Validation of Models for Prediction of BRCA1 and BRCA2 Mutations

Giovanni Parmigiani, The Sidney Kimmel Comprehensive Cancer Center and the Department of Biostatistics, Johns Hopkins University

Tara Friebel, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania

Edwin S. Iversen, Department of Biostatistics and Bioinformatics, Duke University

*Sining Chen**, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, *and others*

**Presenter*

Context. Identification of the BRCA1 and BRCA2 susceptibility genes has generated interest in statistical models for determining the probability of carrying deleterious mutations based on family history. Several such models have been proposed and are used routinely in clinical activities and scientific investigations; the merits and limitations of these models are not fully understood.

Objective. To systematically quantify and compare the reliability of the prediction provided by eight of the more widely used models.

Design, Setting, and Participants. A large-scale, multicenter study across the Cancer Genetics Network, including three prospective community-based cohorts, one focusing exclusively on Ashkenazim; and case-series data on individuals seeking genetic counseling.

Main Outcome Measure. The ability of models to correctly identify mutation carriers, as measured by the mean-squared error of prediction.

Results. Existing models vary in the accuracy of their predictions. The BRCAPRO model provides the most accurate prediction in both the community-based and counseling settings and in most age groups. While most models show a positive correlation between estimated and observed fractions of mutations across risk subgroups, there is a general tendency to underestimate carrier probability in low-risk families.

Conclusions. While existing models provide a reliable approach to identifying likely carriers of deleterious BRCA1 and BRCA2 mutations, their performances are variable. Opportunity exists for improving the prediction performance of each of these models.