**POLYGENIC SCORE PREDICTS EARLY ONSET TRIPLE-NEGATIVE BREAST CANCER IN BLACK WOMEN**

**Introduction**
- Black women in the US often develop more aggressive breast cancer (BC) at earlier ages compared to White women.
- Triple negative breast cancer (TNBC) is an especially aggressive form of BC which is twice as common in Black women than White women and often occurs earlier, before screening would be recommended [1].
- Improved risk prediction methods are urgently needed for more effective identification of young Black women with elevated risk of TNBC.

**Objectives**
- We previously described the development and clinical validation of a multiple-ancestry PRS (MA-PRS) that is based on individual genetic ancestral composition [2].
- MA-PRS has been integrated into the Tyrer-Cuzick model for use in clinical practice and has been shown to substantially improve BC risk prediction [3].
- Here, we evaluated the extent to which the MA-PRS can improve upon clinical factors for the prediction of TNBC and early onset (<50 years) TNBC, in a large cohort of self-reported Black women.

**Methods**
- We examined clinical and genetic records from self-reported Black/African women who were tested with next-generation sequencing for a multigene hereditary cancer panel from 2020 through December 2022 and were negative for pathogenic variants in genes associated with BC.
- MA-PRS was calculated as previously described based on 149 (93 BC and 56 ancestry-informative) SNPs.
- We tested correlation of the MA-PRS with BI-RADS breast density and other risk factors in version 8 of the Tyrer-Cuzick model.
- The association of MA-PRS with TNBC was analyzed using logistic regression adjusted for personal and family cancer history, age, and genetic ancestry.
- Odds ratios (ORs) were reported per standard deviation (SD). P-values were based on likelihood ratio chi-square statistics and reported as two-sided.

**Results**

**Table 1: Patient characteristics by analysis cohort**

<table>
<thead>
<tr>
<th></th>
<th>Full Cohort (N = 20,586)</th>
<th>&lt;50 years old (N = 13,987)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected with TNBC (%)</td>
<td>1,226 (6.0%)</td>
<td>427 (3.2%)</td>
</tr>
<tr>
<td>Age at TNBC Diagnosis</td>
<td>61 (26.4)</td>
<td>61 (25.9)</td>
</tr>
<tr>
<td>Median (years)</td>
<td>54</td>
<td>43</td>
</tr>
<tr>
<td>Family Cancer History*</td>
<td>543 (6.3%)</td>
<td>190 (4.5%)</td>
</tr>
<tr>
<td>Unaffected N (%)</td>
<td>13,363 (64.0%)</td>
<td>13,560 (96.9%)</td>
</tr>
</tbody>
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<th>Full Cohort (N = 20,586)</th>
<th>&lt;50 years old (N = 13,987)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Genetic Testing</td>
<td>14.44 (14.4)</td>
<td>14.49</td>
</tr>
<tr>
<td>Median (years)</td>
<td>42</td>
<td>38</td>
</tr>
<tr>
<td>Family Cancer History*</td>
<td>13,719 (71.1%)</td>
<td>9,994 (73.3%)</td>
</tr>
<tr>
<td>Unaffected N (%)</td>
<td>13,363 (64.0%)</td>
<td>13,560 (96.9%)</td>
</tr>
</tbody>
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*Any affected first- or second-degree relative

**Figure 1: The MA-PRS is independent from breast density**

- We identified 20,885 women who met the study eligibility criteria (Table 1).
- All patients self-reported Black/African ancestry.
- There were 1,226 (6.0%) women diagnosed with TNBC in the full cohort.
- More than one-third (427; 35%) of TNBC patients were under 50 at the time of diagnosis.
- All patients provided detailed information regarding family structure and cancer history. Data were more than 80% complete for other factors in version 8 of the Tyrer-Cuzick model except for BI-RADS breast density which was available for 1,115 women.
- The MA-PRS showed modest correlation with BC family history consistent with previous studies (r=0.09, p=0.002).
- The MA-PRS was independent from breast density (Figure 1) and other clinical factors in version 8 of the Tyrer-Cuzick model.
- MA-PRS significantly improved TNBC risk prediction over clinical factors in the full cohort, and in the subset population of women under 50 (Table 2).
- Women in the top 5% of the MA-PRS distribution were at nearly 2-fold increased risk of TNBC (Table 2).

**Conclusions**

These data show that the MA-PRS is effective at identifying Black women at risk of TNBC regardless of age, family history, or other clinical factors like breast density.

Clinical implementation of risk prediction models that incorporate MA-PRS may lead to improved outcomes through more effective identification of women at risk of TNBC.

**References**
2. Hughes et al., JCO PO 2022; e2200084