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Tailoring BRCAPRO to Asian-Americans

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To the Editor

We read with great interest the work of Kurian et al,¹ investigating the performance of *BRCA1/2* mutation prediction models in Asian-Americans. Their work is of broad impact, as Asians account for 5% of the US population and more than 60% of the world population. Two key observations in their article are that (1) the BRCAPRO model² (<http://astor.som.jhmi.edu/BayesMendel/brcapro.html>) underpredicts the proportion of *BRCA2* mutations relative to the total number of mutations, and (2) it under-predicts the total number of mutations of both genes among Asian-Americans. Motivated by these observations, we have developed a revised version of BRCAPRO, specific to Asian-Americans. Here we present new analyses comparing earlier version of BRCAPRO to this newly developed version, and hopefully provide additional insight into the interpretation of the important study of Kurian et al.

Regarding the underprediction of *BRCA2* mutations, Kurian et al report calculations based on BayesMendel version 1.2-1,³ embodied in CaGene4b.⁴ Allele frequencies used by BRCAPRO had been updated in version 1.3-1. While Kurian et al¹ report having checked that the latter version behaves similarly with regard to the combined prediction of *BRCA1* and *BRCA2*, they do not comment on *BRCA2* specifically. We compared the two versions in a set of 2,087 families from the Cancer Genetics Network.⁵ The ratios between the average *BRCA1* and *BRCA2* probabilities using version 1.2-1 was 4.5, compared with 2.2 using version 1.3-1. At the same time, the combined probability was stable (0.20 v 0.18). This observation suggests that concerns about underestimation of *BRCA2* mutations are substantially mitigated in current versions of BRCAPRO, though additional validation could still provide important insight.

Kurian et al¹ also found that the models BRCAPRO and Myriad II underpredicted the total number of *BRCA1/2* mutation carriers by approximately 50% in a set of 200 Asian families

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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recruited retrospectively from four cancer genetics programs, whereas no underprediction took place in a matching set of white families. Kurian et al suggested a number of possible explanations for these differences. One is that the penetrance and prevalence parameters of BRCAPRO, which were derived from white populations, may be different from those in the Asian population. This is a plausible conjecture. However, a search of published studies does not yet suggest that there may be large differences in the mutation penetrance or prevalence in Asians from those of whites.⁶ On the other hand, the phenocopy rate (the age-specific probability of developing breast and ovarian cancer for women who do not carry mutations) used in BRCAPRO has been the same for all ethnic groups. According to Surveillance, Epidemiology, and End Results data, the risk of developing breast and ovarian cancer among Asians is lower than that of whites.⁷ For example, the cumulative probability of developing breast cancer by age 80 years, in the absence of deaths from other causes, is 8% for Asians, compared with 12% for whites (DevCan 6.3.1.; <http://srab.cancer.gov/devcan/>). Therefore, using race-specific phenocopy rates could have impact on the predicted mutation probabilities.

We have now incorporated Asian-specific phenocopy rates into BRCAPRO, and released a revised version as part of BayesMendel version 2.0-2. We then investigated the relationship between the new predictions and the old on the same 2,087 families previously considered. We find that the predicted probabilities can differ significantly between the two versions, especially in the low range. For example, if we stratify women by deciles of the old probability (Table 1), we observe that the old model predicts 24 mutations in families of the lowest decile, while the new one predicts 42; in the second decile, the numbers of mutations predicted are 22 and 31, respectively. As we move to higher-risk deciles, differences become less pronounced and eventually disappear among obviously Mendelian families. Because the combined mutation rate in the Kurian et al¹ study is 12.3% by the old model, the low-risk deciles are the most relevant for the interpretation of the results. Thus it is possible that our new version may account for a portion of the gap observed in the Kurian et al study. A more comprehensive validation is still needed to evaluate the extent to which this gap is filled, and to potentially reconcile the results of Kurian et al with those of an earlier BRCAPRO validation carried out in 200 Han Chinese families, which showed good calibration (observed 31, predicted 39).⁸

We thank Kurian et al for a stimulating article that has led to what we hope to be a significantly improved and more broadly generalizable version of the BRCAPRO model.

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Table 1

Expected Number of Mutation Carriers Predicted by BRCA^{PRO} v1.2-1 and v2.0-2, Stratified by Deciles of the Probabilities From BRCA^{PRO} v1.2-1

BRCA ^{PRO} Version	Probability (%)										Total
	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	91-100	
1.2-1	24	22	17	29	28	24	25	29	49	168	417
2.0-2	42	31	24	34	31	26	25	29	48	167	455