Development and Validation of a Breast Cancer Polygenic Risk Score on the Basis of Genetic Ancestry Composition

Elisha Hughes, PhD1; Susanne Wagner, PhD1; Dmitry Pruss, PhD2; Ryan Bernhisel, MStat1; Braden Probst, MStat1; Victor Abkevich, PhD1; Timothy Simmons, MStat1; Brooke Hullinger, JD1; Thaddeus Juddsins, PhD1; Eric Rosenthal, PhD1; Benjamin Roa, PhD1; Susan M. Domchek, MD2; Charis Eng, MD, PhD3; Judy Garber, MD, MPH1; Monique Gary, DO, MSc5; Jennifer Klemp, PhD, MPH6; Semanti Mukherjee, PhD7; Kenneth Ofite, MD7; Olufunmilayo I. Olopade, MD8; Joseph Vijai, PhD7; Jeffrey N. Weitzel, MD9; Pat Whitworth, MD10; Lamis Yehia, PhD3; Ora Gordon, MD, MS11; Holly Pederson, MD12; Allison Kurian, MD, MSc13; Thomas P. Slavin, MD1; Alexander Gutin, PhD1; and Jerry S. Lanchbury, PhD1

abstract

PURPOSE Polygenic risk scores (PRSs) for breast cancer (BC) risk stratification have been developed primarily in women of European ancestry. Their application to women of non-European ancestry has lagged because of the lack of a formal approach to incorporate genetic ancestry and ancestry-dependent variant frequencies and effect sizes. Here, we propose a multiple-ancestry PRS (MA-PRS) that addresses these issues and may be useful in the development of equitable PRSs across other cancers and common diseases.

MATERIALS AND METHODS Women referred for hereditary cancer testing were divided into consecutive cohorts for development (n = 189,230) and for independent validation (n = 89,126). Individual genetic composition as fractions of three reference ancestries (African, East Asian, and European) was determined from ancestry-informative single-nucleotide polymorphisms. The MA-PRS is a combination of three ancestry-specific PRSs on the basis of genetic ancestral composition. Stratification of risk was evaluated by multivariable logistic regression models controlling for family cancer history. Goodness-of-fit analysis compared expected with observed relative risks by quantiles of the MA-PRS distribution.

RESULTS In independent validation, the MA-PRS was significantly associated with BC risk in the full cohort (odds ratio, 1.43; 95% CI, 1.40 to 1.46; P = 8.6 × 10⁻³⁰⁸) and within each major ancestry. The top decile of the MA-PRS consistently identified patients with two-fold increased risk of developing BC. Goodness-of-fit tests showed that the MA-PRS was well calibrated and predicted BC risk accurately in the tails of the distribution for both European and non-European women.

CONCLUSION The MA-PRS uses genetic ancestral composition to expand the utility of polygenic risk prediction to non-European women. Inclusion of genetic ancestry in polygenic risk prediction presents an opportunity for more personalized treatment decisions for women of varying and mixed ancestries.

INTRODUCTION

Breast cancer (BC) is a common disease with a substantial hereditary component. Heritable risk of BC is defined primarily by rare causal variants with a highly significant (BRCA1, BRCA2, and TP53) and moderate (CHEK2 and ATM) influence. Polygenic risk scores (PRGs) integrate small effects from tens to thousands of common genetic markers, providing potentially actionable BC risk stratification when combined with clinical and biologic risk factors in patients without highly penetrant or moderately penetrant gene mutations.

Initial development of PRGs for BC was largely limited to genome-wide association studies (GWASs) in women of self-reported European and Ashkenazi Jewish ancestry. Examination of common variation underlying BC risk in non-European women has centered around fine-mapping of loci discovered in European populations or the utility of European-derived PRGs in these groups. Europe-derived PRGs do not stratify risk effectively in different ancestral populations. Improvements could be achieved by addressing allele frequency variations and differential locus contributions. Unique population-specific variations, such as a previously identified protective single-nucleotide polymorphism (SNP) in women of Amerindian ancestry, must also be considered.

Although ancestral homogeneity is necessary for GWAS discovery efforts, human populations are complex and clinical risk stratification tools should...
In independent validation, the MA-PRS was well calibrated and predicted BC risk accurately for both European and non-European populations. The top decile of MA-PRS consistently identified women with two-fold increased risk of developing BC.

Relevance

The MA-PRS uses genetic ancestral composition to expand polygenic risk assessment to women of diverse ancestries. The methodology presented here may lead to the development of equitable PRSs across other common diseases.
ancestry-specific allele frequency and weighted by the ancestry-specific effect size multiplied by the probability of the allele having been inherited from that ancestry (Data Supplement).

Development of the MA-PRS. The development set of 189,230 women was used to combine African-, East Asian– and European-specific PRSs (PRSAf, PRSEA, and PRSEu, respectively) and the Amerindian SNP genotype (xAm = 0, 1, or 2) in a final MA-PRS. Weights for the African-, East Asian–, and European-specific PRSs, denoted by $B_{Af}$, $B_{EA}$, and $B_{Eu}$, respectively, were estimated as log ORs from a multivariable logistic regression model with BC status as the dependent variable and age, personal and family cancer history, self-reported ancestry, genetic ancestry, and interaction between self-reported and genetic ancestry as independent variables. Variables were coded as described in the Data Supplement.

The final MA-PRS was defined as

$$B_{Af} \times PRSAf + B_{EA} \times PRSEA + B_{Eu} \times PRSEu + \beta_{Am} \times x_{Am}. \quad \text{(1)}$$

Independent validation of the MA-PRS. BC risk discrimination of the MA-PRS was evaluated in terms of ORs and $P$ values from multivariable logistic regression models. ORs were normalized to the standard deviation of the MA-PRS distribution in women unaffected by BC and reported with 95% Wald CIs. Additional details are provided in the Data Supplement.

The primary analysis evaluated the association of MA-PRS with BC after accounting for the same independent variables used in logistic regression models for MA-PRS development. This study included two prespecified secondary analyses. First, the MA-PRS was evaluated for improved discrimination compared with a previously published PRS-86, which is based on a subset of 93 BC-associated SNPs used in the MA-PRS. Second, the primary and first secondary analyses were repeated within subcohorts defined by self-reported ancestry.

We evaluated goodness of fit of the relative risks associated with the MA-PRS after accounting for clinical factors. The observed versus predicted effect of the MA-PRS on BC risk was assessed by comparing ORs from the continuous MA-PRS with those obtained from analysis of patients binned in categories according to MA-PRS percentiles.

All analyses were conducted using R version 3.5.3 or higher. $P$ values were calculated from likelihood ratio
chi-squared test statistics and are reported as two-sided. Results are presented in accordance with PRS Reporting Guidelines.29

RESULTS

Genetic Ancestry

Three reference ancestries (African, East Asian, and European) were selected to meet the following criteria. First, reference ancestries combined should represent a significant portion of human genetic diversity. Second, each reference ancestry should be relatively genetically homogeneous. Third, to enable development of an ancestry-specific PRS, data in each ancestry on the association of polygenic variants with BC should be sufficient. Several studies have shown, through principal component analysis, that the first two principal components separate human populations into three distinct clusters corresponding to sub-Saharan Africa, East Asia, and Europe.30,31 African, East Asian, and European are therefore the most suitable ancestries to represent the majority of human genetic diversity. Furthermore, these ancestries are each relatively genetically homogeneous. In addition, available meta-analyses of BC association data were similarly grouped and served as sources of ancestry-specific effect sizes for BC-associated SNPs.12,15 Consequently, a panel of 56 SNP markers was developed to represent the ancestral composition of each patient from the three reference ancestries. The Data Supplement shows the result of applying this approximation to the development cohort. The most homogenous representatives of each of these three populations occupy the apices of the two-dimensional plot. Patients reporting White/non-Hispanic ancestry were genetically homogeneous, whereas all other ancestries showed a high level of genetic diversity. This implies that a PRS on the basis of self-reported ancestry, rather than genetic ancestry, would be accurate for Europeans but inaccurate for non-Europeans.

The Data Supplement shows the estimated average genetic ancestral composition within self-reported ancestries in the development cohort. As expected, there is a high correlation between genetic and self-reported ancestry. The observed admixtures in the major ancestral groups are consistent with previous reports.31

| Characteristic                                    | Variable | Development Cohort (n = 189,230) | Validation Cohort (n = 89,126) |
|--------------------------------------------------|----------|----------------------------------|--------------------------------|
| Personal history of BC                           | No. (%)  | 43,444 (23.0)                    | 20,323 (22.8)                   |
| Patients with first-degree relative(s) with BC   | No. (%)  | 57,741 (30.5)                    | 27,181 (30.5)                   |
| Age at testing, years                            | Range    | 18-84                            | 18-84                          |
|                                                 | Median   | 47                               | 46                             |
|                                                 | % ≤ 50   | 58.8                             | 60.8                           |
| Age at BC diagnosis, years                       | Range    | 18-84                            | 18-84                          |
|                                                 | Median   | 46                               | 45                             |
|                                                 | % ≤ 50   | 62.5                             | 64.0                           |
| Self-reported ancestry, No. (%)                  | Ashkenazi Jewish | 2,487 (1.3)                                      | 981 (1.1)                         |
|                                                 | Asian    | 4,044 (2.1)                      | 2,063 (2.3)                     |
|                                                 | Black/African | 19,460 (10.3)                    | 10,334 (11.6)                   |
|                                                 | Hispanic | 17,749 (9.4)                     | 7,815 (8.8)                     |
|                                                 | Middle Eastern | 860 (0.5)                        | 406 (0.5)                       |
|                                                 | Multiple ancestries* | 4,079 (2.2)                                      | 2,020 (2.3)                         |
|                                                 | Native American | 530 (0.3)                        | 241 (0.3)                       |
|                                                 | Others/unspecifie  | 7,581 (4.0)                      | 3,356 (3.8)                     |
|                                                 | Pacific Islander  | 302 (0.2)                         | 143 (0.2)                       |
|                                                 | White/non-Hispanic | 124,650 (65.9)                  | 58,051 (65.1)                   |
|                                                 | White/non-Hispanic and Ashkenazi Jewish | 3,201 (1.7)                                      | 1,488 (1.7)                         |
|                                                 | White/non-Hispanic and Black | 744 (0.4)                         | 395 (0.4)                       |
|                                                 | White/non-Hispanic and Hispanic | 1,707 (0.9)                                      | 953 (1.1)                         |
|                                                 | White/non-Hispanic and native American | 1,836 (1.0)                                      | 880 (1.0)                         |

Abbreviation: BC, breast cancer.  
*Two or more ancestries including Others, but excluding the following: White/non-Hispanic and Ashkenazi Jewish, White/non-Hispanic and Black, White/non-Hispanic and Hispanic, and White/non-Hispanic and Native American.
MA-PRS Development and Validation

The MA-PRS was developed in 189,230 women and validated in an independent cohort of 89,126 women. Roughly one third of patients reported non-European ancestry (62,441 of 189,230 [33.0%] in development and 27,328 of 89,126 [30.7%] in validation). SNP genotyping failures were rare: of patients who were otherwise eligible, 1 of 189,231 patients were excluded from the development and 0 of 89,126 were excluded from validation because of genotyping failures. Further details of the development and validation study cohorts are provided in Table 1.

Both the allele frequency and the effect size of a SNP can vary between ancestries, potentially leading to biased risk estimates. Differences in allele frequencies cause a shift in the distribution of the PRS. For example, a European PRS applied to non-European women shows a shift to higher values (Fig 2A), an effect that is not related to BC risk but may be misinterpreted as such, as risks of BC are similar in these two populations. Differences in linkage disequilibrium between ancestries can affect the association of individual SNPs with BC risk. This requires a re-estimation of the effect size in each ancestry. In addition, population-specific causal variants can contribute to risk in one ancestry, but not others.

To achieve appropriate PRS calibration in each ancestral group, we built a PRS for each reference ancestry with allele frequencies obtained from the 1000 Genomes Project and effect sizes for each variant obtained from published studies or meta-analysis (Data Supplement). For each patient, the final MA-PRS is a combination of the three ancestry-specific PRSs on the basis of genetic ancestral composition. The improvement in PRS calibration due to ancestry specificity is demonstrated in Figure 2. For a European 86-SNP PRS, the PRS distribution in non-Europeans is not centered, resulting in inflated PRS values (Fig 2A). This effect not only is especially pronounced in women of self-reported Black/African ancestry but also shows significant deviations in women of self-reported Asian and Hispanic ancestry. The MA-PRS, however, is centered for all ancestries, with the sole exception of Hispanic women (Fig 2B). A partially protective variant (rs140068132) contributes to the overall reduced incidence of BC in Amerindian women. Because of the presence of this variant among women of self-reported Hispanic ancestry, the MA-PRS distribution is shifted to lower risk in Hispanic women overall, but remains centered for Hispanic women without the protective variant (Fig 2C).

In independent prespecified validation, the MA-PRS was a highly significant predictor of BC, after accounting for family cancer history, in the overall cohort (OR per standard deviation, 1.43; 95% CI, 1.40 to 1.46; \( P = 8.6 \times 10^{-308} \)) and within each self-reported ancestry (Table 2). In the top decile of the MA-PRS distribution, the relative risk of developing BC was approximately twice the population risk (Data Supplement).

In prespecified secondary analyses, we compared risk stratification because of the MA-PRS against that of a European-derived 86-SNP PRS by including both scores in the same multivariable logistic regression model (Data Supplement). In the full cohort, the MA-PRS was a highly significant (\( P = 8.4 \times 10^{-24} \)) predictor of BC risk after accounting for the 86-SNP PRS. By contrast, the 86-SNP PRS showed only marginal association with BC (\( P = .023 \)) after accounting for MA-PRS. Similar results were observed.
within subcohorts defined by self-reported ancestry: the MA-PRS showed significantly improved risk stratification over the 86-SNP PRS, whereas the 86-SNP PRS showed marginal or nonsignificant stratification independent of MA-PRS. In the mixed-ancestry subpopulation, neither score reached statistical significance, likely because of limited power from the small number of BC cases. Importantly, MA-PRS significantly improved risk stratification for non-European women (P = 1.5 × 10^{-12}) compared with the 86-SNP PRS based solely on European weights and allele frequencies.

Goodness-of-fit tests indicated that MA-PRS relative risk estimates were well calibrated for both European and non-European populations (Fig 3). Importantly, the MA-PRS predicts disease risk accurately in the tails of the distribution. By contrast, the European-derived 86-SNP PRS performed poorly for non-European women at both the lower and higher PRS percentiles (Data Supplement).

**DISCUSSION**

In this report, we describe development and validation of a multiple-ancestry BC PRS (MA-PRS), composed of 93 BC-associated SNPs and 56 ancestry markers, applicable to individuals found in the diverse contemporary US population. The top decile of the MA-PRS identifies women who have BC risks comparable with carriers of pathogenic variants in moderate-risk genes (eg, *ATM* and *CHEK2*). Thus, a substantial fraction of women in each ancestry would qualify for enhanced surveillance measures on the basis of their polygenic risk, including annual contrast-enhanced MRI and consideration of risk-reducing medications that are recommended for those with 20% or greater lifetime risk of BC. Work in progress aims to create a model that combines clinical and genetic factors, further enhancing the ability to identify women at the highest risk levels who are candidates for both enhanced surveillance that detects cancer earlier and risk-reducing medication that can prevent the onset of cancer.

The MA-PRS is unique in two aspects. First, it assumes the MA-PRS showed significantly improved risk stratification over the 86-SNP PRS, whereas the 86-SNP PRS showed marginal or nonsignificant stratification independent of MA-PRS. In the mixed-ancestry subpopulation, neither score reached statistical significance, likely because of limited power from the small number of BC cases. Importantly, MA-PRS significantly improved risk stratification for non-European women (P = 1.5 × 10^{-12}) compared with the 86-SNP PRS based solely on European weights and allele frequencies.

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The MA-PRS is unique in two aspects. First, it assumes that, for the purpose of BC risk prediction, admixed human populations can be described in terms of a genetic mix of three reference ancestries (African, East Asian, and European), consistent with an out-of-Africa model of ancient human dispersion. A second novel aspect of the MA-PRS is the inclusion of PRSs that were optimized for each of the three reference ancestries. The MA-PRS outperforms a PRS built on European weights alone (Data Supplement) and compares favorably with previously published European-derived PRS applied to non-European populations. For example, a study from the Asian BC consortium used European weights to PRSs of 229 and 287 SNPs. Despite the larger number of variants, risk stratification by the PRS287 or PRS229 was similar to that by MA-PRS in Asian women. Importantly, substantial shifts in PRS distribution were observed for the PRS229/PRS287 in Asians relative to European women, indicating poor PRS calibration. In self-reported Hispanic women, the MA-PRS performs comparably with a larger 180-SNP PRS built on European weights. Finally, in a recent meta-analysis in African American women, a 313-SNP PRS and a 179-SNP PRS, on the basis of European weights, performed similar to the 93-SNP MA-PRS, highlighting how ancestry specificity enhances performance. The preceding also spotlights that all BC PRSs thus far have performed less effectively for individuals of African ancestry. Despite many fine-mapping studies, few African-specific variants have been verified, largely because of limited statistical power (Data Supplement).

**TABLE 2.** Association of the MA-PRS With BC Risk in Different Self-Reported Ancestries

| Self-Reported Ancestry | Total No. | Patients With BC (No.) | OR per SD (95% CI) | P | Average OR per SD in Top Decile | Average OR per SD in Top 1% |
|------------------------|-----------|------------------------|--------------------|---|-------------------------------|-----------------------------|
| All                    | 89,126    | 20,323                 | 1.43 (1.40 to 1.46) | 8.6 × 10^{-308} | 1.90                          | 2.61                        |
| Asian                  | 2,063     | 613                    | 1.45 (1.28 to 1.63) | 2.2 × 10^{-3}   | 1.94                          | 2.71                        |
| Black/African          | 10,334    | 2,425                  | 1.23 (1.17 to 1.30) | 2.5 × 10^{-14}  | 1.44                          | 1.74                        |
| Hispanic               | 7,815     | 1,334                  | 1.46 (1.36 to 1.57) | 2.5 × 10^{-25}  | 1.97                          | 2.76                        |
| Mixed Ancestrya        | 4,126     | 560                    | 1.54 (1.38 to 1.72) | 1.1 × 10^{-14}  | 2.17                          | 3.19                        |
| Non-Europeanb          | 21,668    | 4,660                  | 1.35 (1.30 to 1.41) | 2.0 × 10^{-47}  | 1.71                          | 2.24                        |
| White/ Ashkenazi       | 60,520    | 13,880                 | 1.45 (1.42 to 1.49) | 4.2 × 10^{-235} | 1.94                          | 2.71                        |

**NOTE.** Stratification of BC risk by the MA-PRS was tested in multivariate logistic regression in the full cohort and within self-reported ancestries as indicated. Average relative risk (average ORs per standard deviation) for women in the top 10% and top 1% of the MA-PRS distribution is provided.

**Abbreviations:** BC, breast cancer; MA-PRS, multiple-ancestry PRS; OR, odds ratio; PRS, polygenic risk score; SD, standard deviation.

aWomen indicating more than one ancestry on the test request form excluding Others and excluding White/non-Hispanic and Ashkenazi Jewish.

bAny combination of Asian, Black/African, Hispanic, Middle Eastern, Native American, and/or Pacific Islander.
addressed in a number of current studies (CONFLUENCE and BRIDGES) with the intention to bridge the gap in statistical GWAS power between European and non-European ancestries.36,37

Strengths of this study include the use of genetic ancestry composition as part of the MA-PRS. This eliminates inaccuracy inherent in self-reported ancestry and enables expansion of polygenic risk assessment to individuals of mixed ancestries. The large overall and subgroup sample sizes in this study allowed for precise risk estimates, even in the tails of the MA-PRS distribution. The fact that MA-PRS was developed and validated in a high-risk population, with detailed information regarding family cancer history, allowed for estimation of risk attributable to MA-PRS after accounting for family history; these results may inform personalized assessments that combine genetic risks with familial, environmental, and lifestyle risk factors.

The methodology underlying MA-PRS has some limitations. First, we approximate human ancestry to a three-order contribution from African, East Asian, and European population sources. Although an approximation, principal component analysis has shown that these are the three most suitable ancestries to represent the majority of human genetic diversity.30,31 Second, our methodology evaluates the ancestral origin of each BC risk allele on the basis of ancestry-specific allele frequencies and global ancestral composition of an individual. Future improvements may include more extensive evaluation of local genetic ancestry at each BC-associated SNP. Finally, the MA-PRS comprised 93 BC SNPs, and although applicable across ancestries, larger SNP sets have been described for European women.5,6,20,35 Although expansion of SNP numbers provides only incremental improvements in risk stratification in a European population,6 expansion of the MA-PRS is being explored. Notably, recent examinations of European PRSs containing large numbers of SNPs in US populations have either failed to match the performance of the MA-PRS model20 or matched it despite containing approximately 50 times more SNPs.38 One possible explanation is that previous PRS models might have been overfitted.

A possible limitation of the current study is that family history information was collected from the provided completed test request forms and may therefore be incomplete or inaccurate. However, we consider this a minor limitation: we previously published a sensitivity analysis showing that, for the purpose of quantifying associations of genetic

FIG 3. Goodness of fit of MA-PRS relative risk. Relative risk of BC, predicted by the continuous MA-PRS (theoretical) or the average relative risk in categories binned by the indicated percentiles (observed), is graphed against the percentiles of the MA-PRS distribution for (A) all ancestries, (continued in next column)

FIG 3. (Continued). (B) White and/or Ashkenazi ancestries, and (C) non-European ancestries. ORs are for different percentile categories of the PRS relative to the median category. ORs and 95% CIs are shown. BC, breast cancer; MA-PRS, multiple-ancestry PRS; OR, odds ratio; PRS, polygenic risk score.
markers with disease risk, the multivariable regression methodology used here is robust to inaccuracies in family history reporting. Furthermore, a recent study by Kurian et al. evaluated the accuracy of laboratory reported family history data and found high (95%) concordance between the self-report and the laboratory report.

Another limitation of the current study is potential bias from a study population that met clinical criteria for genetic testing. By including factors related to clinical ascertainment in multivariable regression models (specifically personal/family cancer history, age, and ancestry), we obtain estimates of genetic risk that should be unbiased. More specifically, the PRS ORs presented in our work should be consistent with those that would be obtained from a population-based study using either multivariable regression or matched case-control analysis to adjust for personal/family cancer history, age, and ancestry.

Overall, the MA-PRS model described here is an important step forward in the accurate prediction of BC risk in the contemporary US population, irrespective of genetic ancestry and without requiring potentially biased or inaccurate self- or health care provider–reported ancestry. Although a PRS is currently not incorporated into eligibility guidelines for enhanced surveillance, a combination of this PRS model with clinical and biologic factors may provide an opportunity to further enhance risk stratification and appropriate allocation of preventive and screening resources. Future research will apply such a combined model in real-world clinical settings to characterize and quantify its utility. The model created herein may also serve as a framework for developing equitable PRS for other cancers and common health conditions.

Susan M. Domchek, Charis Eng, Judy Garber, Monique Gary, Jennifer Klemp, Semanti Mukherjee, Kenneth Offit, Joseph Vijai, Jeffrey N. Weitzel, Pat Whitworth, Ora Gordon, Holly Pederson, Allison Kurian, Thomas P. Slavin, Alexander Gutin, Jerry S. Lanchbury

MANUSCRIPT WRITING: All authors

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Accountable for all aspects of the work: All authors

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Elisha Hughes
Employment: Myriad Genetics
Stock and Other Ownership Interests: Myriad Genetics

Susanne Wagner
Employment: Myriad Genetics
Stock and Other Ownership Interests: Myriad Genetics

Patents, Royalties, Other Intellectual Property: Coauthor of patents held by Myriad Genetics, no royalties

Travel, Accommodations, Expenses: Myriad Genetics

Dmitry Pruss
Employment: Myriad Genetics
Stock and Other Ownership Interests: Myriad Genetics

Ryan Bernhisel
Employment: Myriad Genetics
Stock and Other Ownership Interests: Myriad Genetics

Braden Probst
Employment: Myriad Genetics

Victor Abkevich
Employment: Myriad Genetics

AFFILIATIONS
1Myriad Genetics, Inc, Salt Lake City, UT
2Basser Center for BRCA, University of Pennsylvania, Philadelphia, PA
3Genomic Medicine Institute, Cleveland Clinic, Cleveland, OH
4Dana-Farber Cancer Institute, Boston, MA
5Grand View Health, Sellersville, PA
6The University of Kansas Cancer Center, The University of Kansas Medical Center, Kansas City, KS
7Memorial Sloan Kettering Cancer Center, New York, NY
8Department of Medicine, University of Chicago, Chicago, IL
9Latin American School of Oncology, Sierra Madre, CA
10Nashville Breast Center, Nashville, TN
11Providence Health and Services, Renton, WA
12Medical Breast Services, Cleveland Clinic, Cleveland, OH
13Stanford University School of Medicine, Stanford, CA

CORRESPONDING AUTHOR
Elisha Hughes, PhD, Myriad Genetics, Inc, 320 Wakara Way, Salt Lake City, UT 84108; e-mail: ehughes@myriad.com.

EQUAL CONTRIBUTION
A.G. and J.S.L. are joint last authors.

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Timothy Simmons
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Brooke Hullinger
Employment: Myriad Genetics
Stock and Other Ownership Interests: Myriad Genetics

Thaddeus Judkins
Employment: Myriad Genetics
Stock and Other Ownership Interests: Myriad Genetics

Eric Rosenthal
Employment: Myriad Genetics
Stock and Other Ownership Interests: Myriad Genetics

Benjamin Roa
Employment: Myriad Genetics
Leadership: Myriad Genetics
Stock and Other Ownership Interests: Myriad Genetics
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Charis Eng
Stock and Other Ownership Interests: Family Care Path, Inc
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Uncompensated Relationships: Family Care Path, Inc

Judy Garber
Stock and Other Ownership Interests: Kronos Bio
Consulting or Advisory Role: Novartis, GTX, Helix BioPharma, Konica Minolta, Aleta BioTherapeutics, H3 Biomedicine, Kronos Bio
Research Funding: Novartis, Ambyr Genetics, Invitae, Myriad Genetics
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Monique Gary
Consulting or Advisory Role: Myriad Genetics
Employment: Caris Life Sciences
Leadership: Cancer Survivorship Training
Stock and Other Ownership Interests: Cancer Survivorship Training
Consulting or Advisory Role: Pfizer, AstraZeneca
Speakers’ Bureau: Pfizer, AstraZeneca
Patents, Royalties, Other Intellectual Property: I am the founder and CEO of Cancer Survivorship Training, Inc, an online learning company for health care providers. The company is the 23rd startup at the University of Kansas and has a license agreement with KU for utilization of my IP

Semanti Mukherjee
Stock and Other Ownership Interests: Regeneron

Kenneth Offit
Patents, Royalties, Other Intellectual Property: Patent pending on therapeutic applications of targeting ERCC3 mutations in cancer. Diagnosis and treatment of ERCC3-mutant cancer US20210137850A1
Other Relationship: AnaNeo Therapeutics, Inc

Olufunmilayo I. Olopade
Employment: CancerIQ
Leadership: CancerIQ
Stock and Other Ownership Interests: CancerIQ, Tempus, 54gene, HealthWell Solutions
Research Funding: Novartis (Inst), Roche/Genentech (Inst), Cepheid (Inst), Color Genomics (Inst), Ayala Pharmaceuticals (Inst)
Other Relationship: Tempus, Color Genomics, Roche/Genentech
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Open Payments Link: https://openpaymentsdata.cms.gov/physician/olopade

Joseph Vijai
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Jeffrey N. Weitzel
Employment: Natera
Stock and Other Ownership Interests: Natera
Consulting or Advisory Role: Myriad Genetics
Speakers’ Bureau: AstraZeneca

Pat Whitworth
Employment: Integra LifeSciences
Leadership: Integra LifeSciences
Stock and Other Ownership Interests: Targeted Medical Education, Inc, Integra LifeSciences
Honoraria: Puma Biotechnology
Consulting or Advisory Role: ImpediMed, Prelude Therapeutics, Becton Dickinson
Research Funding: Prelude Therapeutics, Agenda, Medneon
Travel, Accommodations, Expenses: Targeted Medical Education, Inc

Ora Gordon
Consulting or Advisory Role: Grail, Genetic Technologies
Research Funding: Ambyr Genetics/Konica Minolta, Grail (Inst)
Travel, Accommodations, Expenses: grail

Holly Pederson
Consulting or Advisory Role: Myriad Genetics

Allison Kurian
Research Funding: Myriad Genetics (Inst)
Other Relationship: Ambyr Genetics, Color Genomics, GeneDx/ BioReference, Invitae, Genentech

Thomas P. Slavin
Employment: Myriad Genetics
Leadership: Myriad Genetics
Stock and Other Ownership Interests: Myriad Genetics

Alexander Gutin
Employment: Myriad Genetics
Stock and Other Ownership Interests: Myriad Genetics, Gilead Sciences
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