Breast Risk Reveal™

Impact of Integrated Polygenic Risk, Monogenic Variants and Tyrer-Cuzick Risk Models on Breast Cancer Risk Stratification

Overview

Allelica's Breast Risk Reveal provides a unified, clinically validated framework for genetic risk assessment that integrates monogenic variant interpretation, ancestry-informed polygenic risk scores (PRS) and clinical risk modeling utilizing Tyrer-Cuzick (TC). Monogenic variants are classified using the Allelica Monogenic interpretation software, PRS values are computed using the Allelica PREDICT platform, and clinical factors are incorporated using an extended Tyrer-Cuzick approach recalibrated to U.S. incidence rates.

Together, these components enable comprehensive breast cancer risk assessment that captures genetic and non-genetic contributions and quantifies their combined impact on reclassification, calibration, and clinical decision thresholds. We examined PRS effects in two complementary contexts: (1) among carriers of pathogenic monogenic variants and (2) within the Tyrer-Cuzick clinical model to assess reclassification performance.

Results: Integration of Polygenic Risk with Monogenic Variants

To evaluate the relationship between PRS and breast cancer risk in individuals carrying pathogenic variants, analyses were performed across three large and independent cohorts:

- **All of Us Research Program** (whole-genome sequencing - AoU)
- **UK Biobank** (high-coverage exome sequencing - UKBB)
- **CIMBA** (curated registry of BRCA1/2 carriers)

Cox proportional hazards models were used to assess time-to-event associations within each gene-carrier group (**BRCA1**, **BRCA2**, **CHEK2**, **ATM**, **PALB2**, **BARD1**, and **RAD51C/D**), adjusting for age and ancestry-informative principal components. Only carriers of pathogenic or likely pathogenic variants were included, and analyses focused on incident breast cancer cases.

When pooling results across cohorts, PRS is significantly associated with breast cancer risk for all monogenic variant categories, with the strongest effect on moderate penetrance variants (**OR**

1.8 [1.5 - 2.2]). The magnitude and rank order of carrier ORs were consistent with previously published large-scale studies (Dorling et al., *NEJM*, 2021; Mavaddat et al., *JAMA*, 2019).

AoU

Gene	# Carriers	# Cases	PRS OR x SD (95% CI)	Age OR (95% CI)	Carrier OR (95% CI)
ATM	403	50	1.90 (0.96-3.75)	1.05 (1.01-1.08)	1.94 (1.44-2.62)
BARD1	78	14	4.94 (1.00-24.54)	1.08 (1.00-1.15)	2.95 (1.64-5.32)
BRCA1	252	104	0.96 (0.55-1.67)	1.02 (1.00-1.04)	10.29 (7.94-13.34)
BRCA2	468	143	1.32 (0.89-1.96)	1.00 (0.98-1.02)	6.14 (5.02-7.52)
CHEK2	153	19	1.69 (0.63-4.50)	1.06 (1.00-1.11)	1.69 (1.04-2.74)
PALB2	145	30	2.24 (0.91-5.51)	1.00 (0.96-1.04)	3.86 (2.56-5.81)
RAD51C	59	6	1.73 (0.31-9.63)	1.06 (0.95-1.18)	1.46 (0.62-3.43)
RAD51D	40	4	NA	1.04 (0.92-1.18)	1.48 (0.52-4.20)

Table 1 - Polygenic and monogenic effect on the AoU carriers cohort

CIMBA

Gene	# Carriers	# Cases	PRS OR x SD (95% CI)	Age OR (95% CI)	Carrier OR (95% CI)
BRCA1	6517	3152	1.23 (1.13-1.34)	1.01 (1.00-1.02)	NA
BRCA2	4306	2116	1.42 (1.27-1.58)	0.97 (0.95-0.99)	NA

Table 2 - Polygenic effect on the CIMBA cohort

UKBB

Gene	# Carriers	# Cases	PRS OR x SD (95% CI)	Age OR (95% CI)	Carrier OR (95% CI)
ATM	579	114	1.59 (1.22-2.08)	1.03 (1.00-1.06)	2.69 (2.18-3.31)
BRCA1	165	72	1.19 (0.80-1.75)	1.00 (0.96-1.04)	9.46 (6.93-12.92)
BRCA2	498	170	1.34 (1.05-1.71)	1.02 (1.00-1.05)	6.01 (4.98-7.26)
BRIP1	135	16	2.35 (1.21-4.57)	1.01 (0.94-1.08)	1.48 (0.87-2.50)
CHEK2	429	52	1.76 (1.23-2.53)	1.06 (1.02-1.11)	1.50 (1.12-2.00)
PALB2	283	69	1.68 (1.17-2.40)	1.02 (0.99-1.06)	3.60 (2.74-4.74)

Gene	# Carriers	# Cases	PRS OR x SD (95% CI)	Age OR (95% CI)	Carrier OR (95% CI)
RAD51C	69	8	2.42 (0.74-7.89)	1.00 (0.91-1.10)	1.46 (0.70-3.07)
RAD51D	56	10	3.37 (1.13-10.05)	1.01 (0.92-1.11)	2.37 (1.19-4.71)

Table 3 - Polygenic and monogenic effect on the UKBB carriers cohort

Meta analysis

Penetrance	PRS OR (95% CI)	Carrier OR (95% CI)	Total Carriers	Cases
High	1.30 [1.21-1.39]	7.61 [5.81-9.98]	12206	5757
PALB2	1.75 [1.25-2.44]	3.68 [2.93-4.62]	428	99
Moderate	1.80 [1.50-2.16]	1.95 [1.61-2.36]	2014	296

Table 4 - Polygenic and monogenic effect on the meta analysis, combining monogenic variants by penetrance group

Meta analysis by gene

Gene	PRS OR (95% CI)	Carrier OR (95% CI)	Total Carriers	Cases
ATM	1.63 [1.27-2.09]	2.33 [1.69-3.20]	982	164
BRCA1	1.22 [1.12-1.33]	9.94 [8.14-12.13]	6934	3328
BRCA2	1.40 [1.27-1.54]	6.07 [5.29-6.97]	5272	2429
CHEK2	1.75 [1.25-2.46]	1.55 [1.21-1.99]	582	71
PALB2	1.75 [1.25-2.44]	3.68 [2.93-4.62]	428	99
RAD51C	2.17 [0.82-5.76]	1.46 [0.83-2.55]	128	14
RAD51D	3.67 [1.30-10.36]	2.06 [1.16-3.65]	96	14

Table 5 - Polygenic and monogenic effect on the meta analysis by single gene

To illustrate the modifying effect of polygenic background, we plotted lifetime breast cancer risk among carriers of moderate-penetrance variants across PRS percentiles (Figure 1). The addition of PRS shifts individual risk estimates across clinically actionable boundaries, with 54% of carriers moving above and 46% below the 20% MRI screening threshold. The distribution also sharpens the separation around the 30% lifetime-risk level relevant to surgical decision-making. The figure reveals a smooth gradient of risk modulated by PRS, converting categorical carrier status into a continuous risk spectrum.

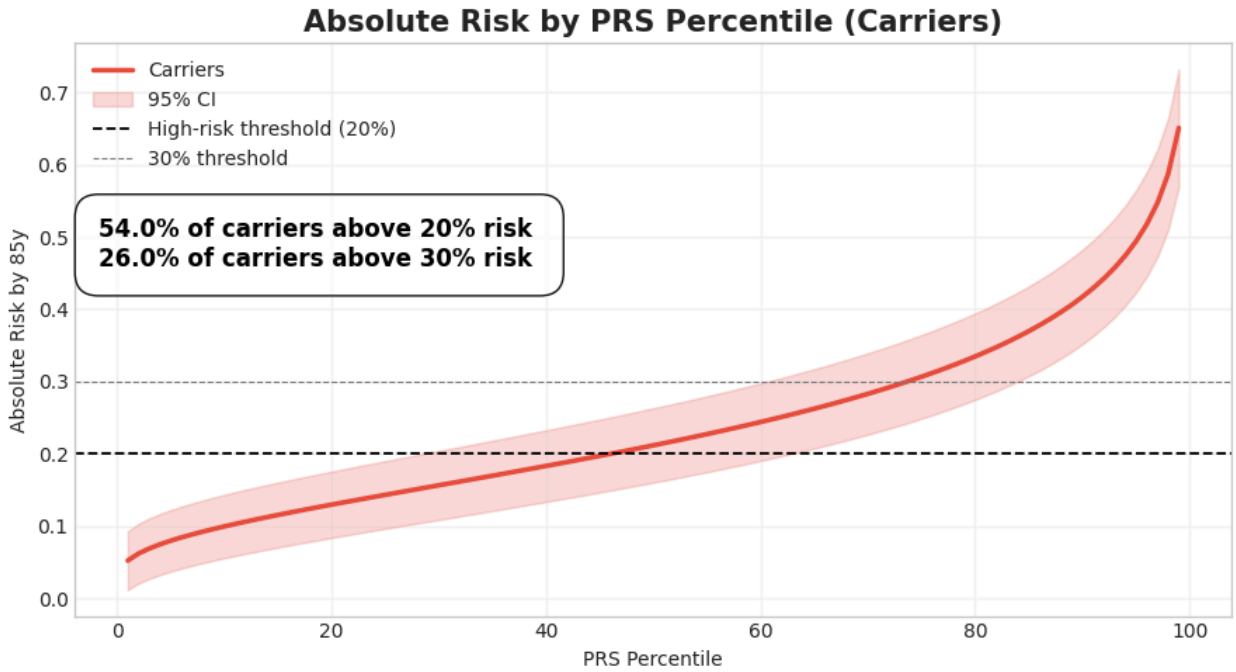

Figure 1 - Polygenic risk score reclassifies lifetime breast cancer risk among carriers of moderate-penetrance variants.

To confirm that adding PRS improved model calibration, we used the Brier score to compare the risk estimation with and without PRS (lower is better). As shown in the table below, PRS integration consistently reduced Brier scores across all genes, including high-penetrance genes like *BRCA1*, with all improvements reaching statistical significance ($p < 0.05$).

Gene	P-value PRS	Brier score		
		No PRS	With PRS	Δ
ATM	1.65E-208	0.106439	0.106318	0.000121
BARD1	4.46E-208	0.106388	0.106261	0.000126
BRCA1	2.81E-207	0.106339	0.1062	0.000139
BRCA2	8.25E-207	0.106235	0.106112	0.000123
CHEK2	1.14E-207	0.106419	0.106283	0.000136
PALB2	5.19E-208	0.106446	0.106316	0.00013
RAD51C	6.09E-208	0.106365	0.10623	0.000135
RAD51D	6.60E-208	0.106375	0.106238	0.000137

Table 7 - Calibration measured by brier score on the meta analysis by single gene

Finally, to visually evaluate model calibration, we generated a calibration plot using data from a meta-analysis of 2,014 pathogenic variant carriers, including individuals from both the UK Biobank (UKBB) and All of Us (AoU) cohorts, among whom 296 were cases. The x-axis represents observed disease risk, while the y-axis indicates the predicted risk from the model. Perfect calibration is illustrated by the 45-degree identity line (x=y). Confidence intervals that intersect this line indicate regions where the model is well-calibrated.

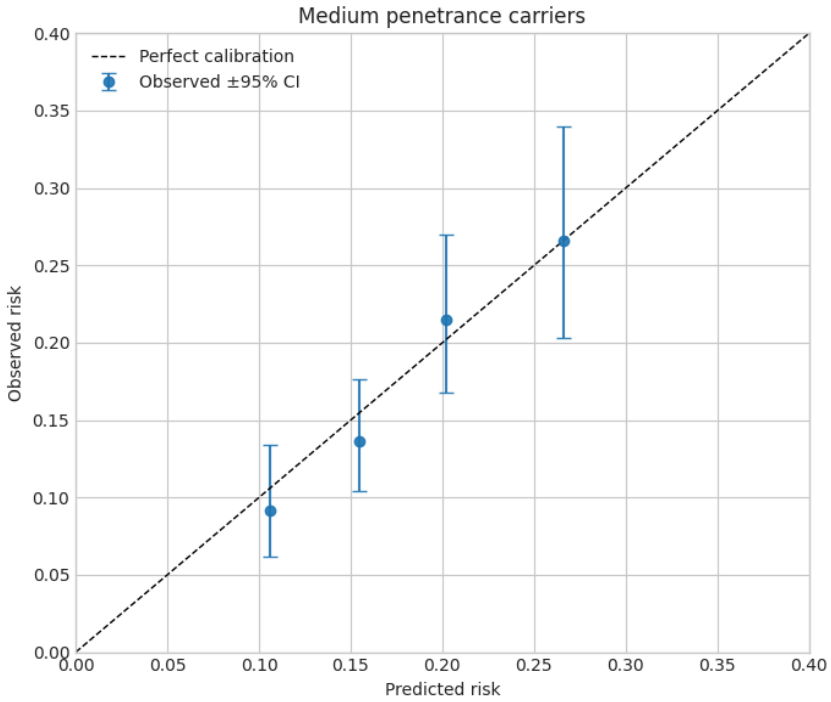

Figure 2 - Calibration of polygenic risk predictions in carriers of moderate-penetrance variants.

Benchmarking PRS Performance

To benchmark the performance of the Allelica breast cancer PRS against established models, we conducted a comparative analysis using individuals from both the All of Us and UK Biobank cohorts, grouped by ancestry in a unified meta-study. As the widely used 313-variant score from Mavaddat et al. is not fully available across all datasets, we implemented a harmonized version consisting of 306 original variants supplemented by four high-LD proxies. These proxies were selected to maintain maximal fidelity to the published MAV313 architecture while ensuring full compatibility with the genotyping and sequencing data available in both cohorts.

This harmonized score (BC313) was computed alongside the Allelica PRS for all individuals included in the meta-analysis. Results for the All of Us cohort are summarized in Table 8, while Table 9 reports the corresponding estimates obtained in the UK Biobank using the same covariate-adjusted models. To integrate evidence across both populations, we combined the

ancestry-specific effect sizes using inverse-variance weighting, yielding pooled estimates for overall discrimination and calibration. These meta-analytic results are presented in Table 10, providing a unified benchmark of PRS performance across cohorts and ancestry groups.

AoU

PRS	Ancestry	Cases	Controls	ORxSD	Brier
Allelica Multi Ancestry	African	1,238	35,359	1.35 (1.30-1.40)	0.045440
BC313	African	1,238	35,359	1.26 (1.19-1.34)	0.046338
Allelica Multi Ancestry	Asian	216	5,698	1.52 (1.45-1.59)	0.032853
BC313	Asian	216	5,698	1.49 (1.15-1.92)	0.036433
Allelica Multi Ancestry	European	6,431	91,222	1.65 (1.64-1.66)	0.056548
BC313	European	6,431	91,222	1.43 (1.40-1.47)	0.058245
Allelica Multi Ancestry	Admixed	1,592	43,384	1.56 (1.46-1.68)	0.051318
BC313	Admixed	1,592	43,384	1.40 (1.23-1.60)	0.059623

Table 8 - PRS performance comparison on AoU

UK Biobank

PRS	Ancestry	Cases	Controls	ORxSD	Brier
Allelica Multi Ancestry	African	120	2,498	1.7 (1.36–2.03)	0.0425
BC313	African	120	2,498	1.53 (1.23–1.82)	0.0428
Allelica Multi Ancestry	Asian	189	2,677	1.81 (1.41–2.20)	0.05895
BC313	Asian	189	2,677	1.57 (1.25–1.89)	0.0594
Allelica Multi Ancestry	European	10,000	111,643	1.77 (1.73–1.80)	0.0729

PRS	Ancestry	Cases	Controls	ORxSD	Brier
BC313	European	10,000	111,643	1.63 (1.60–1.66)	0.0735
Allelica Multi Ancestry	Admixed	100	1544	1.60 (1.37-1.83)	0.0562
BC313	Admixed	100	1544	1.48 (1.25-1.72)	0.0563

Table 9 - PRS performance comparison on UKBB

Meta analysis

PRS	Ancestry	Cases	Controls	ORxSD	Brier
Allelica Multi Ancestry	African	1,358	37,857	1.37 (1.33-1.41)	0.0456
BC313	African	1,358	37,857	1.27 (1.21-1.33)	0.0465
Allelica Multi Ancestry	Asian	405	8,375	1.55 (1.49-1.61)	0.0392
BC313	Asian	405	8,375	1.53 (1.38-1.70)	0.0411
Allelica Multi Ancestry	European	16,431	202,865	1.66 (1.65-1.67)	0.0585
BC313	European	16,431	202,865	1.44 (1.42-1.47)	0.0579
Allelica Multi Ancestry	Admixed	1,692	44,928	1.57 (1.49-1.65)	0.0514
BC313	Admixed	1,692	44,928	1.43 (1.32-1.55)	0.0586

Table 10 - PRS performance comparison in a meta analysis

Results: Integration of Polygenic Risk with Tyrer-Cuzick Clinical Modeling

In addition to evaluating how PRS modifies risk among monogenic variant carriers, we assessed the impact of integrating PRS into the Tyrer-Cuzick clinical risk model to quantify improvements in risk classification across ancestries. To evaluate the contribution of polygenic risk scores (PRS) to breast cancer risk stratification across ancestries, we constructed a unified analytic framework that integrates genetic and clinical data from the Women's Health Initiative

(WHI), UK Biobank (UKBB), and the All of Us Research Program (AoU). A harmonized dataset was generated for WHI and UKBB, and genetic ancestry inference was performed to classify individuals into four major ancestry groups: African, Asian (combining South and East Asian individuals), European, and Admixed American. A fifth Admixed group was defined to include individuals whose genetic ancestry proportions did not exceed 80% for any single major group, ensuring robust representation of genetically heterogeneous individuals.

For each ancestry group, we estimated the effect of the Allelica PRS on breast cancer risk using a Fixed Stratified approach that extends the Tyrer-Cuzick (TC) model. This procedure accounts for the known correlation between family history (FH) and genetic risk by estimating ancestry-specific PRS effects in individuals with and without FH, and then combining these into a unified ancestry-stratified estimate. Effect sizes were computed separately for each ancestry using a logistic regression model adjusted for FH, age at enrollment, and the first four principal components (PCs) of genetic ancestry. These ancestry-specific PRS weights were then incorporated multiplicatively into the TC risk equation, with baseline incidence recalibrated to match U.S. breast cancer rates.

Reclassification and NRI analyses were performed separately for each ancestry group in the combined WHI+UKBB dataset. To ensure consistency across cohorts, we repeated the full analysis in AoU using the same ancestry definitions, covariate adjustments, PRS weighting strategy, and TC integration approach. Results from WHI+UKBB and AoU were finally combined using inverse-variance-weighted meta-analysis to produce ancestry-specific and overall performance estimates.

The comparison between the TC model alone and the TC model with PRS integration is presented across a sequence of tables. Table 11 reports the reclassification results in the AoU dataset, while Table 12 shows the corresponding reclassification obtained in the WHI+UKBB dataset using the same three-category TC thresholds. Table 13 provides the categorical and continuous NRI computed in AoU from the reclassified samples in Table 11, and Table 14 reports the same NRI analysis for WHI+UKBB based on the reclassified samples in Table 12. These ancestry-specific estimates are then combined through inverse-variance weighting, and the resulting meta-analytic categorical and continuous NRI are summarised in Table 15.

For category-based NRI, we used three pre-specified lifetime risk strata from the Tyrer-Cuzick + PRS model: <15%, 15–<20%, and ≥20%. The ≥20% threshold reflects guideline-defined high risk, where intensified screening such as annual breast MRI is typically recommended and the 15–<20% range represents an intermediate risk category.

All Of Us		Residual lifetime risk from Tyrer-Cuzick + PRS			
Genetic Ancestry	**Residual lifetime risk from Tyrer-Cuzick**	[0,0.15)	[0.15,0.2)	[0.2,0.999]	Reclassified %
African	[0,0.15)	5,077	2,101	263	32
	[0.15,0.2)	6,062	8,106	3,168	53
	[0.2,0.999]	149	1,043	6,249	16
Admixed American	[0,0.15)	768	421	322	49
	[0.15,0.2)	725	596	749	71
	[0.2,0.999]	30	79	677	14
Asian	[0,0.15)	2,230	344	57	15
	[0.15,0.2)	163	639	81	28
	[0.2,0.999]	3	7	409	2
European	[0,0.15)	20,959	6,488	3,567	32
	[0.15,0.2)	18,962	10,524	8,674	72
	[0.2,0.999]	1,815	3,651	22,277	20
Admixed	[0,0.15)	1,344	728	833	54
	[0.15,0.2)	1,044	738	1,162	75
	[0.2,0.999]	104	144	1,652	13

Table 11 - Reclassification table from AoU dataset, comparing the residual lifetime risk from Tyrer-Cuzick without PRS integrated, and with Allelica PRS integrated

UKBB + WHI		Residual lifetime risk from Tyrer-Cuzick + PRS			
Genetic Ancestry	**Residual lifetime risk from Tyrer-Cuzick**	[0,0.15)	[0.15,0.2)	[0.2,0.999]	Reclassified %
African	[0,0.15)	3,900	199	35	6
	[0.15,0.2)	158	165	102	61
	[0.2,0.999]	13	53	127	34

UKBB + WHI		Residual lifetime risk from Tyrer-Cuzick + PRS			
Genetic Ancestry	**Residual lifetime risk from Tyrer-Cuzick**	[0,0.15)	[0.15,0.2)	[0.2,0.999]	Reclassified %
Admixed American	[0,0.15)	1,197	106	59	12
	[0.15,0.2)	63	35	45	76
	[0.2,0.999]	26	17	47	48
Asian	[0,0.15)	3,261	407	109	14
	[0.15,0.2)	179	133	81	66
	[0.2,0.999]	15	35	98	34
European	[0,0.15)	93,477	11,131	6,328	16
	[0.15,0.2)	4,653	2,181	2,432	76
	[0.2,0.999]	796	755	2,076	43
Admixed	[0,0.15)	5,343	547	239	13
	[0.15,0.2)	312	163	181	75
	[0.2,0.999]	60	70	191	40

Table 12 - Reclassification table from UKBB and WHI dataset, comparing the residual lifetime risk from Tyrer-Cuzick without PRS integrated, and with Allelica PRS integrated

NRI

AoU

Genetic Ancestry	Categorical NRI (95% CI)	P-Value	Continuous NRI (95% CI)	P-Value
African	0.08 (0.06 - 0.11)	<1e-5	0.19 (0.14 - 0.25)	<1e-12
Admixed American	0.09 (0.01 - 0.16)	0.02	0.31 (0.20 - 0.42)	<1e-8
Asian	0.04 (0.00 - 0.09)	0.04	0.22 (0.09 - 0.36)	<1e-3
European	0.11 (0.10 - 0.12)	<1e-10	0.33 (0.30 - 0.35)	<1e-14
Admixed	0.16 (0.11 - 0.21)	<1e-5	0.39 (0.32 - 0.45)	<1e-7
Overall	0.11 (0.10-0.12)	<1e-10	0.31 (0.29-0.33)	<1e-24

Table 13 - Categorical and continuous NRI based on AoU, based on reclassified sample in table 11

UKBB + WHI

Genetic Ancestry	Categorical NRI (95% CI)	P-Value	Continuous NRI (95% CI)	P-Value
African	0.06 (0.01 - 0.1)	0.01	0.25 (0.14 - 0.37)	<1e-14
Admixed American	0.13 (0.02 - 0.25)	0.02	0.37 (0.14 - 0.60)	<1e-14
Asian	0.12 (0.05 - 0.19)	<1e-3	0.38 (0.31 - 0.45)	<1e-14
European	0.14 (0.13 - 0.15)	<1e-10	0.41 (0.39 - 0.44)	<1e-18
Admixed	0.13 (0.08 - 0.48)	<1e-3	0.37 (0.27 - 0.48)	<1e-7
Overall	0.14 (0.13-0.15)	<1e-10	0.40 (0.38 – 0.42)	<1e-24

Table 14 - Categorical and continuous NRI based on UKBB and WHI, based on reclassified sample in table 13

META

Genetic Ancestry	Categorical NRI (95% CI)	P-Value	Continuous NRI (95% CI)	P-Value
African	0.07 (0.04 - 0.9)	<1e-5	0.21 (0.17 - 0.28)	<1e-18
Admixed American	0.11 (0.04 - 0.18)	<1e-4	0.34 (0.23 - 0.45)	<1e-18
Asian	0.07 (0.04 - 0.12)	<1e-3	0.30 (0.16 - 0.39)	<1e-18
European	0.13 (0.12 - 0.14)	<1e-10	0.37 (0.35 - 0.40)	<1e-20
Admixed	0.14 (0.11 - 0.19)	<1e-6	0.38 (0.32 - 0.45)	<1e-10
Overall	0.11 (0.10–0.13)	<1e-12	0.33 (0.31–0.35)	<1e-24

Table 15 - Categorical and continuous NRI based meta analysis

Conclusion

Breast Risk Reveal quantifies the combined and independent effects of monogenic variants, polygenic background, and Tyrer-Cuzick clinical factors. Integrating PRS with both monogenic testing and Tyrer-Cuzick significantly improves lifetime-risk classification, calibration, and reclassification across clinically meaningful thresholds.

These analyses confirm that Breast Risk Reveal quantifies the combined and independent effects of monogenic and polygenic risk. The data show that PRS modulates lifetime risk across all genes, with the greatest clinical impact observed for moderate-penetrance genes such as ATM, CHEK2, PALB2, and BARD1, where PRS reclassifies a substantial proportion of carriers above or below the 20 - 30% lifetime-risk thresholds used in guidelines for MRI screening or risk-reducing interventions.

By integrating PRS with monogenic testing in a single standardized framework, Breast Risk Reveal enables comprehensive risk estimation and management decisions that cannot be achieved through monogenic assessment alone.

Integrating PRS into the Tyrer-Cuzick model leads to a clear improvement in clinical risk classification. Overall, the categorical NRI was 0.11 (95% CI 0.10-0.13), meaning that PRS meaningfully increases the proportion of individuals correctly reclassified across the 15% and 20% risk-strata thresholds. The continuous NRI was 0.33 (95% CI 0.31-0.35), confirming a substantial gain in discrimination over TC alone.