A Breast Cancer Risk Model Incorporating Tyrer-Cuzick Version 8 and a Polygenic Risk Score for Diverse Ancestries

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Abstract # 557

BACKGROUND

- Breast cancer (BC) risk assessment is important for guiding personalized screening and preventive interventions.
- In clinical practice, Tyrer-Cuzick Version 8 (TCv8) is used to estimate BC risk based on age, breast density, family cancer history, and other clinical factors.
- Accuracy may be improved by combining TCv8 with a polygenic risk score (PRS).
- We recently developed and validated a PRS for diverse ancestries based on 149 common genetic variants (PRS-149).
- PRS-149 incorporates 56 ancestry-informative and 93 BC-associated variants.
- Here, we describe a BC risk model that combines PRS-149 with TCv8 (CRS).
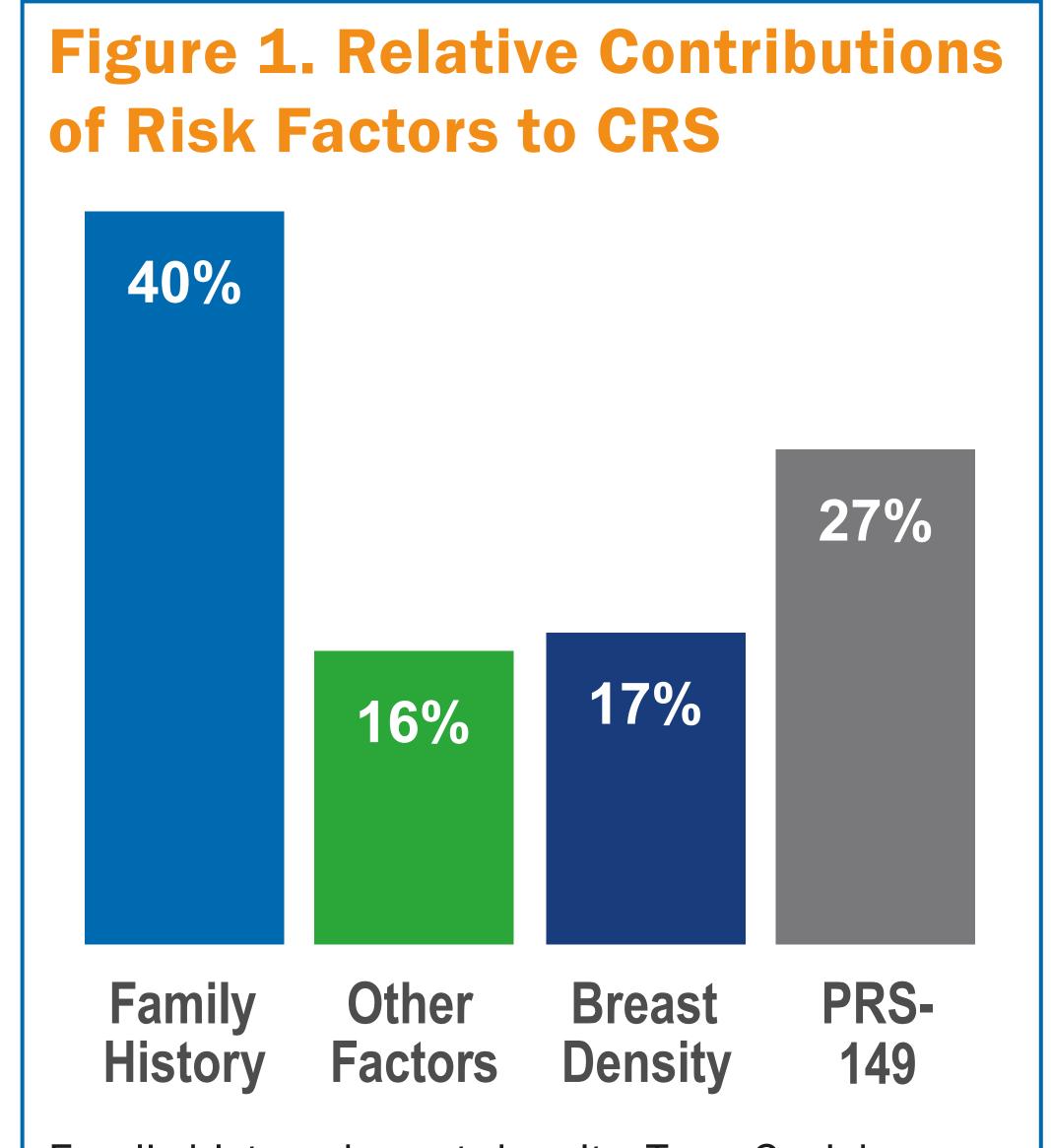
METHODS

- Study subjects were referred for hereditary cancer testing and negative for pathogenic variants in BC susceptibility genes.
- A development cohort of 12,363 women with Breast Imaging Reporting and Data System (BI-RADS) breast density measurements was used to test the extent to which breast density and PRS-149 improve BC risk stratification over family history and other clinical factors.
- Even though PRS-149 uses ancestry-specific SNPs to guide the reported risk value, sub-cohorts herein were grouped for analyses based on self-reported ethnicity.
- We used multivariable logistic regression to test breast density and PRS-149 for association with risk of BC.
- An independent test cohort of 6,030 women with BI-RADS assessment was used to evaluate risk stratification.
- Relative contributions of family history, breast density, other clinical factors in TCv8, and PRS-149 were examined by adding terms sequentially to an ANOVA model.
- We compared differences in classification of women as high (>20%) versus low/moderate (≤20%) remaining lifetime risk according to TCv8 versus CRS.
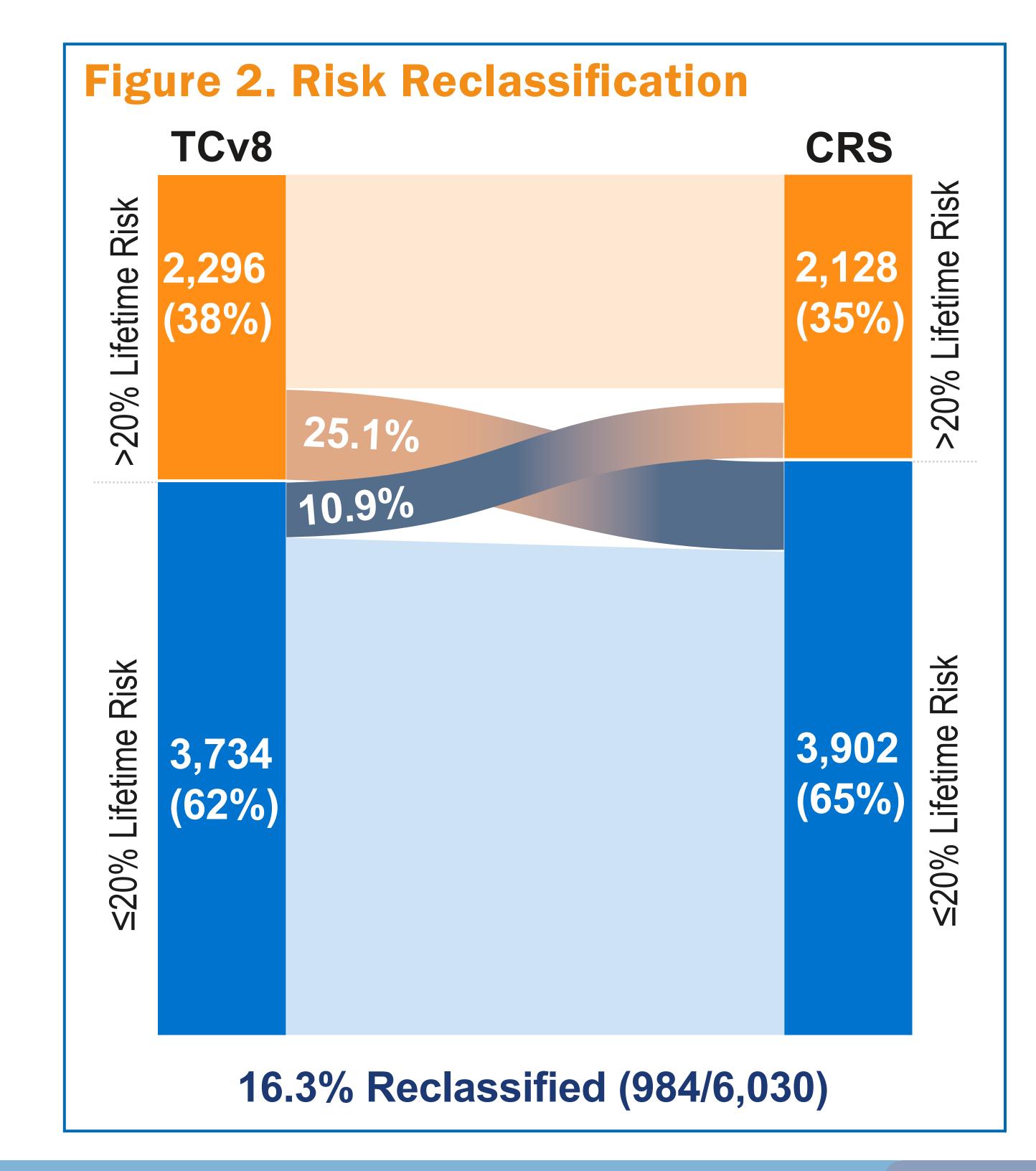
RESULTS

Table 1. Patient Demographics

Characteristic	Variable	Development Cohort		Independent Evaluation Cohort
		All Patients (N = 12,363)	BC Unaffected (N = 11,554)	BC Unaffected (N = 6,030)
First-Degree Relative(s) with BC	N	5,029	4,812	2,490
	(%)	40.68%	41.65%	41.29%
Age at Testing (years)	Range	18-84	18-84	19-83
	Median	49	49	48
	%≤50	55.48%	55.06%	59.65%
Self-Reported Ancesty	Asian	254 (2.05%)	228 (1.97%)	137 (2.27%)
	Black/ African	856 (6.92%)	782 (6.77%)	420 (6.97%)
	European*	9,481 (76.69%)	8,920 (77.20%)	4,635 (76.87%)
	Hispanic	806 (6.52%)	746 (6.46%)	359 (5.95%)
	All Others	966 (7.81%)	878 (7.60%)	479 (7.94%)

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

Figure 1. Relative Contributions of Risk Factors to CRS

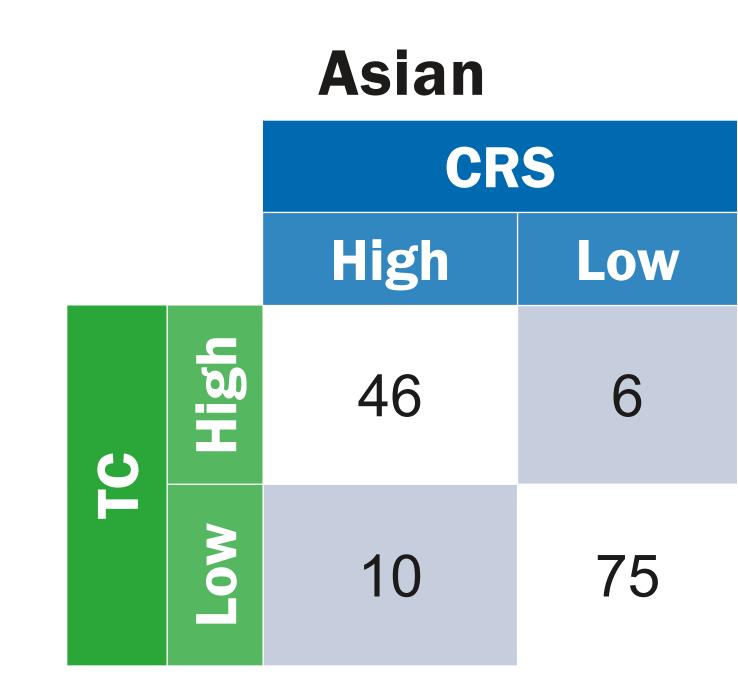| Family History	Other Factors	Breast Density	PRS-149
40%	16%	17%	27%

Family history, breast density, Tyrer-Cuzick clinical factors, and the PRS-149 scores were added sequentially to an ANOVA model. PRS-149 explained 27% of the CRS after accounting for family history, other clinical factors, and breast density.
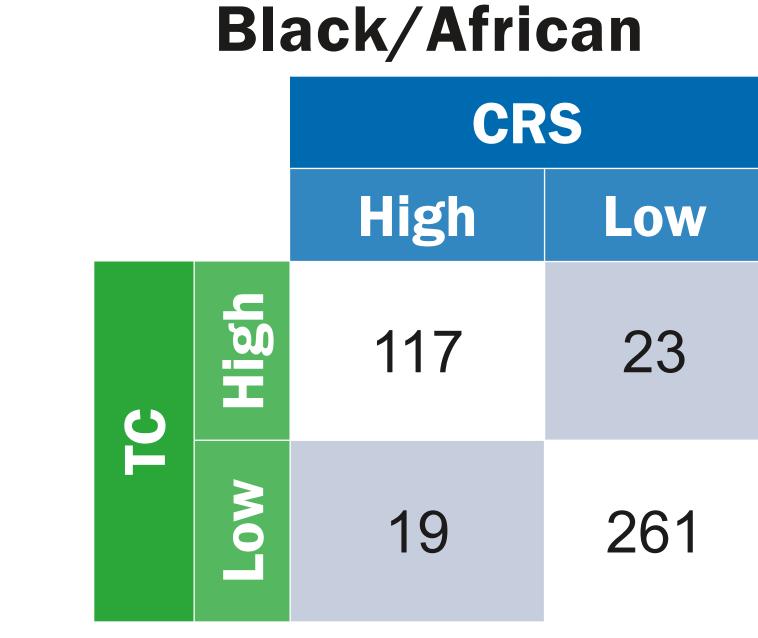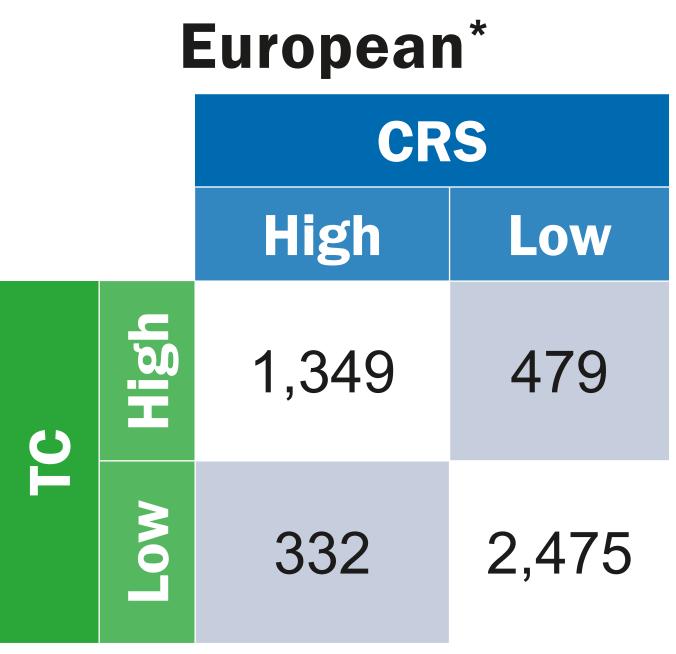
Figure 2. Risk Reclassification

TCv8 | CRS

>20% Lifetime Risk: 2,296 (38%) → 2,128 (35%)
25.1%
10.9%
≤20% Lifetime Risk: 3,734 (62%) → 3,902 (65%)

16.3% Reclassified (984/6,030)

- In the development cohort, increased breast density was significantly associated with higher risk of BC (p=2.4x10^{-6}) with an effect size consistent with its weighting in TCv8.
- PRS-149 improved BC risk stratification over age, breast density, and family history (OR per unit standard deviation: 1.40, 95% CI: 1.36–1.45; p: 3.7x10^{-6}).
- PRS-149 was weakly but significantly correlated with both family history (r=0.08) and breast density (r=0.01).
- After adjusting for multiple testing, no other factors were significantly correlated with PRS-149.
- In the independent test cohort, PRS-149 explained 27% of CRS variability after accounting for family history, breast density, and other clinical factors (Figure 1).
- Adding PRS-149 to TCv8 significantly altered risk estimates for women of all ancestries, with 16.3% of patients classified differently by CRS versus TCv8 In the independent test cohort (Table 2).
- Among patients who were classified as high-risk by TCv8 in the independent test cohort, 25.1% were downgraded by CRS and, among patients classified as low/moderate by TCv8, 10.9% were upgraded by CRS (Figure 2).

Table 2. Risk Reclassification by Ancestry

Asian

		CRS	
		High	Low
TC	High	46	6
	Low	10	75

Black/African

		CRS	
		High	Low
TC	High	117	23
	Low	19	261

Hispanic

		CRS	
		High	Low
TC	High	60	32
	Low	16	251

European*

		CRS	
		High	Low
TC	High	1,349	479
	Low	332	2,475

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

CONCLUSIONS

- **This is the first BC risk model that includes breast density, family history, and a PRS based on genetically determined ancestry that is validated for diverse populations.**
- **The addition of PRS-149 substantially improved risk stratification over TCv8 alone and may therefore lead to enhanced BC risk reduction and early detection strategies such as preventive medications and increased surveillance, respectively.**

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