original reports abstract

Development and Validation of a Clinical Polygenic Risk Score to Predict Breast Cancer Risk

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PURPOSE Women with a family history of breast cancer are frequently referred for hereditary cancer genetic testing, yet < 10% are found to have pathogenic variants in known breast cancer susceptibility genes. Large-scale genotyping studies have identified common variants (primarily single-nucleotide polymorphisms [SNPs]) with individually modest breast cancer risk that, in aggregate, account for considerable breast cancer susceptibility. Here, we describe the development and empirical validation of an SNP-based polygenic breast cancer risk score.

METHODS A panel of 94 SNPs was examined for association with breast cancer in women of European ancestry undergoing hereditary cancer genetic testing and negative for pathogenic variants in breast cancer susceptibility genes. Candidate polygenic risk scores (PRSs) as predictors of personal breast cancer history were developed through multivariable logistic regression models adjusted for age, cancer history, and ancestry. An optimized PRS was validated in 2 independent cohorts (n = 13,174; n = 141,160).

RESULTS Within the training cohort (n = 24,259), 4,291 women (18%) had a personal history of breast cancer and 8,725 women (36%) reported breast cancer in a first-degree relative. The optimized PRS included 86 variants and was highly predictive of breast cancer status in both validation cohorts ($P = 6.4 \times 10^{-66}$; $P < 10^{-325}$). The odds ratio (OR) per unit standard deviation was consistent between validations (OR, 1.45 [95% CI, 1.39 to 1.52]; OR 1.47 [95% CI, 1.45 to 1.49]). In a direct comparison, the 86-SNP PRS outperformed a previously described PRS of 77 SNPs.

CONCLUSION The validation and implementation of a PRS for women without pathogenic variants in known breast cancer susceptibility genes offers potential for risk stratification to guide surveillance recommendations.

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INTRODUCTION

Although breast cancer ranks among the cancer types with the highest heritability,[1] characterization of the underlying genetic causes is still incomplete. Pathogenic variants in high-penetrance genes (eg, *BRCA1, BRCA2, PALB2*) associated with substantial increases in risk are individually rare in the general population.[2-4] All known high- and moderate-penetrance breast cancer susceptibility genes are estimated to account for a combined 20% of familial relative risk.[5] As a result, most women who are referred for hereditary cancer genetic testing are negative for a pathogenic variant and without a clear understanding of the magnitude of their risk.[6]

Genome-wide association studies (GWAS) have identified several hundred, common, single-nucleotide polymorphisms (SNPs) as breast cancer susceptibility variants.[7-11] Although their individual contribution to risk is minor, polygenic risk scores (PRSs) of such variants can define variant combinations with potentially actionable clinical risk.[9,11] Together, pathogenic variants in high- and moderate-risk genes and panels of SNPs are estimated to explain up to 40% of the familial risk for developing breast cancer.[11]

The first well-characterized PRS combined 77 SNPs (PRS77) and was evaluated in > 67,000 women of European ancestry.[9] The score was strongly associated with breast cancer status: women in the highest 1% of the PRS77 score distribution had > 3-fold higher risk of developing breast cancer compared with women with an average score. However, the study was limited by the use of the same patient cohort for development and evaluation, probably overestimating the score's performance. Expansion of the discovery meta-analysis identified additional susceptibility loci that incrementally increased the proportion of familial relative risk explained by polymorphic variants.[10] More

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

To determine whether a polygenic risk score (PRS) could be developed and validated for clinical use in predicting breast cancer risk.

Knowledge Generated

An 86-SNP PRS was developed and adjusted for family history of breast cancer to avoid double counting of risk due to correlation between genetic components of family history and PRS. This PRS was highly predictive of breast cancer in two independent validation cohorts.

Relevance

PRSs that aggregate genotypes from common variants have emerged as a new approach to improve breast cancer risk assessment. Although several PRSs have been developed, they have not been adjusted or controlled for other genetic factors that may be correlated with PRS. We developed and validated an 86-SNP score that was adjusted for family breast cancer history and was highly predictive of breast cancer risk, making it appropriate for clinical use to identify women at increased risk of developing breast cancer.

recently, a polygenic score of 313 SNPs was deduced from the same GWAS and then validated in an independent population cohort.[11] The same study also supported previous work indicating SNP-based risk scores may have to be optimized depending on breast cancer estrogen-receptor (ER) status. Composition and individual contribution of variants of the ideal SNP-based breast cancer risk score remain to be defined.

Family history (FH) of breast cancer, a combination of biologic, social, and environmental factors, includes a genetic component that is expected to overlap with SNP-based risk.[9,11] To avoid double counting of risk due to correlation between genetic components of FH and PRS, joint modeling of both genetic factors is required. Here, we describe the development and validation of a PRS in which we co-estimate SNP-based risk and familial risk to obtain effect sizes independent of FH. Sequential independent studies were designed to confirm breast cancer associations of previously published SNPs, develop a PRS to optimally capture the combined effects of confirmed SNPs after adjusting for FH, and prospectively assess the performance of the optimized PRS in two independent data sets representative of the intended clinical-use population.

METHODS

Patients

The PRS was developed and then validated in three consecutive cohorts of women referred for hereditary cancer testing at a Clinical Laboratory Improvement Amendments and College of American Pathology–approved laboratory (Myriad Genetic Laboratories, Salt Lake City, UT) for a panel of 28 cancer-predisposition genes.[12] Women of European ancestry (Ashkenazi and non-Ashkenazi) were eligible for inclusion if they were 18 to 84 years old at the time of testing and were negative for pathogenic variants in 11 breast cancer–risk genes: *BRCA1*, *BRCA2*, *TP53*, *PTEN*, *STK11*, *CDH1*, *PALB2*, *CHEK2*, *ATM*, *NBN,* and *BARD1*). The development and validation studies were carried out according to institutional review board (IRB) approved protocols (Quorum Review IRB no. 31713). Additional details are provided in the Data Supplement.

SNP Genotyping

Amplicons for 94 SNP markers published at the time of this study were incorporated into a next-generation sequencing panel.[8,9] Two markers failed design due to their location within repetitive elements, leaving 92 markers for evaluation. Details on genotyping and variants are provided in the Data Supplement (Table S1).

Statistical Methods

Modeling. Clinical information from provider-completed test request forms included ancestry, personal and family cancer history, cancer type(s), and age(s) at diagnosis. Breast cancer associations were evaluated in terms of *P* values and odds ratios (ORs) from multivariable logistic regression models adjusted for the variables listed in the preceding sentence, coded as described previously, using R, version 3.4.4 or later (https://cran.r-project.org/).[13,14] ORs were normalized to one unit of standard deviation of the PRS distribution (standardized OR). Differences between models were evaluated by the log likelihood-ratio test comparing a model without the variable in question with a model including the variable. *P* values were calculated from likelihood-ratio χ^2 test statistics and are reported as two-sided.

PRS development. To define a PRS, we developed an iterative method to evaluate SNP markers discovered through GWAS and to select the most informative marker combination. We used multivariable analysis to account for linkage disequilibrium between SNPs, and the overlap between the genetic contribution of individual SNPs with the genetic component of familial cancer history.

Previous work supports a multiplicative model as the best method for capturing the combined SNP effects.[9,11] We centered the multiplicative model according to general-population allele frequencies so the OR for an individual patient represents the fold-change in risk relative to the general population. Specifically, the PRS was defined as a linear combination of centered risk alleles:

$$\text{PRS} = b_1(x_1 - u_1) + b_2(x_2 - u_2) + ... + b_N(x_N - u_N),$$

where N was the total number of SNPs selected, the coefficient b_k was the per-allele log OR for breast cancer association of the k^{th} SNP estimated from meta-analysis of literature and the development cohort; x_k was the number of alleles of the k^{th} SNP carried by an individual patient (x_k = 0, 1, or 2); and u_k was the average number of alleles of the k^{th} SNP reported for individuals included in large, general population studies.[8] Additional details of the PRS development are provided in the Data Supplement.

PRS validation. Both validation studies were conducted according to prespecified statistical analysis plans that were locked before unblinding the study data. The initial validation was based on sample size estimates to ensure that CIs around a 20% lifetime risk estimate would not be wider than 18% to 22%. The second validation cohort included independent clinical testing samples from August 2017 through January 2019. The primary analysis in each validation study tested the association of the PRS with invasive breast cancer after adjusting for age, personal and family cancer history, and ancestry.

In exploratory analyses, we assessed the predictive ability of the optimized PRS compared with a previously described PRS77 by adding both to a multivariable model. The added value of one score, after accounting for the other, was assessed by a log likelihood-ratio test. We evaluated goodness of fit of the PRS after accounting for clinical factors. The observed versus theoretical effect of the PRS on breast cancer risk under the multiplicative polygenic model was assessed by comparing ORs from the continuous PRS with those obtained from analysis of patients binned in categories according to PRS percentiles. Heterogeneity of the PRS effect size according to age, ancestry, and FH of breast cancer was evaluated by fitting additional interaction terms and by repeating the primary analysis restricted to subcohorts stratified by age, ancestry, and FH severity. Nonlinear effects of the PRS were assessed by including quadratic terms in the model.

RESULTS

PRS Development

The PRS was developed in a cohort of 24,259 women, 4,291 (18%) of whom had a personal history of breast cancer. Patient characteristics are detailed in Table 1. The median age at genetic testing was 47 years (interquartile range,

TABLE 1. Patient Clinical Characteristics

	Development		Validation 1		Validation 2	
Characteristic	**All Patients**	**Patients With IBC**	**All Patients**	**Patients With IBC**	**All Patients**	**Patients With IBC**
Total No. of patients (%)	24,259 (100)	4,291 (18)	13,174 (100)	3,293 (25)	141,160 (100)	28,928 (20)
Age at hereditary cancer testing, years						
Range	18-84	22-84	18-84	25-84	18-84	21-84
Median	47	54	49	58	48	59
% ≤ 50 years	61	7	55	30	57	26
Ancestry						
Western/Northern European	18,079 (75)	3,443 (80)	9,505 (72)	2,548 (77)	—	—
Central/Eastern European	5,533 (23)	762 (18)	2,950 (22)	548 (17)	—	—
White/non-Hispanic	—	—	—	—	136,528 (97)	27,942 (97)
Ashkenazi	647 (3)	86 (2)	719 (5)	198 (6)	4,632 (3)	986 (3)
Cancer history in FDRs						
No IBC or OC	13,230 (55)	2,800 (65)	7,115 (54)	1,896 (58)	80,697 (57)	17,211 (59)
≥ 1 IBC	8,725 (36)	1,315 (31)	4,896 (37)	1,258 (38)	48,631 (34)	10,610 (37)
≥ 1 OC	2,978 (12)	251 (6)	1,547 (12)	210 (6)	15,210 (11)	1,679 (6)
≥ 2 IBC	1,626 (7)	293 (7)	1,031 (8)	324 (10)	9,280 (7)	2,572 (9)
≥ 2 OC	104 (< 1)	11 (< 1)	55 (< 1)	7 (< 1)	453 (< 1)	60 (< 1)
≥ 1 IBC and ≥ 1 OC	674 (3)	75 (2)	384 (3)	71 (2)	3,378 (2)	572 (2)

NOTE. Data reported as No. (%) unless otherwise indicated. Dash indicates not evaluable based on fields available for self-reported ancestry on the test-request form.

Abbreviations: FDR, first-degree relative; IBC, invasive breast cancer; OC, invasive epithelial ovarian cancer.

37-56 years). Overall, 8,725 patients (36%) reported a breast cancer diagnosis in ≥ 1 first-degree relative and 13,230 (55%) had no first-degree relatives with breast or ovarian cancer.

Effect sizes and population frequencies were used to rank 92 susceptibility variants by their informativeness and to construct a polygenic score by successive addition of the most informative variant. Results from the iterative development procedure are shown in Figure 1. The contribution of each SNP to the discriminatory accuracy of the polygenic score was measured in terms of the likelihood ratio χ^2 statistic. For the first variants, we saw steep improvement with each added SNP. The increase in discriminatory power diminished as less-informative SNPs were incorporated. The final PRS was based on the 86 most-informative SNPs corresponding to the maximum discriminatory accuracy, hereafter referred to as the 86-SNP score.

86-SNP PRS Validation

The 86-SNP score was assessed in two independent consecutive cohorts of 13,174, and 141,160 women. Clinical characteristics were similar between the development and validation study populations (Table 1).

The 86-SNP score was strongly associated with breast cancer after adjusting for FH and clinical factors in both validation studies. We observed highly consistent ORs per unit standard deviation of the 86-SNP score (validation 1 OR, 1.45 [95% CI, 1.39 to 1.52]; validation 2 OR, 1.47 [95% CI, 1.45 to 1.49]). Distribution of relative risks, or fold changes, in breast cancer risks due to the 86-SNP score in unaffected women was similar between the first and second validations (Data Supplement Figures S1 and S2). ORs for developing breast cancer by 86-SNP score percentile in each of the two validation cohorts are given in Table 2. Consistently, women in the top 95th percentile of the 86-SNP score distribution had a more than 2-fold higher risk of breast cancer development than women with an average 86-SNP score, whereas women with an 86-SNP score in the lowest 10th percentile had a nearly 2-fold reduction in risk of breast cancer development.

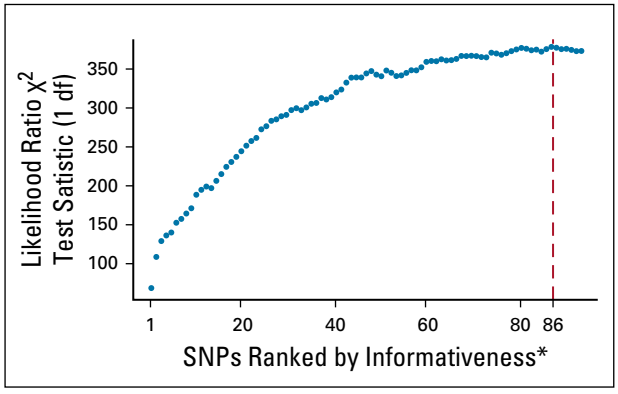

FIG 1. Cumulative likelihood ratio of individual single-nucleotide polymorphism (SNP) contributions to breast cancer risk discrimination. (*) For linked SNPs in *CCND1*, *TERT*, and *ESR1*, only one data point is shown per linkage disequilibrium block. df, degrees of freedom.

The SNP content of the 86-SNP PRS largely overlaps a previously reported PRS77.[9] We examined the predictive strength of both scores in our validation cohorts by testing for the added discrimination provided by each score after accounting for the other. The results of a likelihood ratio test applied to a multivariable model of both scores indicate that the 86-SNP score (validation 1 OR, 1.41 [95%CI, 1.23 to 1.61]; validation 2 OR, 1.35 [95% CI, 1.30 to 1.42]) was a more powerful stratification tool than the PRS77 (validation 1 OR, 1.04 [95% CI, 0.9 to 1.19]; validation 2 OR, 1.09 [95% CI, 1.04 to 1.14]) and PRS77 added less predictive power to the 86-SNP score than the 86-SNP score added to PRS77 (Data Supplement Table S2, Figure S3).

In the goodness-of-fit analysis, testing the association of the 86-SNP score with breast cancer risk on the basis of percentiles of the score, estimates observed from categorical analysis were highly consistent with theoretical estimates based on the multiplicative model for both validation cohorts (Fig 2).

After adjusting for multiple testing, we found no evidence of interaction between the 86-SNP score and age, ancestry, or breast cancer FH. Effect sizes of the 86-SNP score were consistent across subcohorts stratified by age (Table 3; Data Supplement Figure S4), ancestry (Data Supplement Table S3), and FH (Table 4; Data Supplement Figure S5) in both validation cohorts. Quadratic effects of the 86-SNP score were not significant. These results indicate the simple multiplicative model remains the best method for capturing the risk conferred by the combined effects of SNPs after accounting for family cancer history.

DISCUSSION

PRSs aggregating genotypes from common variants offer new ways to improve breast cancer risk assessment and can contribute to better understanding of breast cancer risk in all women. Modification of risk estimates by PRS-based stratification has been shown in a variety of clinical settings, including women who carry a pathogenic variant, high-risk women, and population cohorts.[11,15-17] These novel tools, however, are of particular interest to women who present for genetic risk assessment with increased risk due to a FH of breast cancer. FH and susceptibility variants contribute independently to risk prediction, yet the approximately 13% reduction in the OR for FH when adjusted for the PRS77 (or PRS313) indicates an overlapping contribution to risk.[9,11,18] Adjustment for this correlation between SNPs and FH can be achieved by co-estimating ORs from multivariable models. This adjustment is essential to avoid overestimating risk, in particular when PRS-based risk is combined with traditional breast cancer risk models.

In this study, we designed an 86-SNP PRS to predict breast cancer status in women of European ancestry who

TABLE 2. Effect Sizes by Percentile of 86-SNP Score in the Validation Cohorts

86-SNP Score Percentile	Validation 1				Validation 2			
	No.	OR[a]	95% CI	*P*	No.	OR[a]	95% CI	*P*
≤ 1	132	0.43	0.24 to 0.73	.0029	1,412	0.40	0.33 to 0.48	1.41×10^{-20}
> 1-5	527	0.56	0.42 to 0.73	3.0×10^{-5}	5,646	0.48	0.44 to 0.53	9.89×10^{-52}
5-10	659	0.55	0.43 to 0.70	1.7×10^{-6}	7,058	0.59	0.54 to 0.64	4.52×10^{-37}
10-20	1,317	0.63	0.53 to 0.76	8.4×10^{-7}	14,116	0.69	0.65 to 0.73	4.47×10^{-35}
20-40	2,635	0.80	0.70 to 0.92	0.0020	28,232	0.85	0.81 to 0.89	3.16×10^{-12}
40-60	2,634	1 (referent)	—	—	28,232	1 (referent)	—	—
60-80	2,635	1.19	1.04 to 1.36	.012	28,232	1.30	1.24 to 1.36	5.75×10^{-32}
80-90	1,317	1.62	1.39 to 1.90	1.6×10^{-9}	14,116	1.53	1.45 to 1.61	3.49×10^{-59}
90-95	659	1.77	1.45 to 2.16	1.6×10^{-8}	7,058	1.80	1.69 to 1.92	7.36×10^{-72}
95-99	527	2.18	1.76 to 2.70	6.8×10^{-13}	5,646	2.28	2.13 to 2.44	2.85×10^{-124}
> 99	132	2.14	1.44 to 3.17	1.5×10^{-4}	1,412	2.99	2.64 to 3.37	1.89×10^{-69}

Abbreviations: OR, odds ratio; SNP, single-nucleotide polymorphism.

[a]ORs are for the difference in breast cancer risk between the indicated percentiles of the 86-SNP score relative to the middle quintile (40%-60%).

had hereditary-cancer genetic testing and were negative for pathogenic variants. By deriving effect sizes for individual variants from logistic regression models adjusted for FH, we created a PRS that corrects SNP-based risk for FH.

The 86-SNP PRS incorporates SNPs from the previously described PRS77 as well as variants published subsequently.[8,9] Both PRSs were strongly associated with breast cancer risk in our validation cohorts, with a slightly higher OR for the 86-SNP score compared with OR for the PRS77. In a model including both scores, the 86-SNP score outperformed the PRS77, possibly due to the inclusion of additional variants not present in the PRS77. The reduced OR for PRS77 in our validation studies is consistent with some overfitting in the original study[9] and is equivalent to its performance in a prospective data set.[11]

Previous studies reported a weak decline of PRS stratification with age, primarily observed in ER-positive disease.[11] Despite a slight variation of point estimates, there was no significant performance difference of the 86-SNP PRS between age groups in either of our 2 validations. Possibly the weak effect previously reported is confined to a specific breast cancer subtype or more prevalent in a population less enriched for FH. In contrast to earlier reports, we found no interaction between the 86-SNP score and FH. The reported interaction was only significant in ER-positive disease, a subanalysis not available in our data set.[11]

Since the inception of this study, additional breast cancer risk variants have been described, and expanded breast cancer PRSs have been evaluated and validated in independent data sets.[10,11] The enlarged PRSs are estimated to account for a larger fraction of familial risk and promise

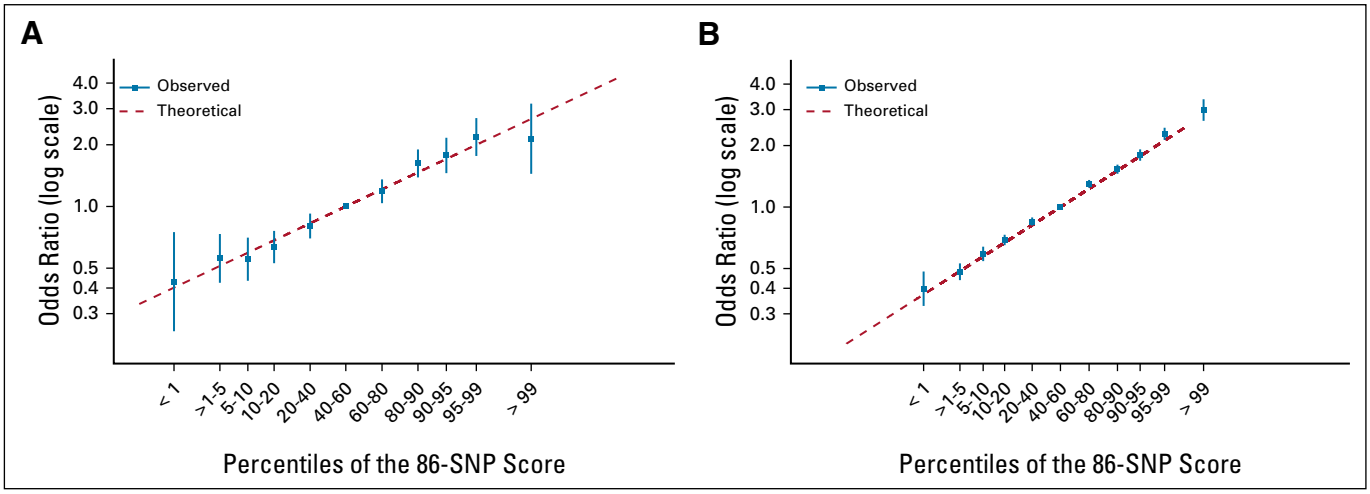

FIG 2. Observed versus theoretical estimates of breast cancer relative risk under the multiplicative polygenic model in (A) validation 1 and (B) validation 2.

TABLE 3. Association Between the 86-SNP Score and Breast Cancer Risk in Different Age Categories

	Validation 1			Validation 2		
Age (years)[a]	No.	OR[b]	95% CI	No.	OR[b]	95% CI
< 40	3,891	1.37	1.23 to 1.53	44,350	1.43	1.38 to 1.49
40-49	3,725	1.46	1.35 to 1.58	39,227	1.52	1.48 to 1.56
50-59	3,187	1.43	1.31 to 1.55	33,343	1.45	1.41 to 1.49
60-69	1,792	1.45	1.30 to 1.62	18,583	1.47	1.42 to 1.52
≥ 70	579	1.59	1.25 to 2.03	5,657	1.39	1.30 to 1.50

Abbreviation: OR, odds ratio.

[a]Age is defined as age at first diagnosis for patients affected by breast cancer, or age at genetic testing for women unaffected by breast cancer.

[b]ORs are per unit standard deviation within each age category.

TABLE 4. Association Between the 86-SNP Score and Breast Cancer Risk in Different Categories of Breast Cancer FH Severity

	Validation 1			Validation 2		
FH Group[a]	No.	OR[b]	95% CI	No.	OR[b]	95% CI
0	3,910	1.44	1.32 to 1.57	40,944	1.46	1.42 to 1.50
0.25	2,527	1.55	1.40 to 1.72	29,851	1.48	1.43 to 1.53
0.5	3,056	1.44	1.31 to 1.58	33,401	1.52	1.47 to 1.57
0.75	1,657	1.46	1.29 to 1.66	17,387	1.46	1.40 to 1.53
1	1,176	1.33	1.14 to 1.55	11,273	1.51	1.44 to 1.59
≥ 1.25	848	1.37	1.16 to 1.62	8,304	1.43	1.35 to 1.51

Abbreviations: FH, family history of breast cancer; OR, odds ratio.

[a]FH is a weighted sum of relatives affected with invasive breast cancer. Each first-degree relative contributes 0.5, and each second-degree relative contributes 0.25.

[b]ORs are per unit standard deviation within each FH group.

better predictive power. However, none of the larger PRSs have been adjusted for confounding with FH, which should be a prerequisite for incorporation into clinical models. The approach described here of co-estimation in multivariate models could be applied to any emerging PRS, irrespective of number of variants or ancestral origin.

Among the strengths of this study are the use of large, contemporary, and fully independent cohorts for development and 2 validation studies. Derivation of the PRS used a modeling approach that accounted for correlation between genetic risk contained in SNPs and FH. Thus, to our knowledge, the 86-SNP score is the first PRS with an SNP component adjusted for FH and, as such, would be an appropriate addition to conventional clinical models.

Limitations of the study include the inability to apply the 86-SNP score to patients of non-European ancestry because changes in genetic structure and linkage disequilibrium may affect the predictive ability of individual risk variants when present in a different ancestral background. Although association studies with equivalent explanatory power in other ancestries have yet to be described, they are the subject of ongoing research and the expansion of breast cancer PRS to other ancestries is a high priority. Family cancer history information in our studies was based on provider-completed test request forms, which may limit the accuracy and/or completeness of that information. There is also possible selection bias from using a population that met clinical criteria for genetic testing. However, previous studies have demonstrated that unbiased risk estimates can be obtained from analysis of a clinical testing population through multivariable adjustment for the factors related to ascertainment.[14,19]

Although the 86-SNP score described here adjusted for FH, genetic factors are not the sole contributors to breast cancer risk, even in cohorts with exceptional FH. Validated clinical risk models incorporate variables such as body mass index, age at menarche, parity, age at first birth and hormone replacement therapy use, as well as details of FH.[20-23] Other important risk factors, such as mammographic density and diet, are not taken into account here.[24-26] More studies will be needed to accommodate these additional variables and to determine their independent contributions. A testing approach that combines monogenic and polygenic genetic risk with FH, clinical, and lifestyle factors may result in improved targeting of risk-reducing options.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Honoraria: AstraZeneca
Consulting or Advisory Role: Change Health Care
Research Funding: AstraZeneca (Inst), Myriad Genetics (Inst), InVitae (Inst), AbbVie (Inst), Tesaro (Inst), Medivation (Inst), Pfizer (Inst)
Travel, Accommodations, Expenses: AstraZeneca, Pfizer
Other Relationship: Research to Practice, Clinical Care Options, Physician Education Resource
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