Integration of an Ancestry-Inclusive Polygenic Risk Score with the Tyrer-Cuzick Breast Cancer Risk Model

Elisha Hughes, PhD[1]; Ryan Bernhisel, MStat[1]; Holly Pederson, MD[2]; Braden Probst, MStat[1]; Timothy Simmons, MStat[1]; Susanne Wagner, PhD[1]; Susan M. Domchek, MD[3]; Charis Eng, MD, PhD[2]; Judy Garber, MD, MPH[4]; Monique Gary, DO, FACS[5]; Ora Gordon, MD[6]; Jennifer Klemp, PhD, MPH[7]; Semanti Mukherjee, PhD[8]; Kenneth Offitt, MD[8]; Olufunmilayo I. Olopade, MD[9]; Joseph Vijai, PhD[8]; Jeffrey N. Weitzel, MD[10]; Pat Whitworth, MD, FACS, FSSO[11]; Lamis Yehia, PhD[2]; Allison Kurian, MD, MSc[12]; Mark Robson, MD[8]; Thomas P. Slavin, MD[1]; Alexander Gutin, PhD[1]; Jerry S. Lanchbury, PhD[1]

1. Myriad Genetics, Inc., Salt Lake City, UT USA 2. Cleveland Clinic, Cleveland, OH, USA 3. University of Pennsylvania School of Medicine, Philadelphia, PA, USA 4. Dana-Farber Cancer Institute, Boston, MA, USA 5. Grand View Health, Sellersville, PA, USA 6. Providence Health and Services, Renton, WA, USA 7. The University of Kansas Medical Center, Kansas City, KS, USA 8. Memorial Sloan Kettering Cancer Center, New York, NY, USA 9. University of Chicago, Chicago, IL, USA 10. Latin American School of Oncology, Sierra Madre, CA 11. Nashville Breast Center, Nashville, TN, USA 12. Stanford University School of Medicine, Stanford, CA, USA

BACKGROUND

- Predisposition to breast cancer has a substantial genetic component that can be used to inform risk prediction and personalized preventive measures.
- Aside from monogenic mutations, genetic risk is estimated from polygenic risk scores (PRSs) which aggregate common risk variants, mainly single-nucleotide polymorphisms (SNPs) identified in genome-wide association studies.[1] To date, these PRSs are largely derived from studies in women of European descent and such PRSs have poor performance in non-European ancestries.[2]
- We recently developed and validated a 149-SNP PRS for women of diverse backgrounds who were negative for pathogenic variants in breast cancer (BC) susceptibility genes.[3] The 149-SNP PRS incorporates 56 ancestry-informative variants with 93 BC-associated variants. It was significantly associated with BC risk after accounting for family cancer history.
- Here, we combine the 149-SNP PRS with version 7 of the clinical and family history-based Tyrer-Cuzick (TC) model.

METHODS

CRS DEVELOPMENT

- A Combined Risk Score (CRS), incorporating the 149-SNP PRS and the TC model, was developed based on a cohort of 145,786 women who were unaffected by breast cancer (Table 1).
  - We examined associations between the 149-SNP PRS and each clinical risk factor in the TC model using linear regression.
  - CRS development followed a previously described Fixed-Stratified method[4] to avoid double-counting risk between confounded factors, in particular, between the 149-SNP PRS and family cancer history.

INDEPENDENT CRS EVALUATION

- A cohort of 68,803 unaffected women, independent from CRS development, was used to evaluate CRS calibration and risk stratification (Table 1).
  - We tested CRS calibration against TC by comparing average risk in the full cohort, and within each self-reported ancestry.
  - We examined relative contributions of the 149-SNP PRS, family history, and other clinical factors to CRS.
  - We compared differences in classification of women as high (>20%) versus low/moderate (≤20%)[5] remaining lifetime risk (RLR) according to TC versus CRS.

Table 1. Patient Characteristics

Characteristic	Variable	Development Cohort (N=145,786)	Independent Evaluation Cohort (N=68,803)
First-Degree Relative(s) with BC	N (%)	45,161 (31.0%)	21,500 (31.2%)
Age at Testing (years)	Range	18-84	18-84
	Median	44	43
	%≤50	68.5%	70.7%
Self-Reported Ancestry	Asian	2,818 (1.9%)	1,450 (2.1%)
	Black/ African	14,585 (10.0%)	7,909 (11.5%)
	European*	100,688 (69.1%)	46,640 (67.8%)
	Hispanic	14,822 (10.2%)	6,481 (9.4%)
	All Others	12,873 (8.8%)	6,323 (9.2%)

*Includes White/Non-Hispanic, and/or Ashkenazi Jewish

RESULTS

Figure 1. Calibration of CRS

Remaining lifetime risk (RLR) as predicted by the CRS and by TC, grouped by quartiles of TC RLR. Calibration is shown by the equivalency of average RLR by CRS and TC.

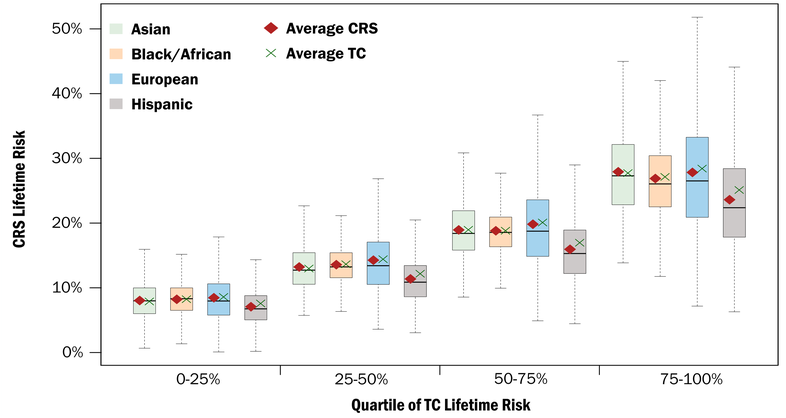


Figure 2. Relative Contributions of Risk Factors to CRS

Family history, other TC factors, and the 149-SNP PRS were added sequentially to an ANOVA model. Percentages were calculated from the total sum of squares.

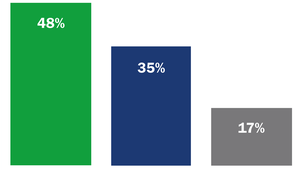
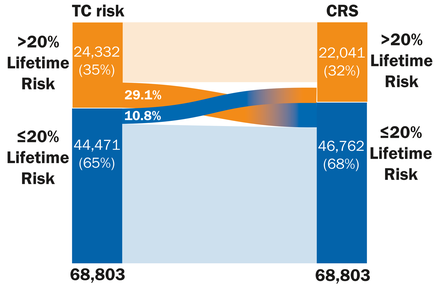


Figure 3. Risk Reclassification



- Family history was highly significant, but weakly correlated with the 149-SNP PRS (r=0.08; $p=6.3x10^{-95}$). After adjusting for multiple testing, no other TC factors were associated with the 149-SNP PRS.
- CRS was well calibrated among all ancestries and across percentiles of risk (Figure 1). Average absolute lifetime risks by CRS were similar to those from the TC model, with the exception of Hispanic carriers of a protective Amerindian SNP who were lower risk by CRS.
- After accounting for family history and clinical factors in TC, the PRS component explained 35% of CRS variability (Figure 2).
- Adding PRS to TC significantly altered breast cancer risks for all ancestries, with 17.3% of patients classified differently by CRS vs TC alone (Table 2, Figure 3).
- Among patients who were classified as high-risk by TC, 29.1% were downgraded by CRS.

Table 2. Risk Reclassification by Ancestry

Self-Reported Ancestry	Number (%) of Patients	High TC	High CRS	High TC / Low CRS	High CRS/ Low TC
All	68,803 (100%)	24,332 (35.4%)	22,041 (32.0%)	7,080 (10.3%)	4,789 (7.0%)
Asian	1,450 (2.1%)	487 (33.6%)	475 (32.8%)	94 (6.5%)	82 (5.7%)
Black/African	7,909 (11.5%)	2,540 (32.1%)	2,473 (31.3%)	435 (5.5%)	368 (4.7%)
European*	46,640 (67.8%)	17,507 (37.5%)	15,733 (33.7%)	5,328 (11.4%)	3,554 (7.6%)
Hispanic	6,481 (9.4%)	1,614 (24.9%)	1,345 (20.9%)	606 (9.4%)	346 (5.3%)

*Includes White/Non-Hispanic, and/or Ashkenazi Jewish

CONCLUSIONS

- This is the first breast cancer risk model based on a polygenic score, the 149-SNP PRS, which incorporates genetically determined ancestral composition and is validated for diverse ancestries.
- Combining the 149-SNP PRS with TC substantially improved risk stratification over TC alone and may therefore lead to enhanced breast cancer risk reduction strategies such as increased surveillance and use of preventive medications.

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