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

By Lauren Cornell, M.D.[1]; Sabrina Sahni, M.D.[1]; Fergus Couch, Ph.D.[2]; Caroline Clune, M.D.[2]; Sara Lester, M.D.[2]; Celine Vachon, Ph.D.[2]; Jessica Fraker, M.D.[3]; and Sandhya Pruthi, M.D.[2]

Author Affiliations:
1. Jacoby Center for Breast Health, Mayo Clinic, Jacksonville, Florida
2. Breast Diagnostic Clinic, Mayo Clinic, Rochester, Minnesota
3. Breast Diagnostic Clinic, Mayo Clinic, Scottsdale, Arizona

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).

ALMAC

Partnering to Advance Human Health

Always a move ahead in precision medicine

Choosing Almac Diagnostic Services ensures you are always a move ahead in the precision medicine field.

Your global partner for biomarker discovery, development and commercialisation.

Our core services:

- **Genomic services**
- **Clinical trial assays**
- **Companion diagnostics**

We offer a collaborative approach with complete flexibility for your biomarker programme.

Make the winning move today:
almacgroup.com/diagnostics

almacgroup.com

Polygenic risk scores

Polygenic risk scores, often referred to as PRS, are a genetic estimate of a person's risk for specific diseases. Researchers and clinicians calculate polygenic risk scores by comparing the genomic data of people with and without a particular disease.

see, e.g., https://www.genome.gov/Health/Genomics-and-Medicine/Polygenic-risk-scores

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.[4] 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.[5]

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.[6]

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.[7,8] 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.[9,10] 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.[11] 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.[12]

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%.[13,14]

> *"By combining both clinical and genomic information, the accuracy of risk assessment with both the BCRAT and IBIS models can be improved."*

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

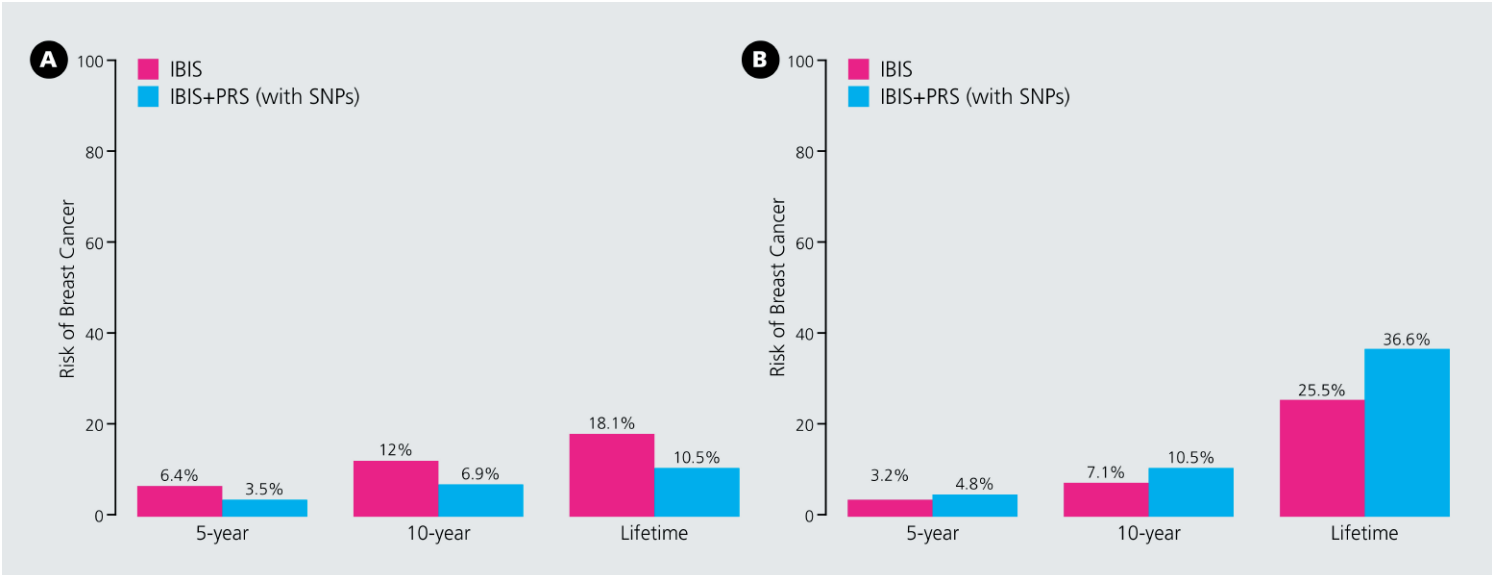
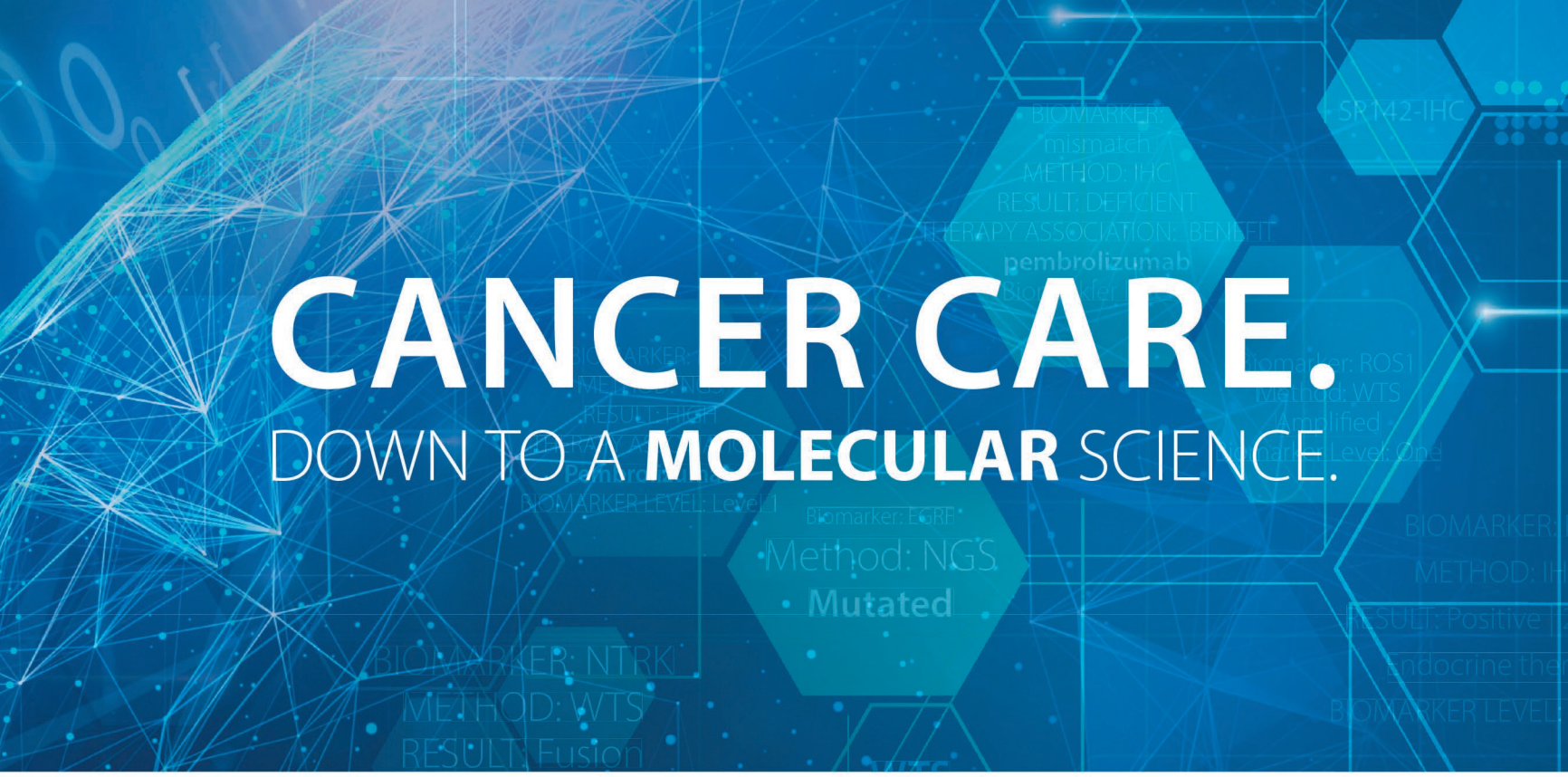


Figure 1: PRS report demonstrating IBIS risk estimate decreasing (**A**) and increasing (**B**) after incorporation of PRS information.



Comprehensive Tumor Profiling

As the pioneer in tumor profiling and leading molecular information company, Caris Life Sciences® provides access to the highest quality, advanced science. Caris molecular profiling assesses DNA, RNA and proteins to reveal a molecular blueprint and guide more personalized treatment decisions.

DNA — **RNA** — **Protein**

Where Molecular Science Meets Artificial Intelligence.

Learn more at CarisLifeSciences.com.

CARIS® LIFE SCIENCES

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.[15]

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.[4] 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.[17] 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

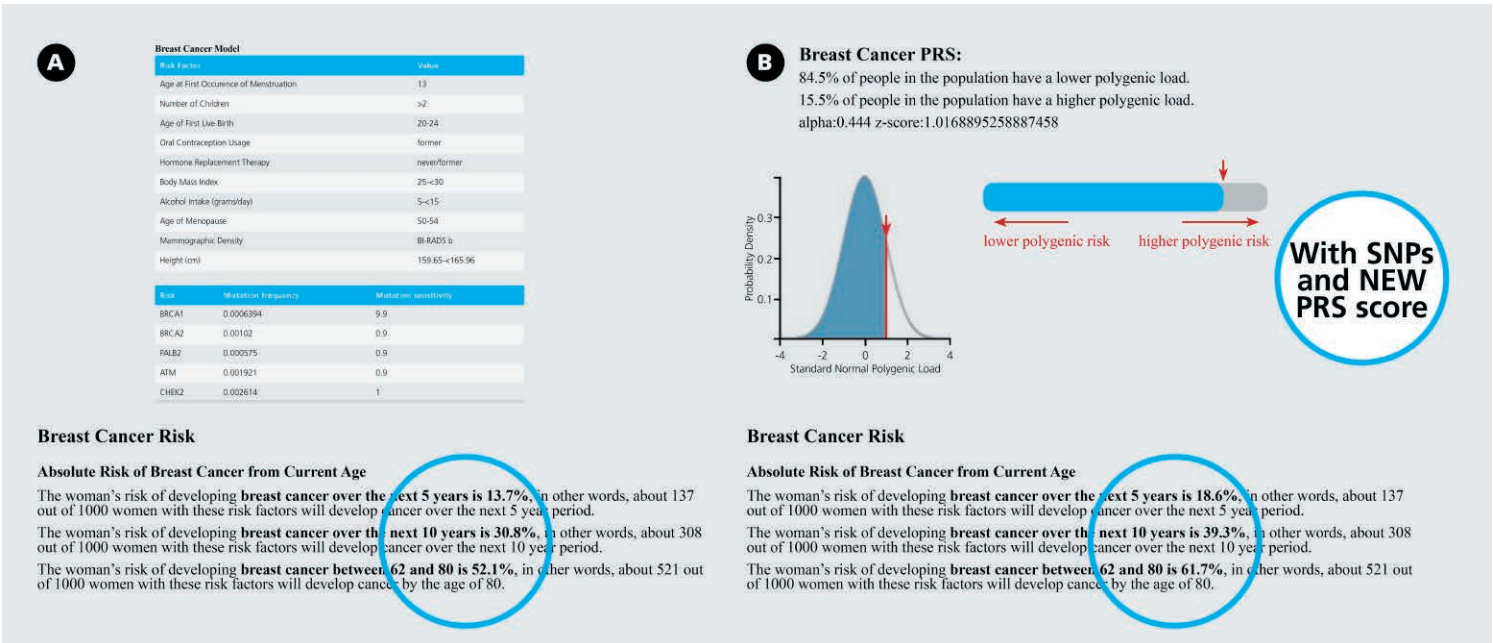


Figure 2: Example of BOADICEA/CanRisk model estimation in BRCA mutation carrier before (**A**) and after (**B**) incorporation of PRS information.

Shaping the forefront of cancer care together

FOUNDATION MEDICINE

ENDLESS POSSIBILITIES FOR YOUR DRUG DEVELOPMENT WITH ONE HIGH QUALITY COMPREHENSIVE PORTFOLIO

CDx DEVELOPMENT

As the leader in companion diagnostic approvals, we are your ideal partner to help make your next breakthrough a standard of care

LIQUID BIOPSY FOUNDATIONONE® LIQUID CDx

8 COMPANION DIAGNOSTIC INDICATIONS

8 TARGETED THERAPIES

TISSUE BIOPSY FOUNDATIONONE® CDx

24 COMPANION DIAGNOSTIC INDICATIONS

3 GROUP INDICATIONS ACROSS

29 TARGETED THERAPIES

PROSPECTIVE CLINICAL TRIALS

Use Foundation Medicine assays to support your trial enrollment and take advantage of the comprehensive gene panel to conduct prospective profiling

RETROSPECTIVE CLINICAL TRIALS

Sequence banked samples to define biomarkers and determine which patient populations could benefit from your therapy

Real-World Data (RWD) Solutions

WHY WE'RE A LEADER IN PRECISION ONCOLOGY RWD:

- Over 1 million patient CGP reports delivered
- Harmonized genomics data
- Linkage to leading Electronic Medical Records (EMR) data
- Fit for purpose in regulatory use cases

www.foundationmedicine.com | Tel. 888.988.3639 | Fax 617.418.2290 | US-FDX-2200075

Contact us for more details at biopharma.leads@foundationmedicine.com

risk in one ethnicity may actually be protective in another.[22] 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]

"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 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. This is an extension of the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) model to combine risk associated with high/moderate risk breast cancer genetic susceptibility variants and PRS. This tool also incorporates clinical information on family history, lifestyle, hormonal and reproductive risk factors, and mammographic density.[23]

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

"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."

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. JoPM

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 clinical 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.

Lauren Cornell, M.D.

Lauren is Assistant Professor of Medicine in the Department of Internal Medicine at Mayo Clinic Florida. She is board-certified in internal medicine and completed specialized post-residency training in Breast Health as a Mayo Clinic Scholar. Her areas of clinical research are focused on individualized management for women at high risk for breast cancer, hereditary breast/ovarian cancer syndromes, and breast cancer survivorship care.

Sabrina K. Sahni, MD, NCMP

Sabrina is a board-certified family medicine physician and is dual fellowship trained in Specialized Women's Health and Medical Breast, both completed at the Cleveland Clinic in Cleveland, Ohio. She currently serves as a breast medicine physician at the Mayo Clinic in Jacksonville, Florida. Her practice focuses on breast cancer risk assessment, new breast cancer diagnoses, breast cancer genetics, menopause, and general midlife women's care.

Caroline Clune , M.D.

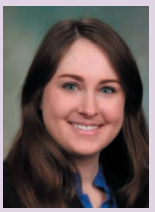
Caroline received her M.D. degree from the Medical College of Wisconsin in 2002. She completed her Internal Medicine Residency, and Chief Residency at Washington University in St. Louis in 2006. She is a consultant in the Department of General Internal Medicine at Mayo Clinic in Rochester, MN as well as Mayo Clinic Health System in La Crosse, WI, and an Assistant Professor of Medicine.

Sara P. Lester, M.D.

Sara is an Assistant Professor of Medicine in the Breast Clinic in the department of General Internal Medicine at Mayo Clinic Rochester. Her interests include benign and malignant breast disease processes, preventative breast health, lifestyle modifications for breast cancer prevention, and counseling regarding a strong family history of breast cancer.

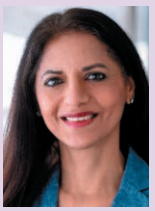
Fergus Couch, Ph.D

Fergus is the Zbigniew and Anna M. Scheller Professor of Medical Research and Chair of the Division of Experimental Pathology and Laboratory Medicine at the Mayo Clinic. Dr. Couch works on the genetics of breast, ovarian and pancreatic cancer, with over 580 publications relating to the discovery and clinical characterization of inherited genetic variants in cancer susceptibility genes.



Jessica Fraker, M.D.

Jessica is a board-certified Internal Medicine physician with a clinical focus on breast medicine. She practices at Mayo Clinic, Arizona. Her practice is focused on the care and evaluation of patients with breast concerns, as well as patients with elevated risk for developing breast cancer.



Sandhya Pruthi, M.D.

Sandhya received her medical degree from the University of Manitoba, Canada in 1990, and completed a Family Medicine residency at the Mayo Clinic. She is a Consultant in the Department of General Internal Medicine and a Professor of Medicine. Dr Pruthi's research area is in breast cancer prevention. She is the Mayo Clinic principal investigator on several national breast cancer prevention and biomarker trials aimed at reducing the risk of breast cancer. Dr. Pruthi is the Chief Medical Editor for MayoClinic.org and Medical Director for Division of Health Education and Content Services.

Celine M. Vachon, Ph.D

Celine is Professor and Chair of Epidemiology at Mayo Clinic and her research focuses on cancer and genetic epidemiology, particularly, to understand cancer through investigating early markers on the carcinogenic pathway, including imaging markers and benign breast disease in context of breast cancer.

References

1. World Health Organization Fact Sheets Breast Cancer,
2. Lilyquist J, Ruddy KJ, Vachon CM, et al: Common Genetic Variation and Breast Cancer Risk-Past, Present, and Future. Cancer Epidemiol Biomarkers Prev 27:380-394, 2018
3. Michailidou K, Lindstrom S, Dennis J, et al: Association analysis identifies 65 new breast cancer risk loci. Nature 551:92-94, 2017
4. Mavaddat N, Michailidou K, Dennis J, et al: Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes. Am J Hum Genet 104:21-34, 2019
5. Network NCC: Breast Cancer Screening and Diagnosis (v1.2022),
6. Nazari SS, Mukherjee P: An overview of mammographic density and its association with breast cancer. Breast Cancer 25:259-267, 2018
7. Boughey JC, Hartmann LC, Anderson SS, et al: Evaluation of the Tyrer-Cuzick (International Breast Cancer Intervention Study) model for breast cancer risk prediction in women with atypical hyperplasia. J Clin Oncol 28:3591-6, 2010
8. Kurian AW, Hughes E, Simmons T, et al: Performance of the IBIS/Tyrer-Cuzick model of breast cancer risk by race and ethnicity in the Women's Health Initiative. Cancer 127:3742-3750, 2021
9. Wacholder S, Hartge P, Prentice R, et al: Performance of common genetic variants in breast-cancer risk models. N Engl J Med 362:986-93, 2010
10. Brentnall AR, van Veen EM, Harkness EF, et al: A case-control evaluation of 143 single nucleotide polymorphisms for breast cancer risk stratification with classical factors and mammographic density. Int J Cancer 146:2122-2129, 2020
11. Muranen TA, Mavaddat N, Khan S, et al: Polygenic risk score is associated with increased disease risk in 52 Finnish breast cancer families. Breast Cancer Res Treat 158:463-9, 2016
12. Hughes E, Tshiaba P, Wagner S, et al: Integrating Clinical and Polygenic Factors to Predict Breast Cancer Risk in Women Undergoing Genetic Testing. JCO Precis Oncol 5, 2021
13. Visvanathan K, Fabian CJ, Bantug E, et al: Use of Endocrine Therapy for Breast Cancer Risk Reduction: ASCO Clinical Practice Guideline Update. J Clin Oncol 37:3152-3165, 2019
14. Moyer VA, Force USPST: Medications to decrease the risk for breast cancer in women: recommendations from the U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 159:698-708, 2013
15. Kim JO, Schaid DJ, Vachon CM, et al: Impact of Personalized Genetic Breast Cancer Risk Estimation With Polygenic Risk Scores on Preventive Endocrine Therapy Intention and Uptake. Cancer Prev Res (Phila) 14:175-184, 2021
16. Network NCC: Genetic/Familial High-Risk Assessment: Breaset, Ovarian, and Pancreatic (v 2.2022),
17. Kuchenbaecker KB, McGuffog L, Barrowdale D, et al: Evaluation of Polygenic Risk Scores for Breast and Ovarian Cancer Risk Prediction in BRCA1 and BRCA2 Mutation Carriers. J Natl Cancer Inst 109, 2017
18. Cybulski C, Wokolorczyk D, Jakubowska A, et al: Risk of breast cancer in women with a CHEK2 mutation with and without a family history of breast cancer. J Clin Oncol 29:3747-52, 2011
19. Schmidt MK, Hogervorst F, van Hien R, et al: Age- and Tumor Subtype-Specific Breast Cancer Risk Estimates for CHEK2*1100delC Carriers. J Clin Oncol 34:2750-60, 2016
20. Gao C, Polley EC, Hart SN, et al: Risk of Breast Cancer Among Carriers of Pathogenic Variants in Breast Cancer Predisposition Genes Varies by Polygenic Risk Score. J Clin Oncol 39:2564-2573, 2021
21. Liu C, Zeinomar N, Chung WK, et al: Generalizability of Polygenic Risk Scores for Breast Cancer Among Women With European, African, and Latinx Ancestry. JAMA Netw Open 4:e2119084, 2021
22. Chen F, Chen GK, Stram DO, et al: A genome-wide association study of breast cancer in women of African ancestry. Hum Genet 132:39-48, 2013
23. Lee A, Mavaddat N, Wilcox AN, et al: BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors. Genet Med 21:1708-1718, 2019
24. Reiner AS, John EM, Brooks JD, et al: Risk of asynchronous contralateral breast cancer in noncarriers of BRCA1 and BRCA2 mutations with a family history of breast cancer: a report from the Women's Environmental Cancer and Radiation Epidemiology Study. J Clin Oncol 31:433-9, 2013
25. Robson ME, Reiner AS, Brooks JD, et al: Association of Common Genetic Variants With Contralateral Breast Cancer Risk in the WECARE Study. J Natl Cancer Inst 109, 2017
26. Kramer I, Hooning MJ, Mavaddat N, et al: Breast Cancer Polygenic Risk Score and Contralateral Breast Cancer Risk. Am J Hum Genet 107:837-848, 2020
27. Vachon CM, Scott CG, Tamimi RM, et al: Joint association of mammographic density adjusted for age and body mass index and polygenic risk score with breast cancer risk. Breast Cancer Res 21:68, 2019
28. Rosner B, Tamimi RM, Kraft P, et al: Simplified Breast Risk Tool Integrating Questionnaire Risk Factors, Mammographic Density, and Polygenic Risk Score: Development and Validation. Cancer Epidemiol Biomarkers Prev 30:600-607, 2021