Evaluation of a polygenic risk score as a predictor of early onset triple-negative breast cancer in Black women

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June 1, 2024

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Conclusions

- We demonstrated that a multiple-ancestry polygenic risk score (MA-385 PRS) identified those at increased risk of breast cancer (BC) in a large cohort of Black women.

- More specifically, MA-385 PRS identified young Black women at risk for triple negative breast cancer (TNBC) who had negative germline testing.

- At least half of those who developed cancer had no family history (FH) of breast or ovarian cancer.

- Women identified early could be offered enhanced surveillance and discussion of risk-reducing interventions (tamoxifen, weight management, reducing alcohol consumption, exercise, encouraging breastfeeding, etc).

BC, breast cancer; MA, multiple ancestry; TNBC, triple-negative breast cancer.
Conclusions

This study, amongst others, may encourage national guidelines to endorse the clinical use of polygenic scores that have been validated for African American women.
Background

- More accurate risk prediction methods are urgently needed to identify young Black women at increased risk of TNBC.

- TNBC is a particularly biologically aggressive BC subtype that occurs ~twice as often in Black women compared to White women.¹

- Breast cancer is more common and mortality rates are much higher in young Black women,¹,² before the age at which regular screening is recommended.

- BC occurs in this group often in the absence of family history.

## Age at BC Diagnosis by Race

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>All Races</th>
<th>NH White</th>
<th>NH Black</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–39</td>
<td>5%</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>40–49</td>
<td>14%</td>
<td>12%</td>
<td>16%</td>
</tr>
<tr>
<td>50–59</td>
<td>23%</td>
<td>22%</td>
<td>27%</td>
</tr>
<tr>
<td>60–69</td>
<td>28%</td>
<td>29%</td>
<td>26%</td>
</tr>
<tr>
<td>70–79</td>
<td>20%</td>
<td>21%</td>
<td>16%</td>
</tr>
<tr>
<td>80+</td>
<td>11%</td>
<td>13%</td>
<td>8%</td>
</tr>
</tbody>
</table>

BC, breast cancer; NH, non-Hispanic.
Background

• Unfortunately, FH documentation and risk assessment of young women is suboptimal in primary care and OB/GYN practices.\(^1\) Even when FH is collected and germline genetic testing is performed, hereditary mutations are usually not identified.

• Previous studies have shown that MA-385 PRS can identify women (of any ancestry) at increased risk of BC,\(^2\) independent of PV/LPV germline findings.

• Notably, incorporating PRS into clinical models substantially improves BC risk assessment.\(^3\)

2. Simmons, T. Presented at ASCO, 3 June 2024. Abstract 10533.  
Incorporating PRS helps identify many more women at increased risk of BC

100 unaffected women undergoing hereditary cancer testing

- 2-3 have pathogenic variants (PVs) in BC genes
- Of these, 1 develops BC

Multigene hereditary cancer panel:

- 34 determined to be high-risk
- Of these, 10 develop BC

However, PRS has not yet been incorporated into clinical care.

Per NCCN guidelines¹:

“There are significant limitations in the interpretation of polygenic risk scores (PRS). PRS should not be used for clinical management at this time and use is recommended in the context of a clinical trial, ideally including diverse populations.”

A primary barrier to the incorporation of PRS into clinical practice is concern about validity in non-European populations; this study (amongst others) specifically addresses this limitation.

Background

- Most PRS for BC risk stratification were developed and validated primarily in European women and had limitations in diverse populations.¹

- We previously described the MA-385 PRS based on 56 ancestry-informative and 329 BC single-nucleotide polymorphisms (SNPs), which is accurate for all ancestries.²

- MA-385 PRS predicts BC risk for diverse populations by characterizing a woman’s genetic ancestral composition and applying ancestry-specific SNP risks and frequencies.²

BC, breast cancer; MA, multiple ancestry; PRS, polygenic risk score; SNP, single nucleotide polymorphism.

Objective

• In the present study, we evaluated the ability of the MA-385 PRS to predict the risk of BC overall, TNBC specifically, and early onset disease in a large cohort of self-reported Black women who presented for multigene panel testing.

• Given the recently updated USPSTF screening recommendations, we also analyzed the group under the age of 40, at which time routine screening would commence.¹

Methods

• We examined clinical and genetic records from 17,529 self-reported Black women referred for multigene panel testing between Aug 2022 and Sept 2023, who were negative for pathogenic variants in BC-associated genes. Some were referred for a personal diagnosis of BC and others, for FH alone.

• The association of MA-385 PRS with BC risk overall and TNBC risk was analyzed using multivariable logistic regression adjusted for personal and family cancer history, age, and genetic ancestry.

• Analyses were conducted in the full cohort and in the subpopulations less than 50 years of age and less than 40 years of age.

BC, breast cancer; MA, multiple ancestry; TNBC, triple-negative breast cancer.
Cohort

- 17,529 women were included in the study, with 62% under age 50.
- 3,426 women (19.5%) had a personal history of BC and 629 (18.4% of patients with BC) had a personal history of TNBC.
- Of those diagnosed with TNBC, 27.5% were <50 years old, and 9.5% were <40 years old.

## Results: Family History in BC-Affected

Many women affected by BC had no family history of breast or ovarian cancer.

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>FH* of Breast Cancer</th>
<th>FH* of Ovarian Cancer</th>
<th>No FH* of Breast or Ovarian Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC at any age</td>
<td>3,426</td>
<td>1,637 (47.8%)</td>
<td>256 (7.5%)</td>
<td>1,675 (48.9%)</td>
</tr>
<tr>
<td>BC &lt;50</td>
<td>1,156</td>
<td>490 (42.4%)</td>
<td>88 (7.6%)</td>
<td>632 (54.7%)</td>
</tr>
<tr>
<td>BC &lt;40</td>
<td>374</td>
<td>148 (39.6%)</td>
<td>29 (7.8%)</td>
<td>216 (57.8%)</td>
</tr>
</tbody>
</table>

*Family history is defined as any first- or second-degree relative.*
Most women affected by TNBC had no family history of breast or ovarian cancer.

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>FH* of Breast Cancer</th>
<th>FH* of Ovarian Cancer</th>
<th>No FH* of Breast or Ovarian Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNBC at any age</td>
<td>629</td>
<td>267 (42.4%)</td>
<td>43 (6.8%)</td>
<td>341 (54.2%)</td>
</tr>
<tr>
<td>TNBC &lt;50</td>
<td>173</td>
<td>72 (41.6%)</td>
<td>10 (5.8%)</td>
<td>96 (55.5%)</td>
</tr>
<tr>
<td>TNBC &lt;40</td>
<td>60</td>
<td>23 (38.3%)</td>
<td>4 (6.7%)</td>
<td>35 (58.3%)</td>
</tr>
</tbody>
</table>

*Family history is defined as any first- or second-degree relative.
Results: Risk of overall BC in Black Women

- MA-385 significantly improved BC risk prediction over clinical factors alone in the overall cohort, in women <50 years of age, and in women <40 years of age.

- The top 5% of the MA-385 PRS distribution consistently identified women at a 2-fold or greater risk of BC compared to the average woman.

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>MA-385 PRS OR per SD (95% CI)</th>
<th>p-value</th>
<th>OR (95% CI) in top 5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC at any age</td>
<td>17,529</td>
<td>1.38 (1.31, 1.44)</td>
<td>1.8 x 10^{-43}</td>
<td>2.31 (1.91-2.81)</td>
</tr>
<tr>
<td>BC &lt;50</td>
<td>10,882</td>
<td>1.39 (1.30, 1.49)</td>
<td>1.2 x 10^{-21}</td>
<td>2.38 (1.80-3.15)</td>
</tr>
<tr>
<td>BC &lt;40</td>
<td>6,095</td>
<td>1.46 (1.30, 1.64)</td>
<td>1.1 x 10^{-10}</td>
<td>2.00 (1.27-3.16)</td>
</tr>
</tbody>
</table>

This effect on risk stratification was comparable to stratification based on all clinical factors.¹

Results: Risk of TNBC in Black Women

- MA-385 PRS significantly improved TNBC risk prediction over clinical factors in the overall cohort, in women <50 years of age, and in women <40 years of age.
- More than 5% of women were identified as having a 2-fold or greater risk of TNBC.

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>MA-385 PRS OR per SD (95% CI)</th>
<th>p-value</th>
<th>MA-385 PRS OR (95% CI) in top 5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNBC at any age</td>
<td>14,728</td>
<td>1.33 (1.21, 1.47)</td>
<td>2.1 × 10⁻⁹</td>
<td>2.13 (1.46, 3.12)</td>
</tr>
<tr>
<td>TNBC &lt;50</td>
<td>9,895</td>
<td>1.43 (1.22, 1.68)</td>
<td>1.2 × 10⁻⁵</td>
<td>2.56 (1.36, 4.84)</td>
</tr>
<tr>
<td>TNBC &lt;40</td>
<td>5,778</td>
<td>1.34 (1.03-1.73)</td>
<td>2.8 × 10⁻²</td>
<td>2.14 (0.72, 6.27)</td>
</tr>
</tbody>
</table>

This effect on risk stratification was comparable to stratification based on all clinical factors.¹

Results: Risk Reclassification

Incorporating the MA-385 PRS into the Tyrer-Cuzick (T-C) v.8 risk model led to the identification of 860 additional women (6.1%) with lifetime risk of ≥20%.

<table>
<thead>
<tr>
<th></th>
<th>T-C without incorporating MA-385 PRS</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;20%</td>
<td>≥20%</td>
</tr>
<tr>
<td>Combined T-C + MA-385 PRS</td>
<td>8,606 (61.0%)</td>
<td>1,209 (8.6%)</td>
</tr>
<tr>
<td></td>
<td>860 (6.1%)</td>
<td>3,424 (24.3%)</td>
</tr>
<tr>
<td>Total N (%)</td>
<td>9,466 (67.1%)</td>
<td>4,633 (32.9%)</td>
</tr>
</tbody>
</table>
Implications

• Ironically, the concern over the validity of polygenic risk scores in Black women is precluding clinical use of the MA-385 PRS in a population that may need it the most, perpetuating disparities in care.

• These findings may inform risk assessment and screening recommendations based on genetics and ancestry in addition to age.
~ Thank you ~

PANEL Q&A