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Title **Contribution of BRCA1/2 Mutation Testing to Risk Assessment for Susceptibility to Breast and Ovarian Cancer**

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Aim

To clarify the contribution of BRCA1/2 molecular tests in risk assessment and genetic counseling of individuals and families with hereditary breast and ovarian cancer (HBOC).

Conclusion and results

This systematic literature review addresses: 1) prevalence and penetrance of BRCA1/2 mutations; 2) risk assessment models and testing indications; 3) clinical validity of molecular tests; and 4) the impact of molecular testing on risk assessment and genetic counseling. The Canadian Agency for Drugs and Technologies in Health (CADTH, formerly known as CCOHTA) also reviewed BRCA1/2 molecular testing. Its report addressed the analytical validity of molecular tests, the impact of molecular testing for clinical management, and psychosocial and ethical issues. The complementary nature of the work by AETMIS and CADTH researchers is clearly an asset, and conclusions must take both reports into account.

This report clarifies the nature of scientific evidence needed to underpin policy questions raised by the use of genetic testing technology and address unresolved questions and uncertainties. Important limitations in the evidence on prevalence, penetrance, and clinical validity include: the lack of a consensual definition of HBOC; the quality of study designs and reporting of data that are not up to epidemiological standards for molecular test evaluation studies; and variability in the study population selection criteria and molecular testing protocols.

The conceptual and empirical limitations in assessing clinical validity led to adopting an alternate definition and computational approach for clinical sensitivity of BRCA1/2 testing. This approach takes into account uncertainty regarding the true mutation status of test-negative families. Future research should rely on sound methodology (eg, avoiding selection biases) and concerted efforts across defined geographical areas, with agreed-upon selection criteria and testing indications, standardized techniques, monitoring of practices, and regular revision of strategies in the light of new data.

Genetic testing is recommended for high-risk families only, and there is general concordance for broadly defined risk factors (eg, early onset of breast cancer, male breast cancer). However, there is little consensus on the criteria to guide testing within these broad risk factors.

To support clinical decision making, different statistical models have been developed to estimate the probability of a BRCA1/2 mutation, or the risk of developing cancer. None of these models has been unanimously adopted in clinical practice.

Regarding its contribution to risk assessment, testing primarily benefits families in which a BRCA1/2 mutation has been discovered. In unaffected relatives who undergo testing and are found not to carry the mutation, breast cancer risk reduces from a high prior probability to a post-test risk comparable to that in the general population. Unaffected relatives who are found to carry the mutation are at substantially higher cancer risk than the general population.

Recommendations

None.

Methods

Systematic literature review.

Further research/reviews required

A followup AETMIS report is in preparation. It builds on the present work, the recent CADTH report, other systematic reviews, and AETMIS research on organizational and economic issues related to cancer genetics services.

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