated risk estimates every 2-3 years and informed by any updates to guideline-based recommendations.

**Future Directions**

**Breast Cancer Patients and PRS**

Women diagnosed with a new breast cancer are typically counseled that the risk for a separate contralateral breast cancer (CBC) is low, and routine contralateral mastectomy is not recommended. However, as survival rates improve and the number of women living with breast cancer increases, concern for subsequent CBCs increase. We know that diagnosis at younger ages and family history of breast cancer may place an individual with unilateral breast cancer at higher risk for development of CBC.²⁴ We now also know that higher PRS may also help predict likelihood of later CBC in breast cancer patients.²⁵

In a recent study utilizing a PRS with 313 separate SNPs linked to breast cancer, the lifetime risks of CBC were 12.4% for European women at the 10th percentile and 20.5% at the 90th percentile of PRS. This was found to be independent of other confounding factors including individual characteristics, tumor type, and treatments received.²⁶ These results suggest that for women concerned about CBC risk, measuring PRS may influence surgical decision-making for contralateral mastectomy at the time of initial diagnosis.

**Breast Density and PRS**

Mammographic breast density is a well-established risk factor for breast cancer, yet we are lacking consistent consensus guidelines for the use of supplemental breast imaging based on the presence of dense tissue alone. Recent studies have examined the joint relationship of mammographic density and PRS on breast cancer risk, demonstrating the risk conveyed by PRS and breast density are independent of each other.²⁷ By combining these risks, we may be able to identify those women with dense tissue who are at higher risk and therefore would benefit the most from supplemental screening strategies and those at lower risk where additional screening strategies may not be indicated.

While the IBIS model incorporates breast density, this particular model is based largely on family history information and can be cumbersome to complete in the clinical setting. Simplified breast cancer risk tools integrating mammographic density and polygenic risk score have been suggested and recently validated for broad use in the clinical setting when counseling women with dense tissue.²⁸

**Assessment of Familial Patterns**

When following families at increased risk, obtaining PRS scores on blood relatives including sisters, mothers, daughters, etc. may be helpful to understand patterns of heritance and the interplay between lifestyle/environment and heritable risk. Little data exists on comparing PRS results within specific families, especially in the clinical setting, and further research is needed to better understand these familial patterns.

**Conclusions**

As the field of clinical genomics evolves, so will our understanding of the clinical implications of SNPs. The accuracy of PRS and breast cancer risk estimation continues to be refined as we identify more SNPs linked to familial breast cancer and expand the potential clinical applications. While not yet widely available in the clinical setting, we anticipate that PRS could potentially enhance personalized risk assessment and be incorporated into the management of women at increased risk for breast cancer. Embracing the use of PRS will allow for a precision approach to prevention and screening when counseling women at risk for breast cancer, whether it be related to family history, known hereditary mutation status, or personal history of breast cancer.²⁹
Summary Points

- PRS may be incorporated into standard risk assessment models to refine risk estimates in women at elevated risk for breast cancer.
- PRS may be used to stratify risk estimates in carriers of hereditary mutations for breast cancer.
- Women should be counseled on combined risk estimates incorporating established clinical factors and polygenic risk to guide decision making on individualized screening and prevention strategies.
- To date most studies on PRS have been done in Caucasian women of European descent. More research with larger sample sizes is needed to improve the use of PRS in women of non-European descent.
- Clinical cancer uses for PRS are potentially broad. Future areas of interest will be in guiding breast cancer patients on risk for contralateral breast cancer and in better understanding familial patterns of PRS heritance.

References