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Title: Validation of OncoVue[®], a new individualized breast cancer risk estimator in the Marin County, California adolescent risk study.

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Background: Improved models for estimating individual breast cancer risk are urgently needed for guiding clinical decisions. The OncoVue model was developed by analysis of a large case-control study genotyped for 117 common, functional single nucleotide polymorphisms (SNPs) in candidate genes likely to influence breast carcinogenesis. Multivariate logistic regression analyses were used to develop a model employing 22 SNPs in 19 genes together with the Gail Model risk factors. In the original studies of the model building set and two independent validation sets, OncoVue exhibited improved individualized risk estimation, compared to the Gail Model alone, by correctly placing more cases and fewer controls at elevated risk. Here, we sought to examine the performance of OncoVue in women from the Marin County, California breast cancer adolescent risk factor study.

Materials and Methods: Buccal cell DNA was isolated from 177 controls and 169 age-matched women diagnosed with breast cancer between 1997 and 1999. All samples were anonymously coded to remove case-control status and provided to InterGenetics along with all other relevant personal history information. DNAs were genotyped for the 22 SNP variants in OncoVue and combined with personal factors to calculate the risk scores for the individual participants. OncoVue scores were then returned to the Marin County study investigators who conducted the analyses using case-control status.

Results: Positive likelihood ratios (PLR) were calculated as the proportion of patients with breast cancer with an elevated risk estimate ($\geq 12\%$) divided by the proportion of disease-free individuals with an elevated risk estimate. For OncoVue the PLR was 2.2, whereas for the Gail Model the PLR was 0.9, demonstrating a 2.4-fold statistically significant ($p=0.036$) improvement. In additional comparisons using normalized control scores, OncoVue exhibited a 51% improvement compared to the Gail Model in assigning elevated risk to cases.

Conclusion: In this blinded validation study OncoVue exhibited significantly improved performance, compared to the Gail model alone, in estimating individual risk among Marin County, California women. The improved performance of OncoVue was similar to that observed in two previous independent validation sets, thus, supporting the clinical utility of OncoVue for more accurate individualized breast cancer risk estimation.