Performance of *BRCA1/2* Mutation Prediction Models in Asian Americans

Allison W. Kurian, Gail D. Gong, Nicolette M. Chun, Meredith A. Mills, Ashley D. Staton, Kerry E. Kingham, Beth B. Crawford, Robin Lee, Salina Chan, Susan S. Donlon, Yolanda Ridge, Karen Panabaker, Dee W. West, Alice S. Whittemore, and James M. Ford

ABSTRACT

Purpose

There are established differences in breast cancer epidemiology between Asian and white individuals, but little is known about hereditary breast cancer in Asian populations. Although increasing numbers of Asian individuals are clinically tested for *BRCA1/2* mutations, it is not known whether computer models that predict mutations work accurately in Asian individuals. We compared the performance in Asian and white individuals of two widely used *BRCA1/2* mutation prediction models, BRCAPRO and Myriad II.

Patients and Methods

We evaluated BRCAPRO and Myriad II in 200 Asian individuals and a matched control group of 200 white individuals who were tested for *BRCA1/2* mutations at four cancer genetics clinics, by comparing numbers of observed versus predicted mutation carriers and by evaluating area under the receiver operating characteristic curve (AUC) for each model.

Results

BRCAPRO and Myriad II accurately predicted the number of white *BRCA1/2* mutation carriers (25 observed v 24 predicted by BRCAPRO; 25 predicted by Myriad II, $P \geq .69$), but underpredicted Asian carriers by two-fold (49 observed v 25 predicted by BRCAPRO; 26 predicted by Myriad II; $P \leq 3 \times 10^{-7}$). For BRCAPRO, this racial difference reflects substantial underprediction of Asian *BRCA2* mutation carriers (26 observed v 4 predicted; $P = 1 \times 10^{-30}$); for Myriad II, separate mutation predictions were not available. For both models, AUCs were nonsignificantly lower in Asian than white individuals, suggesting less accurate discrimination between Asian carriers and noncarriers.

Conclusion

Both BRCAPRO and Myriad II underestimated the proportion of *BRCA1/2* mutation carriers, and discriminated carriers from noncarriers less well, in Asian compared with white individuals.

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INTRODUCTION

Germline mutations in the *BRCA1* and *BRCA2* genes convey five-fold or greater elevations in the risk of breast and ovarian cancer, accounting for 5% to 10% of breast, and 10% to 15% of ovarian cancers.¹⁻⁴ Since identification of these genes, there has been increasing recognition of differences in *BRCA1/2* mutation prevalence and penetrance across populations.⁵⁻⁷ Although most clinically tested patients have been white, recent publications describe testing in ethnic minorities.⁸⁻¹⁰ One problem with testing minorities is a higher prevalence of clinically uninformative *BRCA1/2* sequence variants of uncertain significance (VUS) than in white individuals, resulting from a limited understanding of normal genetic variation in less tested

groups.^{8,11} As testing of minorities increases, there is strong need to target testing optimally, maximizing detection of mutation carriers, and minimizing uninformative results and costs. Several computer models predict *BRCA1/2* mutation carriage based on personal and family history of breast and ovarian cancer¹²⁻¹⁶; although built using data from white individuals, they have performed accurately in minorities including African Americans and Hispanics.^{8,9,17} Two such models, BRCAPRO and Myriad II, are widely used to guide clinical *BRCA1/2* mutation testing.^{18,19}

BRCA1/2 mutations are relatively understudied in Asian individuals. With rising breast cancer rates in China, Korea, and other Asian countries,²⁰⁻²² and among Asian immigrants to the United States,²³⁻²⁷ there are increasing reports of

From the Departments of Medicine, Health Research and Policy, and Genetics, Stanford University School of Medicine, Stanford; Department of Medicine, University of California at San Francisco, San Francisco, CA; Department of Medical Genetics, The Queen's Medical Center, Honolulu, HI; and the Hereditary Cancer Program, British Columbia Cancer Agency, Vancouver, British Columbia, Canada.

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Corresponding author: Allison W. Kurian, MD, MSc, Stanford University School of Medicine, HRP Redwood Building, Room T254A, Stanford, CA 94305-5405; e-mail: akurian@stanford.edu

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BRCA1/2 mutation testing in Asian populations.²⁸⁻⁴⁰ However, there is limited information on the performance of models to guide such testing in Asian or Asian-American patients.⁴¹ Because Asians comprise 57% of the world's population,⁴⁰ optimizing the targeting of *BRCA1/2* mutation testing in Asian individuals will yield substantial public health benefits. We performed a retrospective cohort study of the performance of the BRCAPRO and Myriad II *BRCA1/2* mutation prediction models in Asian-Americans tested clinically for *BRCA1/2* mutations, compared with non-Jewish white individuals tested in the same cancer genetics clinics.

PATIENTS AND METHODS

Study Population

Participants were recruited retrospectively from cancer genetics programs offering clinical testing for *BRCA1/2* mutations. Mutation testing followed existing guidelines of the National Comprehensive Cancer Network (NCCN), updated yearly⁴²; in general, patients were referred for testing because of personal history of early-onset breast or ovarian cancer, and/or a family history of one or more relatives with breast and/or ovarian cancer. North American cancer genetics clinics were invited to participate, using the electronic mailing list of the National Society of Genetic Counselors, if they had tested more than 25 female probands of Asian descent cumulatively by the time of study initiation in August 2004. Asian descent was defined as having four grandparents of Chinese, Filipino, Japanese, Korean, Hawaiian/Pacific Islander, Taiwanese, Thai, or Vietnamese origin; South Asian patients were excluded given low numbers. Responding eligible centers included British Columbia Cancer Agency (BCCA) in Vancouver, British Columbia, Canada; The Queen's Medical Center (QMC) in Honolulu, HI; Stanford University Medical Center (SUMC) in Stanford, CA; and the University of California at San Francisco (UCSF) in San Francisco, CA.

A white comparison group was selected by matching each Asian proband to one white proband. White probands had all four grandparents of white race; white individuals reporting Ashkenazi Jewish or Hispanic ancestry were excluded, given their higher prevalence of *BRCA1/2* mutations.^{6,43-46} Asian individuals were matched to white individuals on year of birth (within 5 years), predicted probability of *BRCA1/2* mutation carriage (within 10%) using the BRCAPRO model, and testing method; whenever possible, Asian individuals were matched to white individuals tested at the same center. Matching was performed by investigators blinded to all data except the matching criteria of birth year, mutation probability, testing method, and center.

Centers conducted database or chart review to obtain the following on all Asian individuals who ever underwent clinical *BRCA1/2* mutation testing, and on all matched white individuals: cancer history and age at diagnosis, cancer history with ages at onset for all first- and second-degree relatives (provided as a pedigree prepared before testing by a genetic counselor), and mutation testing results. Cancers in probands and, whenever possible, relatives, were confirmed by pathology report review. Chart and database review encompassed the period from testing initiation at each center (1995 to 2000) to the conclusion of data collection on June 1, 2007. Each center's institutional review board approved the protocol.

Mutation Testing

Full sequencing of *BRCA1* and *BRCA2* was performed by Myriad Genetics Laboratories (Salt Lake City, UT) in most participants; those tested after August 2002 also underwent evaluation for five common genetic rearrangements, which was then added to full sequencing by Myriad Genetic Laboratories. For all participants from a single center ($n = 93$), an outside laboratory completed testing of *BRCA1*, and partial testing of *BRCA2* (exons 9, 10, 11, 14, 18, 20, 23, and 25) using a combination of protein truncation test (PTT) and fluorescent single-strand conformation polymorphism (SSCP); sequence changes detected by either of these methods were identified by direct sequenc-

Table 1. Participant Characteristics, by Race

Characteristic	Asian Individuals (n = 200)		White Individuals (n = 200)	
	No.	%	No.	%
Ethnicity				
Chinese	89	44.5	0	0
Japanese	48	24	0	0
Filipina	33	16.5	0	0
Korean	5	2.5	0	0
Vietnamese	4	2	0	0
Mixed or other Asian ethnicity*	21	10.5	0	0
White, not Ashkenazi Jewish or Hispanic	0	0	200	100
Testing center†				
British Columbia Cancer Agency	51	25.5	42	21
The Queen's Medical Center	66	33	31	15.5
Stanford University	46	23	94	47
University of California at San Francisco	37	18.5	33	16.5
Criteria for matching Asian to white individuals‡				
Year of birth				
Median		1955		1956
Range		1919-1982		1926-1980
BRCAPRO score, for <i>BRCA1/2</i> mutation				
Median		0.025§		0.025§
Range		0.0-1.0		0.0-1.0
Myriad II score, for <i>BRCA1/2</i> mutation				
Median		0.069		0.069
Range		0.05-0.58		0.01-0.86

*Ethnicities in mixed race group were Chinese ($n = 9$), Japanese ($n = 5$), Filipina ($n = 4$), Korean ($n = 2$), and Hawaiian/Pacific Islander ($n = 6$); ethnicities in other group were Fijian ($n = 1$), Indonesian ($n = 2$), Burmese ($n = 1$), Malaysian ($n = 1$) and Asian, not otherwise specified ($n = 3$).

†Proportions of Asian and white individuals from each testing center are not equivalent; some Asian individuals ($n = 50$) were matched to white individuals tested at another center, because of unavailability of a white with required matching characteristics at the same center.

‡90.5% of Asian-white pairs were matched on *BRCA1/2* mutation testing method.

§84% of matched pairs had a difference in BRCAPRO score $< 5\%$, and 95% had a difference in BRCAPRO score $< 10\%$; all matched pairs had a difference $< 20\%$. Asian individuals scored lower than their white controls in approximately half of matched pairs.

ing. Testing results were reported as no mutation detected, a deleterious mutation, or a VUS, according to the 2006 Technical Specifications criteria of Myriad Genetic Laboratories.⁴⁷ Asian individuals were matched to white individuals tested by the same method (PTT plus SSCP, or full sequencing, with or without rearrangements). Only two probands (one Asian, one white) had also undergone comprehensive rearrangement testing through the BART test initiated by Myriad Genetics in July 2006.

BRCAPRO and Myriad II Model Score Calculation

The probability of *BRCA1*, *BRCA2*, and *BRCA1/2* mutation carriage was calculated using BRCAPRO and Myriad II, as provided by the CancerGene software program, Version 4b (The University of Texas Southwestern Medical Center, Dallas, TX). To minimize variability in model use, all probabilities (hereafter designated as "model scores") were calculated by two investigators (A.W.K., A.D.S.). Score calculation included entry of all first- and second-degree relatives age 20 years or older on both sides of the family, with all invasive cancer diagnoses and ages at diagnosis, and with all relatives' ages at the time of the proband's testing; ductal carcinoma in situ was entered as an in situ, not an invasive, cancer diagnosis.¹³ For BRCAPRO, scores for *BRCA1* and

BRCA2 were recorded separately, and as a composite score for *BRCA1* or *BRCA2* (*BRCA1/2*); for Myriad II, a composite *BRCA1/2* score was recorded.

Statistical Analysis

For each race, we analyzed the calibration of BRCAPRO and Myriad II by comparing observed prevalence of *BRCA1*, *BRCA2*, and *BRCA1/2* mutations to mean model scores. We evaluated statistical significance between observed and predicted mutations using a χ^2 test. We assessed each model's ability to discriminate between mutation carriers and noncarriers by constructing receiver operating characteristic (ROC) curves, and evaluating the area under each ROC curve (AUC). AUC estimates and 95% CIs were obtained using the R package PresenceAbsence.⁴⁸

RESULTS

Study Population

Data on 258 Asian patients tested clinically for *BRCA1/2* mutations as of June 1, 2007, were submitted by collaborating investigators: 66 from BCCA, 90 from QMC, 48 from SUMC, and 54 from UCSF. Per study protocol, only probands who were the first member of their families to be tested for *BRCA1/2* mutations were submitted. Probands were excluded from analysis for the following reasons: fewer than four grandparents were Asian ($n = 29$), testing results or pedigree were absent ($n = 16$), the pedigree duplicated that of another proband ($n = 11$), or no white proband was available for matching ($n = 2$). A total of 200 Asian individuals were included in the analysis, matched to 200 white individuals (Table 1). Most Asian probands were of Chinese ancestry (44.5%), followed by Japanese (24%), Filipina (16.5%), Korean (2.5%), Vietnamese (2%), and mixed or other Asian ethnicity (10.5%; Table 1). Median year of birth was 1955. The median *BRCA1/2* model scores were 2.5% and 6.9% using BRCAPRO and Myriad II, respectively. White individuals were closely matched with Asian probands on the matching criteria of testing method (90.5% matched), median birth year (1956), and median BRCAPRO *BRCA1/2* score (2.5%). Eighty-five percent of Asian-white pairs were matched within 5% of BRCAPRO score, 95% were matched within 10%, and Asian individuals had a lower score than their white controls in approximately half the pairs (Table 1). Fifty Asian probands (25%) were matched to white individuals tested at a different center, because no match could be found at the same center.

BRCA1/2 Mutations and VUS

Table 2 summarizes the observed *BRCA1/2* deleterious mutations and VUS by race and ethnicity. Forty-nine Asian individuals (24.5%; 95% CI, 19% to 30.9%) carried a *BRCA1* or *BRCA2* mutation, and 27 (13.5%; 95% CI, 9.4% to 19%) carried a VUS. Among Asian individuals, there were 23 (11.5%; 95% CI, 7.7% to 16.7%) *BRCA1* mutation carriers, 26 (13%; 95% CI, 9% to 18.4%) *BRCA2* mutation carriers, six (3%; 95% CI, 1.2% to 6.5%) *BRCA1* VUS carriers, and 21 (10.5%; 95% CI, 6.9% to 15.6%) *BRCA2* VUS carriers. Fewer white probands, who represent a selected subgroup of all clinically tested white individuals, carried a *BRCA1/2* mutation (12.5%; 95% CI, 8.6% to 17.9%) or VUS (4.5%; 95% CI, 2.3% to 8.5%). Specific mutations and VUS are listed in Appendix Table A1 (online only).

Performance of BRCAPRO and Myriad II Models

We evaluated both models' accuracy in predicting the total number of mutation carriers by comparing observed versus predicted mutations (Table 3). BRCAPRO and Myriad II accurately predicted white carriers of either a *BRCA1* or a *BRCA2* (*BRCA1/2*) mutation (model scores of 11.8% and 12.7% v 12.5% observed), but both models significantly underpredicted Asian *BRCA1/2* mutation carriers, by two-fold (model scores of 12.3% and 12.9% v 24.5% observed; $P = 2.4 \times 10^{-12}$ and 2.7×10^{-7} , respectively). BRCAPRO accurately predicted *BRCA1* mutations in both Asian (model score 10.1% v 11.5% observed; $P = .39$) and white individuals (model score 9.0% v 7.5% observed; $P = .35$), but underestimated *BRCA2* mutations in both races, more markedly in Asian (model score 2.2% v 13% observed; $P = 1.1 \times 10^{-30}$) than white individuals (model score 2.9% v 5.5% observed; $P = .01$).

ROC curves, which measure the models' ability to discriminate between mutation carriers and noncarriers, are presented for BRCAPRO *BRCA1*, BRCAPRO *BRCA2*, BRCAPRO *BRCA1/2*, and Myriad II *BRCA1/2* in Figure 1A to 1D, respectively. Curves overlap for all models, indicating that there is no statistically significant difference in model discrimination between races. Corresponding model AUCs, or the likelihood that a mutation carrier will score higher than a noncarrier, are reported in Table 3. There is no statistically significant racial difference in AUCs; however, for BRCAPRO *BRCA1*,

Table 2. *BRCA1/2* Mutation Testing Results of Participants, by Race/Ethnicity

Race	Mutations				Variants*			
	<i>BRCA1</i>		<i>BRCA2</i>		<i>BRCA1</i>		<i>BRCA2</i>	
	No.	%	No.	%	No.	%	No.	%
Asian (n = 200)	23	11.5	26	13	6	3	21	10.5
Chinese (n = 89)	10	11.2	18	20.2	5	5.6	10	11.2
Japanese (n = 48)	1	2.1	4	8.3	0	0	6	12.5
Filipina (n = 33)	6	18.2	1	3	1	3	3	9.1
Korean (n = 5)	1	20	0	0	0	0	1	20
Vietnamese (n = 4)	3	75	0	0	0	0	0	0
Mixed/other (n = 21)†	2	9.5	3	14.3	0	0	1	4.8
White (n = 200)‡	15	7.5	11	5.5	4	2	5	2.5

*Variant of uncertain significance; specific variants are listed in Appendix Table A1 (online only).

†Ethnicities in mixed race group were Chinese (n = 9), Japanese (n = 5), Filipina (n = 4), Korean (n = 2), and Hawaiian/Pacific Islander (n = 6); ethnicities in other groups were Fijian (n = 1), Indonesian (n = 2), Burmese (n = 1), Malaysian (n = 1) and Asian, not otherwise specified (n = 3).

‡One white carried mutations in *BRCA1* and *BRCA2*, so the total number of white mutation carriers was 25.

Table 3. BRCAPRO and Myriad II Model Performance, by Race

Predictive Model	Asian (n = 200)						White (n = 200)					
	Observed Mutations		Predicted Mutations (%)	P for Comparison*	AUC		Observed Mutations		Predicted Mutations (%)	P for Comparison*	AUC	
	No.	%			%	95% CI	No.	%			%	95% CI
<i>BRCA1 or BRCA2</i>												
BRCAPRO,† <i>BRCA1</i>	23	11.5	10.1	.39	69	57% to 81%	15	7.5	9.0	.35	79	64% to 93%
BRCAPRO,† <i>BRCA2</i>	26	13	2.2	1.1×10^{-30}	73	62% to 84%	11	5.5	2.9	.01	70	53% to 87%
<i>Combined BRCA1/2</i>												
BRCAPRO	49	24.5	12.3	2.4×10^{-12}	71	63% to 80%	25‡	12.5	11.8	.69	77	66% to 88%
Myriad II			12.9	2.7×10^{-7}	67	59% to 76%			12.7	.91	78	67% to 89%

Abbreviation: AUC, area under the receiver operating characteristic curve.

*Comparison of observed to predicted mutation prevalence.

†Separate probabilities of *BRCA1* and *BRCA2* mutation carriage are reported only by BRCAPRO.

‡One white participant carried mutations in both *BRCA1* and *BRCA2*, so the total number of observed white mutation carriers was 25.

BRCAPRO *BRCA1/2*, and Myriad II *BRCA1/2*, there is a trend toward higher AUCs suggestive of better discrimination between mutation carriers and noncarriers, in white (77% to 79%) than in Asian individuals (67% to 71%) (Table 3).

Cancer in Probands and Relatives

To explore the reasons for differences in model performance, we evaluated the data used as model inputs for BRCAPRO and Myriad II: personal and family history of breast and ovarian cancer.

Fig 1. Receiver operator characteristic curves for (A) BRCAPRO *BRCA1*, (B) BRCAPRO *BRCA2*, (C) BRCAPRO *BRCA1/2*, and (D) Myriad II *BRCA1/2*, by race.

Cancers in probands and relatives are presented in Appendix Table A2 (online only). More white (14.5%; 95% CI, 10.2% to 20.1%) than Asian (4.5%; 95% CI, 2.3% to 8.5%) probands never had any cancer; however, the prevalence and ages at onset of breast and ovarian cancers were similar among Asian individuals (65.5% had breast cancer; median age, 43 years; 10.5% had ovarian cancer; median age, 49 years) and white individuals (60.5% had breast cancer; median age, 44 years; 8% had ovarian cancer; median age, 51 years). There was no significant difference in the proportion of Asian (25%; 95% CI, 19.5% to 31.5%) versus white (14.5%; 95% CI, 10.2% to 20.1%) probands who lacked family members affected by breast or ovarian cancer, or in the proportion of Asian (7%; 95% CI, 4.1% to 11.5%) versus white (13.5%; 95% CI, 9.4% to 19%) probands who had relatives affected by both breast and ovarian cancer. Median numbers of relatives affected by breast (Asian individuals: one [range, zero to four]; white individuals: one [range, zero to five]) or ovarian cancer (Asian individuals: zero [range, zero to three]; white individuals: zero [range, zero to two]) were equal between races. The median number of relatives per pedigree was similar in Asian (19 [range, five to 56]) and white individuals (15 [range, five to 56]).

DISCUSSION

We evaluated the performance of the BRCAPRO and Myriad II models in Asian and non-Jewish white Americans tested clinically for *BRCA1* and *BRCA2* mutations. To our knowledge, this is the first study to compare *BRCA1/2* mutation prediction model performance between these races. Asian *BRCA2* mutation carriers were six times more prevalent than expected by BRCAPRO; BRCAPRO and Myriad II predicted significantly fewer Asian *BRCA1/2* mutation carriers than expected, in contrast to their accurate prediction of the number of white *BRCA1/2* mutation carriers. Although AUCs were generally higher for white (70% to 79%) than for Asian individuals (67% to 73%), there was no statistically significant difference. This apparent anomaly of comparatively good model discrimination in Asian individuals, yet relatively poor prediction of the number of mutation carriers, can be understood with the following example. If each mutation carrier's score exceeds those of all noncarriers, then a model discriminates perfectly (AUC = 100%). However, each proband's score could be systematically lower than her true probability of mutation carriage, yielding an underestimate of the number of mutation carriers despite perfect model discrimination. Such a scenario may explain the observed equivalent model AUCs between races, despite substantial underprediction of Asian mutation carriers.

BRCAPRO and Myriad II are two among many models that predict the probability of *BRCA1/2* mutations based on personal and family history of breast and ovarian cancer. BRCAPRO is a Bayesian statistical model, developed using data from white individuals;¹³ it is highly dependent on *BRCA1/2* mutation allele frequency and penetrance inputs, and in one Italian study, its accuracy was improved by substituting Italian population-specific penetrance estimates.⁴⁹ Myriad II is an empirical model based on the testing experience of Myriad Genetics Laboratories.¹⁴ In validation studies of BRCAPRO and Myriad II, AUCs ranged from 60% to 83%, equaling or exceeding those of similar models.^{8,10,12,16-19,41,50-57} Of all *BRCA1/2* mutation pre-

diction models, BRCAPRO and Myriad II are the most conveniently and broadly available, through the frequently updated CancerGene software package provided free of charge for Internet download. Given their availability and their generally superior performance on validation, BRCAPRO and Myriad II are by far the most widely used models to guide clinical *BRCA1/2* mutation testing in the United States; consequently, their performance in Asian-Americans has high clinical relevance, which guided our selection of these two models for study.

Prediction model results depend on probands' reports of their family cancer history⁵⁸ because pathologic confirmation of cancer diagnoses is rarely available for second-degree relatives. Therefore, we considered the possibility that racial variation in family history reporting caused the observed differences in model performance. If Asian individuals underreported relatives' cancers, models would likely underpredict Asian mutation carriers; however, we did not observe significantly fewer affected relatives in Asian versus white individuals. Another possibility is a racial difference in the number of relatives reported; BRCAPRO and Myriad II underestimate mutations in probands with limited family structure, defined as fewer than two female first- or second-degree relatives surviving beyond age 45 years.⁵⁹ However, Asian probands in our study reported as many or more relatives (median, 19; range, five to 56) than white individuals (median, 15; range, five to 56), making limited Asian family structure an unlikely explanation for model underprediction. Because we did not explicitly evaluate racial variation in family structure, or in the ages of onset of relatives' cancers, we cannot exclude subtle differences in family cancer patterns (whether true or the result of reporting error) as a potential cause of our findings. However, it seems unlikely that the BRCAPRO model would predict Asian *BRCA1* mutation carriers as accurately as it did if Asian individuals systematically and substantially underreported relatives' cancers. Consequently, we conclude that the observed results are less likely caused by reporting bias, and more likely the result of true racial differences in *BRCA1/2* mutation epidemiology.

Consistent with prior studies, we found that BRCAPRO underpredicted *BRCA2* mutations in all probands,^{17,50} but more markedly in Asian individuals. BRCAPRO's observed six-fold underprediction of Asian *BRCA2* mutation carriers may result from a higher *BRCA2* mutation prevalence; we found that 53.1% of Asian *BRCA1/2* mutations occurred in *BRCA2*, whereas *BRCA1* mutations predominate in other races.⁸⁻¹⁰ An ongoing study of the Breast Cancer Family Registry found fewer *BRCA1* mutations in Asian-Americans than in other races, and will report on the prevalence of *BRCA2* mutations in the broader Asian-American population.⁶ Finally, BRCAPRO's more substantial underprediction of Asian than white *BRCA2* mutation carriers might reflect racial differences in the cancer risk from a *BRCA2* mutation. Recent studies have reported broader variation than anticipated in *BRCA1/2* mutation penetrance.^{7,60} In general, Asian individuals have lower breast cancer incidence than do white individuals;⁶¹ genetic or environmental exposures that differ between these populations might modify hereditary breast cancer risk, reducing breast cancer incidence in Asian compared with white *BRCA2* mutation carriers.

Some study limitations warrant consideration. Participants were recruited from cancer genetics clinics, so the findings cannot be generalized to nonclinical settings; however, these results are

relevant to the many patients who present for clinical testing. Because several sites lacked research databases, data were collected on a limited number of white probands, because comprehensive chart review was not feasible. However, these selected white individuals closely matched Asian probands on age and predicted *BRCA1/2* mutation probability (most within 5%); consequently, they are an informative comparison group in terms of model performance, although not representative of all white individuals in terms of mutation prevalence. All participants from one institution underwent a less sensitive mutation testing method (PTT and SSCP);⁶² because an equivalent proportion of Asian and white probands were tested by this method, this limitation is unlikely to have yielded racial bias in results. We used an older version of the CancerGene software, Version 4B; however, we found no significant difference in model scores when we evaluated a more recent version of the CancerGene program on a subset of 181 Asian probands.⁶³ Study strengths include participation of multiple North American cancer genetics clinics, family history compilation by certified genetic counselors, and consistent calculation of model scores according to published instructions.¹³

In conclusion, we found that one in four clinically tested Asian-Americans carries a *BRCA1/2* mutation, with a six-fold greater number of observed Asian *BRCA2* mutation carriers than estimated by the BRCAPRO model. Although we found no statistically significant racial difference in BRCAPRO and Myriad II model discrimination as measured by ROC curves, both models' two-fold underprediction of the total number of Asian *BRCA1/2* mutation carriers argues for caution in their use to guide clinical testing in patients of Asian descent. Should Asian-specific estimates of *BRCA1/2* mutation prevalence and penetrance become available in future, they may guide modifications to existing models, or development of new ones, to predict *BRCA1/2* mutations

more accurately in Asian individuals. Further study of racial differences in *BRCA1/2* mutation epidemiology, with attention to potential modifiers of hereditary cancer risk, is consequently a high priority for future research.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Allison W. Kurian, Nicolette M. Chun, Meredith A. Mills, Susan S. Donlon, Dee W. West, Alice S. Whittemore, James M. Ford

Financial support: Allison W. Kurian, James M. Ford

Administrative support: Nicolette M. Chun, Meredith A. Mills, Ashley D. Staton, Kerry E. Kingham, Susan S. Donlon

Provision of study materials or patients: Allison W. Kurian, Nicolette M. Chun, Kerry E. Kingham, Beth B. Crawford, Robin Lee, Salina Chan, Susan S. Donlon, Yolanda Ridge, Karen Panabaker, James M. Ford

Collection and assembly of data: Allison W. Kurian, Nicolette M. Chun, Meredith A. Mills, Ashley D. Staton, Beth B. Crawford, Robin Lee, Salina Chan, Susan S. Donlon, Yolanda Ridge, Karen Panabaker

Data analysis and interpretation: Allison W. Kurian, Gail D. Gong, Beth B. Crawford, Dee W. West, Alice S. Whittemore, James M. Ford

Manuscript writing: Allison W. Kurian, Gail D. Gong, Alice S. Whittemore, James M. Ford

Final approval of manuscript: Allison W. Kurian, Gail D. Gong, Nicolette M. Chun, Meredith A. Mills, Ashley D. Staton, Kerry E. Kingham, Beth B. Crawford, Robin Lee, Salina Chan, Susan S. Donlon, Yolanda Ridge, Karen Panabaker, Dee W. West, Alice S. Whittemore, James M. Ford

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).