Association of a Polygenic Risk Score With Breast Cancer Among Women Carriers of High- and Moderate-Risk Breast Cancer Genes

Shannon Gallagher, MPH; Elisha Hughes, PhD; Susanne Wagner, PhD; Placede Tshiaba, MS; Eric Rosenthal, PhD, MSc; Benjamin B. Roa, PhD; Allison W. Kurian, MD; Susan M. Domchek, MD; Judy Garber, MD, MPH; Johnathan Lancaster, MD, PhD; Jeffrey N. Weitzel, MD; Alexander Gutin, PhD; Jerry S. Lanchbury, PhD; Mark Robson, MD

Abstract

IMPORTANCE To date, few studies have examined the extent to which polygenic single-nucleotide variation (SNV) (formerly single-nucleotide polymorphism) scores modify risk for carriers of pathogenic variants (PVs) in breast cancer susceptibility genes. In previous reports, polygenic risk modification was reduced for BRCA1 and BRCA2 PV carriers compared with noncarriers, but limited information is available for carriers of CHEK2, ATM, or PALB2 PVs.

OBJECTIVE To examine an 86-SNV polygenic risk score (PRS) for BRCA1, BRCA2, CHEK2, ATM, and PALB2 PV carriers.

DESIGN, SETTING, AND PARTICIPANTS A retrospective case-control study using data on 150,962 women tested with a multigene hereditary cancer panel between July 19, 2016, and January 11, 2019, was conducted in a commercial testing laboratory. Participants included women of European ancestry between the ages of 18 and 84 years.

MAIN OUTCOMES AND MEASURES Multivariable logistic regression was used to examine the association of the 86-SNV score with invasive breast cancer after adjusting for age, ancestry, and personal and/or family cancer history. Effect sizes, expressed as standardized odds ratios (ORs) with 95% CIs, were assessed for carriers of PVs in each gene as well as for noncarriers.

RESULTS The median age at hereditary cancer testing of the population was 48 years (range, 18-84 years); there were 141,160 noncarriers in addition to carriers of BRCA1 (n = 2,249), BRCA2 (n = 2,638), CHEK2 (n = 2,564), ATM (n = 1,445), and PALB2 (n = 906) PVs included in the analysis. The 86-SNV score was associated with breast cancer risk in each of the carrier populations (P < 1 × 10^-4). Stratification was more pronounced for noncarriers and CHEK2 pathogenic variant carriers than for BRCA1 or BRCA2 pathogenic variant carriers, with ATM and PALB2 pathogenic variant carriers being intermediate between those groups.

CONCLUSIONS AND RELEVANCE In this study, the 86-SNV score was associated with modified risk for carriers of BRCA1, BRCA2, CHEK2, ATM, and PALB2 PVs. This finding supports previous reports of reduced PRS stratification for BRCA1 and BRCA2 PV carriers compared with noncarriers. Modification of risk in CHEK2 carriers associated with the 86-SNV score appeared to be similar to that observed in women without a PV. Larger studies are needed to provide more refined estimates of polygenic modification of risk for women with PVs in other moderate-penetrance genes.
Introduction

The likelihood that a woman will develop breast cancer during her lifetime is influenced by her genetic inheritance. Family history of breast cancer is a significant determinant in the development of the disease, and 3 types of genetic variation are known to contribute to the risk.\(^1\) First, high-risk pathogenic or likely pathogenic variants (PVs) in \textit{BRCA1} (OMIM 113705) and \textit{BRCA2} (OMIM 600185) (\textit{BRCA1}/\textit{2}) have been known since the mid-1990s to influence familial risk and are routinely tested for in families with a significant family history. Individually, these PVs are rare, but collectively, the more than 10,000 individual \textit{BRCA1}/\textit{2} PVs characterized so far account for up to 20% of familial risk.\(^2\) Increased understanding of \textit{BRCA1}/\textit{2} function and the DNA damage response pathway led to the discovery of a second class of breast cancer susceptibility genes, accounting for an additional 5% of familial risk.\(^1,3,4\) These genes include \textit{PALB2} (OMIM 610355), \textit{CHEK2} (OMIM 604373), and \textit{ATM} (OMIM 607585), with \textit{CHEK2} and \textit{ATM} PVs about as common as those noted in \textit{BRCA1}/\textit{2}.\(^5-9\)

The third class of breast cancer susceptibility genes is common risk variants, mostly single-nucleotide variations (SNVs) (formerly single-nucleotide polymorphisms), which have been associated with breast cancer risk in large, whole-genome association studies and are estimated to explain an additional 18% of familial risk.\(^10\) While odds ratios (ORs) for individual SNVs tend to be modest and are not clinically useful, combinations of SNVs can be aggregated into polygenic risk scores (PRSs) that stratify unaffected women for breast cancer risk, irrespective of the presence or absence of a family history of the disease.\(^11-13\) For women in the highest percentiles of the PRS distribution, the estimated risk levels approach those reported for women with PVs in moderate-risk genes.\(^14\)

Improved stratification of breast cancer risk is essential for optimizing clinical benefit from screening and prevention procedures. With this goal, clinical risk assessment tools have been modified by incorporation of novel risk factors, such as breast density, ovarian and exogenous hormonal exposure, and genetics.\(^15-18\) Gene risk-adapted modifications to screening and prevention protocols have been introduced or proposed in response to evidence from gene-focused epidemiologic studies.\(^19-22\) Polygenic risk scores can be expected to add an additional layer of stratification, although precisely how best to combine the scores with traditional risk tools remains unclear.

Previous studies have explored the influence of genetic modifiers on breast cancer risk in carriers of a PV in \textit{BRCA1}/\textit{2}.\(^23-27\) However, early studies were limited to small numbers of SNVs, and most studies assumed theoretical rather than empirical levels of polygenic stratification for PV carriers. More recently, an 88-SNV PRS showed reduced risk modification in \textit{BRCA1}/\textit{2} PV carriers compared with the modification observed in large, general population samples.\(^28\) This observation suggests potential stratification differences depending on genetic context. In this study, we evaluated a previously defined\(^13\) 86-SNV PRS for association with the risk of breast cancer development in women carrying PVs in \textit{ATM}, \textit{CHEK2}, and \textit{PALB2}. We estimated absolute risks of breast cancer to age 80 years to examine the potential clinical utility of polygenic stratification in women with PVs in \textit{BRCA1}/\textit{2}, \textit{ATM}, \textit{CHEK2}, and \textit{PALB2}.

Methods

Patient Cohort

The population for this retrospective case-control study was drawn from a consecutive cohort of women referred for commercial hereditary cancer testing with a 25-gene panel (eMethods in the Supplement provides the full gene list) at a Clinical Laboratory Improvement Amendments- and College of American Pathology–approved laboratory (Myriad Genetic Laboratories Inc) between July 19, 2016, and January 11, 2019. For women without PVs in breast cancer susceptibility genes, we restricted inclusion to patients tested after August 10, 2017, to ensure independence from previous development and validation cohorts.\(^23\) Eligible patients were aged 18 to 84 years at testing and...
reported any combination of Ashkenazi Jewish, white/non-Hispanic, Western/Northern European, or Central/Eastern European ancestry on the test request form. This ancestry selection emulates the discovery cohorts for the breast cancer risk SNVs included in the 86-SNV score.¹¹,¹² Patients were excluded if they did not receive 25–gene panel testing, were residents of states that disallow use of genetic data after completion of genetic testing, tested positive for a PV in multiple breast cancer susceptibility genes, or did not complete the self-reported ancestry section of the test request form. Patient selection using these criteria was performed before calculation of the 86-SNV score. All patient data were anonymized before analysis.

This study was approved by the Advarra Institutional Review Board (formerly Quorum Review IRB) with a waiver of informed consent, as all data were already collected, patients were not contacted during the course of the study, and the sample size was prohibitively large for individual informed consent. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for case-control studies.

**Genetic Testing**

Breast cancer variant detection via next-generation sequencing has been described in detail elsewhere.²⁹ Women were classified as positive for at least 1 PV in a gene associated with breast cancer (ie, **BRCA1**, **BRCA2**, **TP53**, **PTEN**, **STK11**, **CDH1**, **PALB2**, **CHEK2**, **ATM**, **NBN**, and **BARD1**) using American College of Medical Genetics and Genomics recommendations and Association for Molecular Pathology guidelines, as well as previously described statistical variant classification methods.³⁰

Single-nucleotide variation genotyping by next-generation sequencing and details for calculating the 86-SNV score have been described previously.¹³ Briefly, from a panel of 94 previously identified breast cancer–associated SNVs published at the start of this study,¹¹,¹² 86 variants were selected based on a ranking of informativeness for their contribution of breast cancer risk. The 86-SNV score is the linear combination of the centered risk alleles weighted by the per-allele log OR for the association of each variant with breast cancer (eMethods in the Supplement). Calculation of the 86-SNV score was fixed in previous cohorts and applied unchanged to the genotype data in this study.

**Statistical Analysis**

Analyses were conducted according to a prespecified statistical analysis plan. Associations with invasive breast cancer were evaluated in terms of *P* values and ORs (95% CIs) from multivariate logistic regression models constructed using R, version 3.4.4 or higher (R Foundation for Statistical Computing). Odds ratios are reported per unit SD of the PRS in unaffected controls. *P* values were calculated from likelihood ratio χ² test statistics and are reported as 2-sided; *P* < .05 was considered the level of significance. All models included independent variables for age at first invasive breast cancer diagnosis or age at genetic testing if unaffected, personal history of cancer not affecting the breast, family history of any cancer, and ancestry (European and/or Ashkenazi Jewish); additional details are presented in the eMethods in the Supplement.

The primary analysis examined the association of the 86-SNV score with invasive breast cancer in each gene carrier group. In exploratory analyses, we compared the performance of the 86-SNV score in carriers of **CHEK2** 1100delC or other **CHEK2** PVs. To test for the interaction with family history, we used either a binary variable (presence or absence of an affected first-degree relative) or the sum of relatives affected with invasive breast cancer in a weighted relative count; additional details are available in the eMethods in the Supplement. To test for interaction with gene carrier status, we created a categorical variable for noncarrier or gene-specific carrier status.

To examine relative risks by percentiles of the 86-SNV score, the noncarrier and **BRCA1**, **BRCA2**, **CHEK2**, and **ATM** PV-positive cohorts were each binned into quintiles based on the 86-SNV score. The **PALB2** cohort was binned into tertiles to account for the smaller sample size. The median
percentile bin (33rd-66th percentile tertile for PALB2, 40th-60th percentile quintile for all others) was set as the reference group in a model that also included the above-described covariates.

Absolute lifetime risks of developing breast cancer were calculated for unaffected study participants by combining the 86-SNV score-based risk with previously published gene-specific risk estimates for PV carriers\(^7,13\) or lifetime breast cancer risk estimates from Surveillance, Epidemiology, and End Results 2009 to 2014 data for noncarriers.\(^{32,33}\)

Results

The study cohort comprised 152,012 women of European and Ashkenazi ancestry with a median age of 48 years (range, 18-84 years), including 32,812 women with a diagnosis of breast cancer and 119,200 women who did not have breast cancer at the time of testing. Among these women, 10,852 carried a germline PV in 1 of the 11 breast cancer-associated genes (eTable 1 in the Supplement). Since there were insufficient numbers of carriers in breast cancer genes with a lower prevalence to obtain statistical power, 10,502 women carrying PV in BARD1, CDH1, NBN, PTEN, STK11, and TPS3 were excluded. In the analysis cohort, PV-positive women comprised 10.9% of those with breast cancer and 5.3% of those without breast cancer. The largest number of PVs was observed in BRCA2, followed by CHEK2 and BRCA1. Pathogenic variants were also relatively common in ATM and PALB2 (Table 1). Among breast cancer cases, the number of PVs in BRCA1/2 was close to the combined occurrences of PVs in CHEK2, ATM, and PALB2.

To evaluate the association of the 86-SNV score with modification of breast cancer risk in PV carriers, we constructed multivariable logistic regression models testing the association of the 86-SNV score with breast cancer status among PV carriers in each gene. Each model included family history as a covariate to estimate the OR for the PRS independent from family history. For comparison, we have included the 86-SNV score performance in noncarriers from a previous validation study.\(^13\) The 86-SNV score was associated with modified risk for breast cancer in all carrier groups (Table 2). Similar to reported observations, the effect sizes of the 86-SNV score in BRCA1 (OR, 1.20; 95% CI, 1.10-1.32) and BRCA2 (OR, 1.23; 95% CI, 1.12-1.34) PV carriers were smaller compared with the ORs observed for women without a PV (OR, 1.47; 95% CI, 1.45-1.49) and CHEK2 PV carriers (OR, 1.49; 95% CI, 1.36-1.64). The effect size of the 86-SNV score in ATM (OR, 1.37; 95% CI, 1.21-1.55) and PALB2 (OR, 1.34; 95% CI, 1.16-1.55) PV carriers was similar to that observed for noncarriers.\(^14,28\)

Point estimates for risk stratification by the 86-SNV score in women with PVs in moderate-risk breast cancer genes were higher than those for BRCA1/2 carriers (Table 2; eFigure 1 in the Supplement). A test for interaction between the 86-SNV score and gene carrier type was significant (\(P = 1.3 \times 10^{-5}\)). The most pronounced risk discrimination was observed for CHEK2 carriers (OR, 1.49;\(P = 1.3 \times 10^{-5}\)).

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**Table 1. Summary of the Clinical Characteristics and Demographic Data of the Study Cohort**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>141,160</td>
</tr>
<tr>
<td>Age at hereditary cancer testing, median (range), y</td>
<td>48 (18-84)</td>
</tr>
<tr>
<td>Breast cancer history*</td>
<td></td>
</tr>
<tr>
<td>Personal</td>
<td>28,928 (20)</td>
</tr>
<tr>
<td>≥1 First- or second-degree relative</td>
<td>100,216 (71)</td>
</tr>
<tr>
<td>Ashkenazi Jewish</td>
<td>2924 (2)</td>
</tr>
<tr>
<td>White/non-Hispanic</td>
<td>134,819 (96)</td>
</tr>
<tr>
<td>Ashkenazi Jewish and white/non-Hispanic</td>
<td>3417 (2)</td>
</tr>
</tbody>
</table>

* Invasive breast cancer.
95% CI, 1.36-1.64), in which the effect size was equivalent to the OR observed in noncarriers and for the general population.12,13 Significant risk modification was observed for CHEK2 PV carriers in the lowest (OR, 0.59; 95% CI, 0.44-0.80) and highest (OR, 1.67; 95% CI, 1.26-2.20) quintiles of 86-SNV scores compared with the middle quintile (Table 3). Relative risk for ATM PV carriers in the lowest quintile (OR, 0.46; 95% CI, 0.31-0.69) of the 86-SNV score was also substantially reduced, while modification for the highest quintile was more modest (OR, 1.18; 95% CI, 0.82-1.71). Overall, ORs for patients binned by percentile of the PRS were consistent with estimations from the continuous score for all genes examined (eFigure 2 in the Supplement). These findings appear to support the multiplicative polygenic model of inheritance defined by the PRS and therefore the risk estimates for women at the lowest and highest percentiles of the risk distribution.

In an exploratory analysis, we compared 86-SNV score discrimination in carriers of CHEK2 1100delC and carriers of other CHEK2 PVs. A slight reduction in the OR in CHEK2 1100delC carriers did not remain significant after correction for multiple testing (unadjusted P = .04) (eTable 2 in the Supplement). In previous reports, risks associated with the PRS were dependent on age and/or family history.14 We found no evidence supporting an interaction of the 86-SNV score with age (eTable 3, eFigure 3 in the Supplement) or with family history of breast cancer (eTable 4, eFigure 4 in the Supplement) for any of the PV carrier populations after correction for multiple testing. We reexamined family history with a weighted relative count as a more quantitative and powerful family history measure. A reduced effect size for the 86-SNV score in CHEK2 PV carriers with a high count of affected relatives was not statistically significant after adjustment for multiple testing (eFigure 5 in the Supplement). This finding is consistent with a lack of interaction between a PRS and family history in CHEK2 1100delC carriers reported previously.34

To illustrate potential modifications in absolute lifetime breast cancer risk associated with the 86-SNV score for PV-positive women, we calculated breast cancer risk by age 80 years using published, gene-specific baseline risks combined with risk estimates from the 86-SNV score, assuming independence.17,31 As shown in the Figure, the adjusted risk estimates suggest a reduction in lifetime risk to a level comparable to the population average for women with a PV in ATM or CHEK2 who are in the lowest 86-SNV score percentile. For example, stratification of CHEK2 risk by the 86-SNV score identified 1079 CHEK2 PV carriers (65.4%) with a lifetime risk of at least 20% and 571 women (34.6%) with CHEK2 PV and a lifetime risk of less than 20%. Lifetime risk for PV carriers of moderate-risk genes in the highest 86-SNV score percentiles approached risks estimated for BRCA1/2 PV carriers (Table 4, Figure).

Discussion

To our knowledge, this study is the first empirical evaluation of a PRS as a risk modifier in women carrying a germline PV in CHEK2, ATM, or PALB2. In a large cohort of women, we observed significant stratification of risk by an 86-SNV score in carriers of a PV in moderate-risk breast cancer genes. Risk modification associated with the 86-SNV score was most pronounced for CHEK2 PV carriers, with an OR similar to the OR observed in noncarriers.13 These results are consistent with the reported PRS-based risk modification in carriers of the CHEK2 founder mutation 1100delC.34-36 A 74-SNV
<table>
<thead>
<tr>
<th>86-SNV score</th>
<th>Noncarriers</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>ATM</th>
<th>CHEK2</th>
<th>PALB2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentile</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>≤20</td>
<td>NA</td>
<td>6.0 × 10⁻²⁰</td>
<td>8.6 (0.61-1.10)</td>
<td>.18</td>
<td>0.67 (0.50-0.91)</td>
<td>.006</td>
</tr>
<tr>
<td>&gt;20 to ≤40</td>
<td>0.85 (0.81-0.89)</td>
<td>3.4 × 10⁻¹²</td>
<td>0.94 (0.70-1.26)</td>
<td>.70</td>
<td>1.02 (0.78-1.35)</td>
<td>.86</td>
</tr>
<tr>
<td>&gt;60 to ≤80</td>
<td>1.30 (1.24-1.36)</td>
<td>6.4 × 10⁻¹²</td>
<td>1.08 (0.81-1.45)</td>
<td>.59</td>
<td>1.11 (0.85-1.46)</td>
<td>.44</td>
</tr>
<tr>
<td>&gt;80</td>
<td>1.79 (1.72-1.87)</td>
<td>1.5 × 10⁻¹⁶</td>
<td>1.52 (1.14-2.03)</td>
<td>.004</td>
<td>1.31 (1.00-1.72)</td>
<td>.054</td>
</tr>
<tr>
<td>≤33</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>&gt;33 to ≤66</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>&gt;66</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; OR, odds ratio; PV, pathogenic variant; SNV, single-nucleotide variant.

* Invasive breast cancer.

** The middle percentile was used as the referent. P values are for the difference in effect size between the percentile of the 86-SNV score and the referent group.

*** The PALB2 cohort was binned into tertiles to account for the smaller sample size.
score stratified CHEK2 1100delC carriers, with an OR of 1.59 (95% CI, 1.21-2.09). Both the OR for stratification of CHEK2 PV carriers and the effect size for CHEK2 1100delC or other CHEK2 PVs in our study are contained within the 95% CI of this previously reported estimate. The slightly higher point estimate for both carriers and noncarriers reported by Muranen et al. may in part be owing to overfitting, as the study cohort was part of the development set for the 74-SNV PRS.

The potential for risk modification associated with PRS for women carrying PVs in moderate-risk breast cancer genes has been investigated by theoretical modeling and is supported by SNV-associated modification observed for high-risk breast cancer genes. Modification of BRCA1/2 overall breast cancer risk has been reported for an 88-SNV PRS, largely based on the published 77-SNV score. Discrimination by the 88-SNV PRS in BRCA1/2 PV carriers was less pronounced compared with the general population—a reduction putatively attributed to overfitting of the 77-SNV score or a deviation from the multiplicative model. Herein we report risk modification associated with an 86-SNV score in BRCA1 or BRCA2 PV carriers and found ORs that appear to be in agreement with those reported by Kuchenbaecker et al. Given the independence of the cohorts studied and the differences in methods used, these results are comparable and, considering the sample sizes, possibly represent true estimates of the extent to which polygenic effects are associated with modified risk for BRCA1/2 PV carriers. Reasons that PRS stratification should be reduced in carriers of high penetrance PVs remain unclear. Several PRS loci are related to the DNA damage repair pathway, implying a partial overlap between highly penetrant breast cancer genes and potential redundancy. At least in the case of BRCA1 PV carriers, most tumors are estrogen receptor (ER)-negative. Most currently known breast cancer–associated SNVs show a preferential association with ER-positive disease, possibly owing to the increased prevalence of ER-positive breast cancer in the mostly population-based discovery cohorts. Consequently, reports have

### Table 4. Estimated Lifetime Breast Cancer Risk to Age 80 Years and Modification by an 86-SNV Score

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene-based risk, %</th>
<th>Adjusted lifetime risk, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimum</td>
<td>Quintile 1</td>
</tr>
<tr>
<td>ATM</td>
<td>12.9</td>
<td>23.9</td>
</tr>
<tr>
<td>BRCA1</td>
<td>31</td>
<td>53.1</td>
</tr>
<tr>
<td>BRCA2</td>
<td>73.8</td>
<td>50.8</td>
</tr>
<tr>
<td>CHEK2</td>
<td>22.1</td>
<td>6.6</td>
</tr>
<tr>
<td>PALB2</td>
<td>50.1</td>
<td>26.2</td>
</tr>
<tr>
<td>Noncarriers</td>
<td>12.7</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Abbreviation: SNV, single-nucleotide variant.

References denote sources of gene-based risk.
shown reduced discrimination by various PRSs in ER-negative cancers.14,39 In a previous BRCA1 PV carrier analysis,28 a PRS selectively composed of SNVs associated with ER-negative breast cancer outperformed both a PRS comprising overall breast cancer SNVs and an ER-positive breast cancer PRS, suggesting some level of tumor type specificity.40

The risk stratification of CHEK2, ATM, and PALB2 PV carriers by the 86-SNV score highlights the need for integrative testing. In a more patient-specific approach, multiple genetic contributions would be combined with conventional risk factors to provide the best risk estimate for every woman that could guide appropriate clinical care. Several clinical risk assessment tools have been updated to include novel risk factors, such as breast density, and the integration of PRS-based risk has been explored as well.15-18 Preventive options for women with an increased risk of developing breast cancer range from more frequent and earlier mammography, surveillance augmentation by breast magnetic resonance imaging, or pharmacologic prevention to risk-reducing mastectomy, although the most effective measure to identify women for preventive interventions remains under discussion.20,21 Guidelines in the US recommend annual breast magnetic resonance imaging for women with greater than 20% lifetime risk based on models with family history, although different thresholds are applied in other countries.19,41 Incorporating PRS risk may identify additional women with PVs in moderate-penetrance genes who exceed this risk threshold owing to a combination of genetic and clinical factors. As seen in this study, stratification of CHEK2 risk by the 86-SNV score resulted in 65.4% of this population having a lifetime risk of developing breast cancer of at least 20%.

Limitations
This study has limitations. The patient population was drawn from a commercial genetic testing cohort with the attendant concerns about ascertainment bias, primarily owing to family history. Previous studies have shown that adjusting for family history in multivariable models can correct for ascertainment bias due to family history and provide similar effect size estimates as population-based studies.34,42 Patient clinical data were taken from health care professional–supplied test request forms, which did not always contain complete information. Despite the cohort size, there were insufficient numbers of PV carriers to allow assessment of the association between the 86-SNV score and other breast cancer genes (eg, BARD1, NBN). Larger data sets will permit analysis of PRS modification for less commonly mutated breast cancer genes and will refine risk modification associated with PVs in ATM and PALB2. Additional breast cancer–associated SNVs have been described since the initiation of this study, and PRSs including more SNVs may offer further improvements in stratification.14,43 In addition, the performance of known PRSs in individuals of non-European ancestry remains to be defined.

Conclusions
In this study, stratification of breast cancer risk by an 86-SNV score in PV carriers of moderate-risk breast cancer genes was associated with risk changes for women at the lower and higher ends of the risk distribution. The results outlined herein suggest that the 86-SNV score may be incorporated into breast cancer risk prediction models for patients carrying a PV in BRCA1, BRCA2, and particularly CHEK2. Future work might extend risk modification to the estimation of a second breast cancer for women with a personal and/or family history of breast cancer. Refinement of risk models may enable better definition of personalized risks for women and could enhance the quality of clinical care offered.

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Corresponding Author: Mark Robson, MD, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065 (robsonm@mskcc.org).

Author Affiliations: Myriad Genetics Inc, Salt Lake City, Utah (Gallagher, Hughes, Wagner, Tshiaba, Rosenthal, Roa, Lancaster, Gutin, Lanchbury); Department of Medicine, Stanford University, Palo Alto, California (Kurian); Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia (Domchek); Dana-Farber Cancer Institute, Boston, Massachusetts (Garber); Regeneron Pharmaceuticals Inc, Tarrytown, New York (Lancaster); City of Hope Comprehensive Cancer Center, Duarte, California (Weitzel); Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York (Robson).

Author Contributions: Ms Gallagher and Dr Hughes contributed equally to the study, had full access to all of the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Gallagher, Hughes, Domchek, Garber, Lancaster, Gutin, Lanchbury, Robson.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Gallagher, Hughes, Wagner, Lancaster, Lanchbury, Robson.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Gallagher, Hughes, Tshiaba.

Administrative, technical, or material support: Hughes, Wagner, Roa, Lanchbury.

Supervision: Hughes, Roa, Lancaster, Gutin, Lanchbury.

Conflict of Interest Disclosures: Ms Gallagher reported receiving personal fees from Myriad Genetics Inc during the conduct of the study. Dr Hughes reported receiving personal fees from Myriad Genetics Inc during the conduct of the study. Dr Wagner reported receiving salary and restricted stock from Myriad Genetics Inc. Ms Tshiaba reported receiving personal fees from Myriad Genetics Inc during the conduct of the study. Dr Rosenthal reported receiving personal fees from Myriad Genetics Inc during the conduct of the study. Dr Kurian reported receiving grants from Myriad Genetics Inc outside the submitted work. Dr Domchek reported receiving personal fees from AstraZeneca, BMS, and Clovis outside the submitted work and research funding for clinical trials provided to the University of Pennsylvania from Clovis, AstraZeneca, and Pharmamar. Dr Garber reported serving as an uncompensated advisory board member for Konica-Minolta and receiving research support from Ambry, Invitae, and Myriad outside the submitted work. Dr Lancaster reported being a previous employee of Myriad Genetics and a current employee of Regeneron Pharmaceuticals. Dr Gutin reported being an employee of Myriad Genetics Inc and owning Myriad Genetics Inc stock. Dr Robson reported receiving nonfinancial support from Invitae outside the submitted work and honoraria from AstraZeneca; uncompensated consulting or advisory positions for AstraZeneca, Change Healthcare Daiichi-Sankyo, Epic Sciences, Merck, and Pfizer; research funding to Memorial Sloan Kettering Cancer Center from AbbVie, AstraZeneca, Merck, Pfizer, and Tesaro; travel, accommodation, and expenses reimbursement from AstraZeneca and Merck; compensation for editorial services from AstraZeneca and Pfizer; and grant P30 CA008748 from the National Institutes of Health/National Cancer Institute. No other disclosures were reported.

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SUPPLEMENT.

eMethods. Detailed Methods
eTable 1. Numbers of Individuals With Pathogenic or Likely Pathogenic (PV) Variants in One of Eleven Breast Cancer Genes
eFigure 1. Standardized ORs for the Association Between an 86-SNV Score and Personal BC History for Carriers for each Gene and Non-Carriers
eFigure 2. Observed (Solid Lines) Versus Expected (Dashed Lines) ORs per Percentile of an 86-SNV Score by Carrier Gene

eTable 2. ORs for Developing Breast Cancer for the Continuous 86-SNV Score in Carriers of CHEK2 1100delC and Other CHEK2 PVs

eTable 3. ORs for Developing Breast Cancer for the Continuous 86-SNV Score by Age Bin and by Carrier Status for a PV in a BC-Associated Gene

eFigure 3. ORs for the Association of an 86-SNV Score With the Risk of Developing Breast Cancer by Age Bin and Carrier Gene

eTable 4. ORs for Developing Breast Cancer by BC Affected Status of a First-Degree Relative and by Carrier Status for a PV in a BC-Associated Gene

eFigure 4. ORs for the Association of an 86-SNV Score With Breast Cancer Risk by Family History and Carrier Gene

eFigure 5. ORs for the Association of an 86-SNV Score With Breast Cancer Risk by Weighted Relative Count and Carrier Gene

eReferences.