ANCESTRALLY UNBIASED POLYGENIC BREAST CANCER RISK ASSESSMENT

Presented by: Holly Pederson, MD

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Background

- Large-scale GWAS (N ~ 170,000) of European women have identified many variants (mainly single nucleotide polymorphisms, SNPs) associated with the development of breast cancer.

- Polygenic risk scores (PRSs) are powerful breast cancer risk prediction tools for European women.

- SNPs discovered through GWAS are typically not thought to be causal; they are linked (co-inherited) with causal variants.
Goal: To develop and validate PRS for women of all ancestries

- Define a PRS for all ancestries that combines 56 ancestry-specific SNPs with 93 selected breast cancer SNPs for a total of 149 SNPs.

- Achieve a high level of accuracy for all women in terms of:
  - Good risk discrimination
  - Accurate risk calibration
The challenge of using PRS across Ancestries

- SNP frequencies differ by ancestry.
  - Current PRSs are not properly calibrated for non-Europeans; i.e., risk estimates are overestimated for non-Europeans.

- Linkage between SNPs differs by ancestry.
  - Current PRSs have weaker discrimination for non-Europeans; i.e., less effective separation of high-versus low-risk individuals.
Distribution of a pre-defined 86-SNP PRS in clinically-tested patients

PRSs are artificially high among non-Europeans due to ancestry-specific differences in allele frequencies of high-risk breast cancer SNPs.

Any European-based PRS would therefore need to be recalibrated to avoid over-estimating breast cancer risk for non-European ancestries.
Discrimination of a pre-defined 86-SNP PRS in clinically-tested patients reporting a single ethnicity

<table>
<thead>
<tr>
<th>Self-Reported Ethnicity</th>
<th>N</th>
<th>P-Value</th>
<th>OR per SD (95% CI)</th>
<th>86-SNP PRS SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>10,334</td>
<td>2.4 x 10^{-11}</td>
<td>1.20 (1.14 - 1.27)</td>
<td>0.456</td>
</tr>
<tr>
<td>Asian</td>
<td>2,063</td>
<td>2.9 x 10^{-8}</td>
<td>1.42 (1.25 - 1.61)</td>
<td>0.419</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7,815</td>
<td>4.7 x 10^{-21}</td>
<td>1.39 (1.30 - 1.49)</td>
<td>0.441</td>
</tr>
<tr>
<td>White/Non-Hispanic</td>
<td>60,520</td>
<td>1.1 x 10^{-232}</td>
<td>1.45 (1.42 - 1.48)</td>
<td>0.448</td>
</tr>
</tbody>
</table>

For accurate risk prediction, any European-based PRS would therefore need to be re-engineered to account for differential risk discrimination across non-European ancestries.
Methods: Genetic ancestry

Continental Ancestry Decomposition
The major source ancestries of the contemporary US population are African, East Asian, and European.\textsuperscript{1-6}

The ancestry of any person can be measured by quantifying the relative continental components.

We selected 56 ancestral SNPs to quantify these 3 continental ancestries in a given subject.
Genetically-determined ancestry is diverse for non-Europeans

For each patient, ancestry-informative SNPs were used to calculate the fractional ancestry attributable to each of the 3 continents.

Self-Reported Ancestry:
- Hispanic
- Black/ African
- White/ Non-Hispanic
- Asian
PRS is informed by genetic ancestry

56 Ancestral SNPs
Selected to distinguish between Continental Ancestries: African, East Asian and European

93 Breast Cancer SNPs
(92 found in Europeans and 1 in Hispanics)

93 SNP selection was based on:
• The strongest SNPs for predicting breast cancer
• Relatively common across diverse ancestries
• Possible to estimate ancestry-specific effects for the 3 continental ancestries

African PRS
East Asian PRS
European PRS

Same SNPs
Different SNP Weights
Derived using data from myRisk commercial samples

PRS for all Ancestries
Sum of Continental PRS weighted by individual ancestry

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Methods: Determining ancestry-specific SNP weights

- African SNP weights were based on analysis of 31,126 self-reported African patients referred for hereditary cancer genetic testing.

- Asian SNP weights were based on Shu et al.,\textsuperscript{7} (from the Asian Breast Cancer Consortium) where available. European weights were used for remaining SNPs.

- European SNP weights were based on a meta-analysis of GWAS literature\textsuperscript{8} and self-reported White/non-Hispanic patients referred for hereditary cancer genetic testing as previously described.\textsuperscript{9}

- The weight of one protective Amerindian SNP\textsuperscript{10} was estimated from 9,322 self-reported Hispanic patients.
Methods: Validation in an independent cohort

• Primary Analysis:
  • Evaluate discrimination of the PRS developed for all ancestries in a large cohort independent from the development set.

• Secondary Analyses:
  • Test whether the PRS for all ancestries improved discrimination over the 86-SNP PRS in the full cohort.
  • Repeat above analyses in sub-cohorts defined by self-reported ancestry.

• Exploratory Analyses:
  • Confirm that the PRS for all ancestries is centered around zero for unaffected patients overall and in each subpopulation except carriers of the protective Amerindian SNP.
## Results: Clinical characteristic by analysis cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Variable</th>
<th>Development</th>
<th>Independent Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>N</td>
<td>189,230</td>
<td>89,126</td>
</tr>
<tr>
<td><strong>Personal History of Breast Cancer (BC)</strong></td>
<td>N (%)</td>
<td>43,444 (23.0%)</td>
<td>20,323 (22.8%)</td>
</tr>
<tr>
<td><strong>First-Degree Relative w/ BC</strong></td>
<td>N (%)</td>
<td>57,741 (30.5%)</td>
<td>27,181 (30.5%)</td>
</tr>
<tr>
<td><strong>Age at Testing</strong></td>
<td>Range</td>
<td>18-84</td>
<td>18-84</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>47</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>% ≤ 50</td>
<td>58.8%</td>
<td>60.8%</td>
</tr>
<tr>
<td><strong>Age at BC Diagnosis</strong></td>
<td>Range</td>
<td>18-84</td>
<td>18-84</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>46</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>% ≤ 50</td>
<td>62.5%</td>
<td>64.0%</td>
</tr>
</tbody>
</table>
## Results: Clinical characteristic by analysis cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Variable</th>
<th>Development (n = 189,230)</th>
<th>Independent Validation (n = 89,126)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Self-Reported Ethnicity N (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ashkenazi Jewish</td>
<td>2,487 (1.3%)</td>
<td>981 (1.1%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>4,044 (2.1%)</td>
<td>2,063 (2.3%)</td>
<td></td>
</tr>
<tr>
<td>Black/ African</td>
<td>19,460 (10.3%)</td>
<td>10,334 (11.6%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>17,749 (9.4%)</td>
<td>7,815 (8.8%)</td>
<td></td>
</tr>
<tr>
<td>Middle Eastern</td>
<td>860 (0.5%)</td>
<td>406 (0.5%)</td>
<td></td>
</tr>
<tr>
<td>Multiple Ancestries</td>
<td>4,079 (2.2%)</td>
<td>2,020 (2.3%)</td>
<td></td>
</tr>
<tr>
<td>Native American</td>
<td>530 (0.3%)</td>
<td>241 (0.3%)</td>
<td></td>
</tr>
<tr>
<td>Other/ Unspecified</td>
<td>7,581 (4.0%)</td>
<td>3,356 (3.8%)</td>
<td></td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>302 (0.2%)</td>
<td>143 (0.2%)</td>
<td></td>
</tr>
<tr>
<td>White/ Non-Hispanic</td>
<td>124,650 (65.9%)</td>
<td>58,051 (65.1%)</td>
<td></td>
</tr>
</tbody>
</table>
Results: European-derived breast cancer SNPs are common to all ancestries

- At least 95% of breast cancer SNPs have a ≥1% frequency of risk alleles within each of the self-reported patient populations:

  - African (89/93)
    - 96%
  - Asian (88/93)
    - 95%
  - Hispanic (91/93)
    - 98%
### Results: Discrimination

<table>
<thead>
<tr>
<th>Validation Cohort</th>
<th>Total N</th>
<th>N w/ BC</th>
<th>OR per SD (95% CI)</th>
<th>P-value</th>
<th>Average OR per SD in Top Decile</th>
<th>Average OR per SD in Top 1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>White and/or Ashkenazi</td>
<td>60,520</td>
<td>13,880</td>
<td>1.45 (1.42 – 1.49)</td>
<td>4.2 x 10^{-235}</td>
<td>1.94</td>
<td>2.71</td>
</tr>
<tr>
<td>Asian</td>
<td>2,063</td>
<td>613</td>
<td>1.45 (1.28 - 1.63)</td>
<td>2.2 x 10^{-9}</td>
<td>1.94</td>
<td>2.71</td>
</tr>
<tr>
<td>Black/African</td>
<td>10,334</td>
<td>2,425</td>
<td>1.23 (1.17 - 1.30)</td>
<td>2.5 x 10^{-14}</td>
<td>1.44</td>
<td>1.74</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7,815</td>
<td>1,334</td>
<td>1.46 (1.36 - 1.57)</td>
<td>2.5 x 10^{-25}</td>
<td>1.97</td>
<td>2.76</td>
</tr>
<tr>
<td>Mixed Ancestry</td>
<td>4,126</td>
<td>560</td>
<td>1.54 (1.38 - 1.72)</td>
<td>1.1 x 10^{-14}</td>
<td>2.17</td>
<td>3.19</td>
</tr>
<tr>
<td>Non-European</td>
<td>21,668</td>
<td>4,660</td>
<td>1.35 (1.30 –1.41)</td>
<td>2.0 x 10^{-47}</td>
<td>1.71</td>
<td>2.24</td>
</tr>
<tr>
<td>All</td>
<td>89,126</td>
<td>20,323</td>
<td>1.43 (1.40 – 1.46)</td>
<td>8.6 x 10^{-308}</td>
<td>1.90</td>
<td>2.61</td>
</tr>
</tbody>
</table>

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Results:

As intended, the PRS for all ancestries is centered around zero for unaffected patients, except for self-reported Hispanic patients where we see a slight shift due to the protective Amerindian SNP.
Protective effect of the Amerindian SNP

Looking more closely at self-reported Hispanic patients, we see that the PRS is centered around zero for patients who do not carry the protective Amerindian SNP and shifted toward lower risk for carriers.
Summary

• We developed a framework for a PRS that is accurate for women of all ancestries and can be adapted as additional data becomes available.

• This clinically validated PRS provides calibrated genomic risk discrimination for all women.
Thank you for your time!
References


