Rubinstein and colleagues provide an excellent review of mathematical models for estimating breast cancer risk, including the risk of carrying inherited mutations of BRCA1 and BRCA2. Since we and others reviewed early models to predict the likelihood of inherited susceptibility to breast cancer,[1] newer quantitative tools, most notably by Parmigiani and colleagues,[2] have been developed. These models have been made available on CD-ROM, over the Internet, and in other electronic versions that are accessible to most clinicians and researchers. These quantitative resources constitute useful and important aids in genetic counseling.

With this commentary, I will provide additional perspective to the excellent overview presented by Rubinstein et al, addressing several areas that the authors did not fully touch upon. These topics include (1) the importance of being aware of genetic testing guidelines propagated by insurers, (2) the probability of detecting missense variants of unknown significance as a result of genetic testing, (3) the psychological implications of testing unaffected probands, and (4) special aspects of testing individuals of Ashkenazi ancestry.

Finally, I will review a general caution that affects all quantitative modeling for hereditary breast cancer. This relates to the highly selected (ie, biased) nature of the ascertainmentsthat have been used to generate risk (penetrance) information.

Quantitative Estimates and Insurance Reimbursement
Perhaps the most clinically relevant application of quantitative risk estimates relates to the use of quantitative models by third-party carriers. In contrast to the early dire forecasts regarding insurance abuse of genetic information, several large carriers include BRCA testing in their coverage plans (without penalty) if specific family history criteria are met. For example, Blue Cross/Blue Shield has issued centralized guidelines on BRCA testing.[3] However, Blue Cross guidelines vary according to the policies of local plans in each state. As part of an American Medical Association conference, the Kaiser system circulated proposed criteria for BRCA testing,[4] and guidelines have also been issued by Aetna/US Healthcare.[5] These policies may be of as much interest to health-care providers as the theoretical models presented in this excellent review. Citation of the theoretical models may be useful for clinicians seeking to obtain insurance coverage for testing services provided to those insured by companies without established policies.

Detecting Missense Mutations of Unknown Significance
A surprisingly overlooked aspect of BRCA testing relates to the frequent occurrence of "ambiguous" results. Missense mutations of unknown significance are found in up to 10%-15% of patients tested. The probability of detecting these variants depends on the ethnic origin of the proband, the gene tested, and the test method utilized. None of the current quantitative models address these aspects of the prediction of these variants. Counseling of individuals with missense mutations of unknown significance can be psychologically challenging. Such counseling can also be complex because the clinician must be prepared to embark upon cosegregation analysis within these families.

Psychological Implications of Testing Unaffected Probands
Another specific aspect raised in this review relates to the desirability (from both an economic and counseling perspective) of initiating testing in relatives who are affected by early-onset disease.
Although the strong rationale for this approach is well summarized, there are psychological aspects that should also be recognized. Affected sisters, mothers, or aunts may feel coerced into undergoing testing by their unaffected relatives. If the affected relative is receiving treatment for advanced disease, testing may prove an added burden.

In such circumstances, identification of a mutation in an unaffected individual may obviate the need for approaching the affected relative. This course may be reasonable if accompanied by appropriate counseling, and if the posterior probability of finding a mutation is sufficiently increased (for example, in a patient of Ashkenazi background with a strong family history).

**Testing Individuals of Ashkenazi Ancestry**

In those of Ashkenazi origin, certain caveats are appropriate regarding testing in the setting of a negative screen for the three founder mutations (case C in the article by Rubinstein et al). First, the recalculation of "residual" risk for nonfounder mutations, assuming the family is not Ashkenazi (as suggested in the review), has not been formally evaluated in large studies. Such an approach may, in fact, represent an overestimation of mutation frequency.[6] The testing of paraffin blocks for specific mutations, although technically feasible, is also not recommended outside the context of a research study. The sensitivity and specificity of clinical testing of paraffin blocks has not been established, and there is the possibility of false-positive results.[7]

**Overestimation of Penetrance**

On a more general note, the major models cited in this review—particularly those developed at the University of Pennsylvania by the Myriad organization in Utah, at the National Cancer Institute (NCI), and at Duke University—were based on, and potentially biased by, ascensions that were highly selected for the presence of a family history of breast cancer. As Rubenstein et al comment, with the exception of the Gail model developed at the National Cancer Institute, none of the models has been validated in a population-based cohort. However, several validation studies of the BRCAPRO model are ongoing.

Population-based models that were not cited,[8] notably those developed in Australia, New York, and Toronto/New Haven, have resulted in markedly lower estimates of breast and ovarian cancer risk associated with mutations of the BRCA1 and BRCA2 cancer susceptibility genes. In some of these studies, family history did not predict likelihood of carrying a mutation. These observations suggest that other genetic factors may not only modify the likelihood of detecting a BRCA mutation, but may themselves constitute independent risk factors for the development of breast or ovarian cancer. As Rubinstein et al point out, model-based risk assessments can be an important adjunct to comprehensive cancer genetic counseling. However, it is important to note that no currently available model is an adequate substitute for a detailed family evaluation conducted by an appropriately trained cancer care provider.

**References:**


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