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

Summary Report

AGENCE D'ÉVALUATION DES TECHNOLOGIES
ET DES MODES D'INTERVENTION EN SANTÉ

Québec

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

Summary Report

Report prepared for AETMIS by Julie Tranchemontagne, Lucy Boothroyd and Ingeborg Blancquaert

March 2006

Agence d'évaluation des technologies et des modes d'intervention en santé
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MISSION

The mission of the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS) is to contribute to improving the Québec health-care system and to participate in the implementation of the Québec government's scientific policy. To accomplish this, the Agency advises and supports the Minister of Health and Social Services as well as the decision-makers in the health-care system, in matters concerning the assessment of health services and technologies. The Agency makes recommendations based on scientific reports assessing the introduction, diffusion and use of health technologies, including technical aids for disabled persons, as well as the modes of providing and organizing services. The assessments take into account many factors, such as efficacy, safety and efficiency, as well as ethical, social, organizational and economic implications.

NOTE TO READER

This report is a summary of a monograph intended as a first step in a broader analysis of the use of tests for detecting *BRCA1/2* gene mutations and the issues relating thereto. The monograph, like this summary report that stems from it, describes the nature of the evidence concerning the use of this genetic technology and discusses the unresolved questions and uncertainties that complicate the decision-making process. AETMIS is also preparing a complementary report, which examines, among other things, the organizational and economic aspects. This second report will make it possible to draw conclusions regarding the decision-making issues raised by the use of molecular testing.

FOREWORD

CONTRIBUTION OF *BRCA1/2* MUTATION TESTING TO RISK ASSESSMENT FOR SUSCEPTIBILITY TO BREAST AND OVARIAN CANCER

SUMMARY REPORT

This health technology assessment was undertaken following a request from the Québec Ministry of Health and Social Services (MSSS, Ministère de la Santé et des Services sociaux). Questions had been brought to the attention of the MSSS by the Québec health insurance agency (RAMQ, Régie de l'assurance maladie du Québec) regarding whether sending samples to a private laboratory for the sequencing of *BRCA1* and *BRCA2* genes was justified, and which indications for testing should be followed. Additional concerns were raised by the Québec Association of Medical Geneticists (AMGQ, Association des médecins généticiens du Québec) regarding the organization of cancer genetics services in the province. The MSSS request asked AETMIS to consider a broad range of issues, including 1) *BRCA1/2* molecular test validity; 2) testing indications; 3) psychosocial and ethical implications; 4) impact on clinical management; 5) cost-effectiveness; and 6) organizational aspects of cancer genetics service delivery.

Since the Canadian Coordinating Office of Health Technology Assessment (CCOHTA) had also received a mandate to review *BRCA1/2* testing, a collaboration between CCOHTA and AETMIS was established to avoid duplication of work. The present document summarizes a monograph which is the result of the analysis undertaken at AETMIS on 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 counselling. The forthcoming CCOHTA report will address the analytical validity of molecular tests, the potential benefits of molecular testing for clinical management, and the psychosocial and ethical issues. The complementary nature of the work undertaken by the AETMIS and CCOHTA researchers is clearly an asset, but overall conclusions in this area will need to take the content of both reports into account. The scope of the present work does not therefore allow recommendations to be made regarding the complex range of questions related to the clinical use of *BRCA1* and *BRCA2* molecular tests.

A follow-up AETMIS report is also in preparation, which will build upon the present work, the CCOHTA report, and other systematic reviews on selected topics, as well as the research undertaken at AETMIS with respect to organizational and economic issues related to cancer genetics services. This broader-ranging review will allow conclusions to be drawn with regard to the policy questions raised by the use of genetic testing technology. The current summary report provides an understanding of the nature of the scientific evidence that needs to underpin these decisions and of the unresolved questions and uncertainties that complicate the decision-making process.

The purpose of health technology assessment is to examine the use of a specific technology for a given target condition and population. For diagnostic tests, the central question is that of the contribution of the technology to the diagnosis and management of the target condition (be it a disease or a risk factor for disease). Defining the target condition is somewhat problematic in the case of the present assessment. Current clinical practice does not support the widespread use of *BRCA1* and *BRCA2* molecular testing for all cases of breast cancer and their families. Instead, families with

a high prior probability of carrying a genetic susceptibility to breast and ovarian cancer, on the basis of family history and ethnic origin, are targeted. With a view to coherence with the above perspective and given that clinical management was not covered in this review, the present report focuses on the contribution of *BRCA1* and *BRCA2* testing to risk assessment for susceptibility to breast and ovarian cancer.

Dr. Luc Deschênes
President and Chief Executive Officer

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AETMIS would like to express its appreciation to the members of the Genetics Advisory Committee, who took the time to read and comment on the monograph on which this summary report is based:

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DISCLOSURE OF CONFLICT OF INTEREST

None declared.

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1 INTRODUCTION

For both breast and ovarian cancer the strongest known risk factor, after adjusting for age, is family history. The figure most often cited is that approximately 1/3 of breast cancer is *familial*, where family history is defined by the presence of at least two cases of breast cancer, at any age, in first- or second-degree relatives. Approximately 5% of all breast cancer cases are currently thought to be hereditary, that is, related to the transmission of mutations in a single gene. Clustering of cancer cases in families does not imply that genetic susceptibility is always present, since environmental factors and chance can also play a role. Conversely, the presence of a genetic susceptibility will not always translate into the occurrence of multiple cancer cases within one family. However, persons considered to be at highest risk of carrying a mutation in a breast or ovarian cancer susceptibility gene are those displaying the characteristics of a hereditary breast and ovarian cancer syndrome, HBOC. The HBOC syndrome is characterized by a pattern of occurrence of cancers in a family, involving multiple relatives affected by breast and/or ovarian cancer, and by early age at diagnosis. Currently, there is no consensus as to the minimal set of criteria defining an HBOC family.

Two genes conferring susceptibility to breast and ovarian cancer have been associated with HBOC: BReast CAncer gene 1 (*BRCA1*) on chromosome 17 and BReast CAncer gene 2 (*BRCA2*) on chromosome 13. The mutations[1] in the *BRCA1* or *BRCA2* genes are transmitted via an autosomal dominant mode of inheritance.[2] Since the cloning of *BRCA1* and *BRCA2*, in 1994 and 1995 respectively, more than a thousand mutations have been identified in these very large genes.[3] Many of the *BRCA1/2* mutations occur in only one or a few families, except in certain ethnic groups where a founder effect[4] appears to exist. Slight homology exists between the *BRCA1* and *BRCA2* proteins, and both have a function in DNA repair. *BRCA1/2* genes are considered to be tumour suppressor genes. In general, tumour development related to this class of genes occurs when two copies of mutated alleles[5] are present. This implies that carrying an inherited mutated allele is not a sufficient condition for abnormal cell growth and that inactivation of the second, normal allele is a necessary step for carcinogenesis.

According to population-based studies, *BRCA1/2* mutations explain 16–17% of the clustering of breast cancer in families,[6] compared to 55–60% of the clustering in ovarian cancer. However, the contribution of *BRCA1/2* to familial breast or ovarian cancer may be greater in certain ethnic groups with a founder effect, such as Ashkenazi Jewish or Icelandic. At the moment, a substantial proportion of familial breast cancer cases has not been linked to any known breast or ovarian cancer susceptibility gene, and clustering of cancer cases in these families is most likely related to low penetrance[7] genes, environmental factors or a combination of both. The isolation of genetic variants associated with a lower risk of developing cancer poses an important challenge, even though their prevalence could be substantially greater than that of high penetrance genes such as *BRCA1/2*. Indeed, they rarely produce a familial pattern that is striking enough for the traditional analysis used to localize genes.

Since the cloning of *BRCA1/2*, considerable progress has been made in the understanding of the role of the *BRCA1/2* mutations in carcinogenesis, in their characterization in a variety of populations,

1. A mutation is an alteration occurring in the deoxyribonucleic acid or DNA sequence that can result in pathological manifestations.

2. This mode of inheritance implies that mutations on chromosomes other than sex chromosomes have a 50% risk of being transmitted to a carrier's offspring.

3. Each gene spans more than 100 kb of DNA.

4. A founder effect refers to the occurrence of a higher frequency of one or more specific mutations in descendants of a group of common ancestors (founder population), as a result of geographic and/or ethnic isolation.

5. Alleles are alternate forms of a given gene that differ in their nucleotide sequence.

6. Familial cancer is defined here as at least two family members being affected by cancer among first-degree relatives (parent, sibling or child).

7. Penetrance refers to the proportion of individuals with a given genetic variant in whom the manifestations related to that genetic variant are expressed. Penetrance of *BRCA1/2* mutations is measured by the cumulative risk of cancer at a given age.

and in the assessment of the risk of developing cancer for *BRCA1/2* mutation carriers. Molecular tests to detect mutations have been developed, but the transition from research to clinical practice has occurred under a variety of conditions and at a different pace from one centre to the next. Even today, substantial heterogeneity can be observed in terms of the precise testing indications, the analytical techniques used, the organization of services accompanying testing, and the professionals involved in these services. This heterogeneity, in turn, means that combining and making sense of the evidence in this complex field is particularly challenging.

In order to reflect both current clinical practice and the emphasis in the scientific literature, our analysis of the contribution of *BRCA1/2* testing to risk assessment focuses on individuals with a high prior probability (that is, at high risk) of carrying a genetic susceptibility to breast and ovarian cancer. This includes families thought to fit the definition(s) of a hereditary cancer syndrome, as well as individuals with other risk-related characteristics, such as early age at onset of cancer.

The present summary report summarizes a monograph[8] that is part of a broader project. As a first step, a systematic literature review was conducted with respect to:

1) the prevalence of *BRCA1/2* mutations in HBOC families, breast or ovarian cancer cases, and certain founder populations,
2) the penetrance associated with *BRCA1/2* mutations,
3) the available risk assessment models,
4) existing guidelines as to testing indications, and
5) the clinical validity of available molecular tests.

The evidence retrieved from the systematic review was integrated to provide an understanding of the contribution of molecular tests to risk assessment and genetic counselling of individuals and families with HBOC, understood in a broad sense, and to situate these findings within the wider context of decision and policy-making issues related to the clinical use of *BRCA1/2* mutation testing. A complete reference list is presented at the end of this summary report; citation of data sources can be found in the full monograph.

Important considerations, such as the analytical validity or technical performance of available tests, the psychosocial consequences of testing, the impact of testing on clinical management, and the ethical and legal issues raised by the use of these tests in clinical practice, either have been dealt with in recent systematic reviews or are the object of ongoing projects elsewhere.[9] Such topics will not be covered here, but the conclusions of these reviews will be taken into account in a follow-up document to the present report,[10] which will cover issues of particular concern to policy makers. This companion report will include a review of organizational modalities of cancer genetics services in different jurisdictions, a review of the impact of models of care delivery on psychosocial consequences of testing, and a comparative cost analysis for different organizational modalities.

8. Tranchemontagne J, Boothroyd L, Blancquaert I. Contribution of *BRCA1/2* Mutation Testing to Risk Assessment for Susceptibility to Breast and Ovarian Cancer. Montréal: AETMIS, 2006.

9. Foundation for Blood Research (FBR). Family history and *BRCA1*/2 testing for identifying women at risk for inherited breast/ovarian cancer (preliminary report) (www.cdc.gov/genomics/gtesting/ACCE/FBR.htm); CCOHTA (Canadian Coordinating Office for Health Technology Assessment). Systematic review of *BRCA1* and *BRCA2* genetic testing for breast and ovarian cancer susceptibility (in preparation); US Preventive Services Task Force/Agency for Healthcare Research and Quality (USPSTF/AHRQ). Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility. Evidence Synthesis No. 37, 2005 (www.ahrq.gov/clinic/uspstf/uspsbrgen.htm).

10. AETMIS. Cancer Genetic Services: Economic and Organizational Issues (in preparation).

2 METHODS

A comprehensive search strategy using key words was designed in order to identify published, 'grey', and unpublished literature for each topic. The search was limited to human studies, and there were no language restrictions. A draft set of key words was tested for its precision before finalization. Databases of published literature were searched through December 2004. The reference lists of primary research studies, review articles, and reports were searched to identify other relevant articles. The detailed literature search strategies and study selection criteria used for the assessment are presented in Appendix A.

Two reviewers independently made the final selection of studies to be included in the review based on the selection criteria. Study selection forms were developed and pilot tested for this purpose. The decision to order an article was based on the title and abstract, where available. In cases where these offered insufficient information, the article was ordered for further information. The degree of agreement between reviewers was noted, and any persisting differences were resolved by consensus. For articles containing quantitative data, forms that were specifically developed and pilot tested for this project were used to extract data. Various procedures were put in place to ensure quality control, including checking of extracted data by a second reviewer, discussion of all particularly complex articles by several reviewers, and reading of text and tables by a scientific reviewer not directly involved in data extraction.

3 MUTATION PREVALENCE

The prevalence of mutations varies according to the geographic and ethnic origin(s) of the population. Prevalence estimates also vary substantially according to study sample selection criteria, in particular with respect to family history and age at diagnosis. Therefore, *BRCA1/2* mutation prevalence data are reviewed separately for 1) individuals with a family history of breast or ovarian cancer; 2) individuals with these cancers that were not selected on the basis of family history; 3) the general population; and 4) several founder populations.

Table 1 provides an overview of the ranges of values observed depending on the type of population under study. Where several studies were reviewed for a given category, only the extreme values are reported, that is, the results of the studies yielding the lowest and highest point estimates of mutation prevalence. Data were not combined across studies because of the heterogeneity of results and variability in inclusion criteria, mutation detection techniques, and mutation frequency distributions. Confidence intervals for single studies are presented when available. A number of trends can be observed but formal statistical comparisons across study results were not performed. Estimated frequency of *BRCA1/2* mutations in families ascertained because of multiple cases of cancer is, in general, higher than in individuals referred to cancer clinics due to family history, at least on the basis of point estimates for proportion of linked families or mutation prevalence, respectively. In cancer cases unselected for family history, prevalence point estimates tend to be lower for breast than for ovarian cancer cases, unless breast cancer cases are selected on the basis of early age at onset.

TABLE 1
***BRCA1/2* mutation prevalence in different populations**

TYPE OF POPULATION		FREQUENCY OF *BRCA1/2* MUTATIONS, % (95% CI, IF AVAILABLE)			
		BRCA1		*BRCA2*	
		MINIMUM VALUE*	MAXIMUM VALUE*	MINIMUM VALUE*	MAXIMUM VALUE*
Families ascertained for gene identification (multiple cases of cancer)		52†‡ (42–62)		32†‡ (22–43)	
Individuals referred to cancer clinics due to family history		3.5	45.0	1.2	22.5
Breast cancer cases§	Unselected for age at diagnosis	1.1 (0.4–2.2)	2.6 (0–5.5)	1.1‡ (0.4–2.2)	
	Selected for early age at diagnosis	0.7 (0.3–1.3)	6.0 (3.8–8.8)	1.3 (0.8–2.1)	3.9 (2.2–6.3)
Ovarian cancer cases (unselected for age at diagnosis and family history)		1.9	9.6 (6.7–13.5)	0.9	4.1

* Where several studies were reviewed for a given category, only the results of the studies yielding the lowest and highest point estimates of mutation prevalence are presented.
† These figures are proportions of linked families and incorporate partial *BRCA1* mutation analysis.
‡ Only one study was identified by our search methodology.
§ All but one study include cases unselected for family history of breast/ovarian cancer and are from heterogeneous populations.

Up to 36% of women with breast cancer who are mutation carriers report no family history of breast or ovarian cancer. In the Ashkenazi Jewish population, between 1.9 and 2.7% of individuals are estimated to be carriers of one of three common mutations, which is approximately ten times the overall carrier prevalence estimated in heterogeneous[11] populations. *BRCA1/2* mutation frequencies in heterogeneous general populations have been extrapolated from breast cancer series.

Stratified analyses show that mutation prevalence is associated with various risk factors: breast cancer diagnosed at an early age, specific ethnic origin (e.g., Ashkenazi Jewish), ovarian cancer and male breast cancer. Cut-off values for defining 'early' age at diagnosis of breast cancer vary widely in the literature, and there is no general agreement as to the value that justifies offering tests on the basis of age as the only risk factor. The discriminating power of the number of breast cancer cases and the presence of bilateral cancer as risk factors appear to depend on the presence of ovarian cancer in the family history and age of onset of cancer, respectively.

The fact that recurrent mutations have been discovered in certain populations makes the molecular analysis of the *BRCA1/2* genes easier for these groups, since one can screen for common mutations first rather than proceeding directly to screen all exons.[12] However, the testing strategy should take the importance of the founder effect into account. The three most striking examples of founder mutations are those in the Ashkenazi Jewish (AJ), Icelandic and Polish populations. When testing is performed, it is common to screen for selected founder mutations in some ethnic groups (e.g., AJ), while optimal approaches have not yet been established in other founder populations, such as French Canadians.[13]

Currently, the molecular testing of *BRCA1/2* genes yields a fairly large proportion of variants of unknown clinical significance. This raises the problem of classifying and interpreting these test results, deciding whether or not to include them in prevalence calculations, and choosing appropriate clinical follow-up strategies.

11. Heterogeneous refers to the diverse ethnic and geographic origins of the population.

12. Exons are gene sequences whose transcripts persist in the final messenger RNA and which can therefore be translated into a polypeptide chain.

13. A variety of reasons explain this situation, including a higher number of common mutations, a limited number of studies, and possibly, geographic variation of mutation distribution in the province of Québec.

4 PENETRANCE

For *BRCA1/2* mutation carriers, penetrance is defined as the cumulative risk of developing cancer, either up to a specific age or during lifetime. The penetrance of the *BRCA1/2* genes is less than 100% and is therefore said to be incomplete. *BRCA1/2* mutations are nevertheless associated with a high risk of breast and ovarian cancer, clearly elevated over that of the general population. Absolute risks of cancers other than breast or ovarian, such as prostate or male breast cancers, appear to be relatively small.

Tables 2 and 3 provide, for breast and ovarian cancer respectively, an overview of the ranges of penetrance values observed for multiple-case families, clinic-based families, and cancer cases unselected for family history. As in Table 1, data were not combined across studies and only extreme estimates are presented. In studies on families with more than four affected individuals, estimated risk of breast cancer at age 70 is similar for *BRCA1* mutations and *BRCA2* mutations, but risk of ovarian cancer appears to be higher for *BRCA1* than for *BRCA2*. The only published meta-analysis, in which data from 22 studies on heterogeneous and founder populations unselected for family history were pooled, yields lower point estimates for risk of breast cancer at age 70 than studies of highly selected families (i.e., 65% for *BRCA1* mutations and 45% for *BRCA2* mutations). In this meta-analysis, ovarian cancer risk was statistically significantly higher for mutations in *BRCA1* (39%) than in *BRCA2* (11%). Breast cancer risk point estimates for individuals referred to specialized clinics due to family history seem to fall in between the values reported above.

The risk of developing breast and ovarian cancer for carriers of the three founder mutations in the Ashkenazi Jewish (AJ) population has been extensively studied and some studies provide mutation-specific estimates. In contrast, penetrance of *BRCA1/2* mutations has only been estimated in one study of French Canadian high-risk families. Results are in line with estimates of penetrance among high-risk families from other ethnic groups, but confidence intervals are particularly large.

Penetrance estimates with respect to breast and ovarian cancer vary widely from study to study. In general, confidence intervals are wide, rendering most differences between point estimates statistically non-significant. Analyses are under way to examine whether the observed differences are attributable to the effects of disparate designs and analytical methodologies, or to real differences between high-risk and moderate-risk populations. With the exception of certain populations, where penetrance has been determined for specific founder *BRCA1/2* mutations (e.g., AJ, Icelandic, Norwegian), estimates to date are mean values for a broad range of *BRCA1/2* mutations. Given the number of different factors that influence the phenotypic expression of hereditary breast cancer,[14] a more precise personal cancer risk assessment is likely to be unrealistic, especially in heterogeneous populations. Contradictions exist between studies on cancer risk modifiers and these cannot be used presently at the clinical level. At the moment, the information on penetrance is conveyed to patients and families as a range of values derived from empirical data on groups of families with similar risk factors. No biological markers are currently available to predict which *BRCA1/2* mutation carriers will develop cancer. In practice, family pedigree information and ethnicity are used to modulate risk assessment.

14. Factors modulating cancer risk include the type of *BRCA1/2* mutation as well as risk modifiers such as reproductive, environmental and other genetic factors.

TABLE 2

Penetrance of *BRCA1/2* mutations for breast cancer estimated in different populations

TYPE OF POPULATION	PENETRANCE OF *BRCA1/2* MUTATIONS AT 70 YEARS, % (95% CI, IF AVAILABLE)			
	BRCA1		*BRCA2*	
	MINIMUM VALUE*	MAXIMUM VALUE*	MINIMUM VALUE*	MAXIMUM VALUE*
Families ascertained for gene identification (multiple cases of cancer†)	85	87 (72–95)	52.3 (41.7–61.0)	84 (43–95)
Individuals referred to cancer clinics due to family history	73‡ (68–78)		Not available	
Cases of breast or ovarian cancer unselected for family history (meta-analysis§)	65‡ (51–75)		45‡ (33–54)	

* Where several studies were reviewed for a given category, only the results of the studies yielding the lowest and highest point estimates of penetrance are presented.

† The study families yielding the minimum penetrance estimate for *BRCA2* met selection criteria of ≥ 2 cases (or more restrictive criteria in some centres), whereas all other studies in this row selected families with ≥ 4 cases.

‡ Only one study was identified by our search methodology.

§ Meta-analysis combining data from 22 studies from heterogeneous and founder populations.

TABLE 3

Penetrance of *BRCA1/2* mutations for ovarian cancer estimated in different populations

TYPE OF POPULATION	PENETRANCE OF *BRCA1/2* MUTATIONS AT 70 YEARS, % (95% CI IF AVAILABLE)			
	BRCA1		*BRCA2*	
	MINIMUM VALUE*	MAXIMUM VALUE*	MINIMUM VALUE*	MAXIMUM VALUE*
Families ascertained for gene identification (multiple cases of cancer†)	44 (28–56)	63	15.9 (8.8–22.5)	27 (0–47)
Individuals referred to cancer clinics due to family history	40.7‡ (35.7–45.6)		Not available	
Cases of breast or ovarian cancer unselected for family history (meta-analysis§)	39‡ (22–51)		11‡ (4.1–18)	

* Where several studies were reviewed for a given category, only the results of the studies yielding the lowest and highest point estimates of penetrance are presented.

† The study families yielding the minimum penetrance estimate for *BRCA2* met selection criteria of ≥ 2 cases (or more restrictive criteria in some centres), whereas all other studies in this row selected families with ≥ 4 cases.

‡ Only one study was identified by our search methodology.

§ Meta-analysis combining data from 22 studies from heterogeneous and founder populations.

5 RISK ASSESSMENT

Given the complexity of the data on prevalence and penetrance of *BRCA* mutations, statistical modelling has been seen as a means of simplifying risk assessment and of identifying those families that are most likely to carry *BRCA* mutations. The earliest statistical models were designed to predict risk of breast cancer and did not integrate results of molecular testing. Subsequently, several models have been developed to estimate the probability of a *BRCA1/2* mutation explaining the familial aggregation of cancer. These models are either based on published data on population mutation prevalence, age-specific and cumulative penetrance and cancer incidence, or are derived from the analysis of samples of high-risk families fulfilling particular eligibility criteria and for whom molecular testing was performed. Some models are limited to *BRCA1* only, whereas others consider *BRCA1* and *BRCA2*. The range of risk factors integrated in these models is variable (AJ ancestry or male breast cancer may or may not be considered, for example), and such factors are not defined in a consistent way (for early onset of cancer, for instance). The complete family structure is not systematically considered. Most models, therefore, do not apply to all possible familial constellations of risk factors.

Some common predictors of *BRCA* mutation status have been identified through multivariate analysis. Among these, the presence of ovarian cancer and age at diagnosis are prominent. Although similar patterns emerge in the various models, specific results are still dependent upon the particular study samples, the testing methods and the precise definitions of variables used.

A number of authors have compared the carrier probabilities generated by one or several models with *BRCA* mutation testing results. Others have compared the predictions of several models to each other. On the whole, these models are reported to have fairly high sensitivity[15] and negative predictive value,[16] but disappointing specificity[17] and positive predictive value.[18] The approaches used to compare the performance of these models are varied and sometimes questionable. In addition, most comparative studies have been performed on samples of exclusively high-risk families, so that the ability to discriminate between carrier and non-carrier families among borderline low- to moderate-risk families may not have been assessed accurately. More recent risk models strive to account for all facets of the familial aggregation of breast cancer and these may become important tools for risk assessment in the low- to moderate-risk range in the future. Efforts are also under way to develop more user-friendly tools for use in risk assessment in tertiary care and as referral guidelines for primary care.

The lack of proper validation and the numerous classification schemes of risk factors may contribute to the fact that none of these models has been unanimously adopted in clinical practice. Indeed, these statistical models are currently used as supplements to the genetic counsellor or clinical geneticist's own judgement of risk.

15. Sensitivity is the proportion of all persons with the target condition (be it a disease or a risk factor) for whom the test is positive.

16. Negative predictive value is the probability that individuals with negative results will not develop the disease.

17. Specificity is the proportion of all persons free of the target condition (be it a disease or a risk factor) for whom the test is negative.

18. Positive predictive value is the probability that people with positive test results will develop the disease.

6 GUIDELINES FOR TESTING INDICATIONS

Clinical guidelines have been produced by a variety of bodies on indications for performing molecular testing for *BRCA1/2* mutations or on risk classification schemes, with a view to referring families to the appropriate level of care. Most guidelines are based on expert opinion or are extrapolated from research study evidence. However, the links between the recommendations and the supporting evidence, i.e., the source and the specific levels of mutation penetrance and prevalence associated with familial and personal risk factors, are not stated.

Genetic testing is currently recommended for high-risk families only, and there is general concordance between the various guidelines as to the most important risk factors used to define high-risk families. The identified risk factors are consistent with findings from the literature on penetrance and prevalence and with the common results of the risk assessment statistical models discussed earlier. It should be noted that this concordance applies to broadly defined risk factors, such as early onset of breast cancer, male breast cancer, bilateral breast cancer, ovarian cancer, multiple affected family members and Ashkenazi Jewish ancestry. In contrast, there is little consensus as to the precise criteria that should guide testing within each of these broad risk factors, or the combination thereof. This is not a trivial issue, particularly if some risk factors are used in isolation. If, for instance, early age at diagnosis is used as a sufficient criterion for testing (without requirements with respect to number of cancer cases in relatives for instance), the choice of age cut-off greatly influences the number of tests being requested and the ability of laboratories and the health-care system to assume these activities. A similar situation arises if male breast cancer or ovarian cancer is used without additional criteria related to age at onset or family history. If such guidelines were to be considered in Québec, the probability of detecting mutations under these conditions would have to be appropriately documented and the implications estimated, in terms of impact on services and health-care organization.

The most recent guidelines have placed more emphasis on criteria for referral to tertiary genetic services or for access to genetic counselling than on precise testing indications. Likewise, the 2003 statement from the American Society of Clinical Oncology has backed away from the use of a numerical threshold as a criterion to recommend *BRCA1/2* mutation testing, placing greater emphasis on the role of the evaluation made by health-care professionals experienced in cancer genetics in determining appropriateness of testing. Such a position may be more coherent with current practices and more realistic at the present time, given the limitations of available data and the lack of consensus around precise guidelines and statistical models. In terms of planning of clinical and laboratory services, flexible testing indications make it more difficult to predict volume of testing. Cost implications could be significant, if testing were to extend beyond the environment of specialized centres. In addition, flexible testing indications will defer standardization of practices and will thus have implications on future data collection, unless clear selection criteria are agreed upon for research and monitoring purposes.

7 CLINICAL VALIDITY

The length of the *BRCA1* and *BRCA2* genes, the distribution of mutations throughout these genes, and the diversity of types of mutations found markedly complicate molecular analyses. No single technique is appropriate to detect all mutation types. The sequencing[19] of all exons and splice site junctions[20] has traditionally been considered the gold standard technique to detect point mutations, small insertions and deletions[21] in these parts of the genes. Sequencing is both costly and labour-intensive and is not an appropriate technique to detect large rearrangements, such as large deletions or insertions. The proportion of *BRCA1/2* mutations that cannot be detected by sequencing has been the object of research only in the past few years, and it has become clear that the proportion of large rearrangements, for *BRCA1* in particular, cannot be neglected.

Molecular tests are assessed for both their technical and clinical performance. Analytical validity refers to the technical performance of the test and reflects the comparison of test results with the genotype, or the DNA sequence. A literature review on analytical validity did not fall within the purview of this assessment. Clinical validity refers to the comparison of test results with the phenotype, i.e., the clinical expression of disease. Clinical validity is a function of the target population, depending both on the ethnic group and on the familial risk factors used to select study samples. Data were extracted from the literature to estimate clinical sensitivity[22] of:

1) exon and splice site screening techniques (EX/SP screening, involving a variety of methods) for heterogeneous (non-founder) populations, by examining the proportion of HBOC families carrying point mutations and small rearrangements in *BRCA1*, as opposed to large genomic rearrangements and non-coding region mutations;
2) testing for common mutations in different populations with founder effects (Ashkenazi Jewish, Polish, Dutch, Finnish, Hungarian and French Canadian), using the distribution of common and non-common *BRCA1/2* mutations; and
3) the protein truncation test (PTT).[23]

Several methodological challenges were encountered in reviewing this literature. The approach we developed for deriving clinical sensitivity estimates accounts for the conceptual problems underlying these difficulties and the empirical constraints resulting from the quality and nature of available data. A wide variety of different molecular techniques are used both for the point mutation/small rearrangement search and for the detection of large rearrangements. Therefore, resulting data are implicitly dependent on the various levels of analytical sensitivity associated with these methods, and it is thus problematic to combine values across investigations. To account for the limited analytical sensitivity of most techniques used and the possibility of misclassification of families in which all genetic tests were negative (likely a mixture of false negative and true negative results), our clinical sensitivity estimates of EX/SP screening are expressed as a range of values. The minimum value places all the tested families in the denominator, including those who tested negative (with the assumption that they actually carry mutations); the maximum value excludes all negative families from the denominator (by assuming they are truly negative). At the time of our analysis, the literature on large *BRCA2* rearrangements was limited; our computations of

19. Sequencing is a molecular technique used to determine the exact nucleotide sequence of the DNA fragment.

20. Each gene contains several non-contiguous exons. Non-coding sequences (introns) are removed at the junction of exons and introns, also referred to as splice sites, to form the mature messenger RNA for translation into a protein.

21. A point mutation is a single nucleotide base pair change in DNA, whereas insertions and deletions refer to the presence and the loss of one or more consecutive base pairs, respectively.

22. Clinical sensitivity is one measure of clinical validity and refers to the proportion of individuals with the phenotype of the disease (or who will develop this phenotype) in whom the test will be positive.

23. This molecular method is based on the detection of a truncated (shortened) protein.

clinical sensitivity of EX/SP screening methods in heterogeneous populations therefore apply only to *BRCA1* mutations. Finally, the studies we identified involved testing only affected cases from HBOC families, which precludes evaluation of clinical specificity.[24]

Among eligible studies, a single, small-scale study used sequencing for all families and the estimated clinical sensitivity varies from 65 to 76.5%. A greater range of estimates is obtained from the studies which used other EX/SP screening methods. If point mutation/small rearrangement and large rearrangement/non-coding region screening were systematically combined, a higher level of clinical sensitivity would be reached; however, exhaustive testing for large rearrangements and non-coding region mutations is not routine in the clinical setting. A number of laboratories have recently switched to combining the DHPLC technique with MLPA[25] analysis, but there were not enough data in the literature we reviewed to examine a joint clinical sensitivity for this approach.

Large variations in estimates of clinical sensitivity of techniques designed to detect point mutations and small insertions/deletions in exons and splice site junctions are observed in the literature. These variations are in part related to founder effects for large deletions, described in the Dutch population, for example, in which large genomic rearrangements could contribute up to 38% of all clinically important *BRCA1* mutations in high-risk families; they are also the result of differences in study selection criteria and in methods for estimating clinical sensitivity. Underlying these discrepancies is the lack of an unequivocal definition of clinical validity and of the reference phenotype, as well as the progressive and technique-dependent accrual of knowledge. The result is an as yet incomplete portrait of the distribution of *BRCA1/2* mutations in most populations.

In populations with strong founder effects, such as the Ashkenazi Jewish, Icelandic and Polish populations, the testing protocol can be restricted to the search for the common founder mutations. Such testing strategies achieve comparable or even higher clinical sensitivity than the screening of all coding regions in heterogeneous populations. In Finland and Québec, in contrast, several common founder mutations have been identified, but their prevalence is lower and their distribution could vary by region.

24. Clinical specificity refers to the proportion of individuals who do not have the phenotype of the disease (and who will not develop this phenotype) and in whom the test will be negative.

25. DHPLC, or denaturing high performance liquid chromatography, is a technique recently used to detect point mutations and small rearrangements, whereas MLPA, or multiplex ligation-dependent probe amplification, is a recent technique detecting large rearrangements.

8 IMPACT OF TESTING ON RISK ASSESSMENT AND GENETIC COUNSELLING

The utility of testing is determined, in part, by the extent to which test results contribute to a more definite and precise risk assessment, both in terms of personal and familial risk. With respect to the establishment of an increased **familial** risk of breast and ovarian cancer, the identification of a *BRCA1/2* mutation provides confirmation of an increased risk, information which may be useful for families with an *a priori* moderate risk on the basis of the pedigree. In families with an *a priori* high risk, molecular testing may not substantially modify breast or ovarian cancer risk assessment, even if the test result is inconclusive (negative), because of the limited clinical sensitivity of most techniques. The detection (or not) of a *BRCA1/2* mutation may also affect the assessment of risk for other types of cancer (e.g., prostate cancer, male breast cancer).

The impact of testing on the **personal** risk assessment within moderate- to high-risk families is a different issue, and depends on whether a mutation has previously been identified in the family or not. If a mutation has been previously documented in a given family, a negative test result for that particular mutation brings the test-negative individual's risk down to that of the general population, assuming that the test's analytical validity is high and that only one mutation runs in the family. This finding has clear implications in terms of clinical management in the sense of a 'demedicalization' for the individual and her/his offspring. A positive test result, on the other hand, indicates a risk level clearly above that of the general population, but does not necessarily yield a precise estimate of the age-specific or cumulative risk of developing breast and/or ovarian cancer. Precise individual estimates would require detailed knowledge about the joint impact of genetic and environmental risk factors on disease probability, which is unlikely to become available. For current counselling purposes, a wide range is usually provided for the cumulative risk of disease expression. In some founder populations (e.g., Ashkenazi Jewish), risk figures that are specific to particular mutations can be provided. In terms of consequences for family members, first-degree relatives can be informed of their 50% probability of having inherited the same mutation. This information may modify their risk perception and their interest in counselling and testing.

When a mutation has not been previously detected in the family, three outcomes are possible. If a mutation is detected in the index case[26] and is known to be deleterious, the interpretation of the test result is not particularly problematic, since it should be considered a true positive. In contrast, when a variant of unknown clinical significance (VUC) is detected, the *a priori* risk estimate remains applicable as long as the clinical significance of the sequence variation has not been clarified. This result should not be used to guide management decisions, and tests are usually not offered to other family members. To clarify whether the sequence variation has any impact on cancer risk, different types of investigations—both laboratory-based and epidemiological—may be required (e.g., analysis of proteins, association studies). For the genetic counsellor, this situation is particularly complex, and for the family, such an uninformative result is unlikely to relieve anxiety. The third possible outcome—when no DNA alteration is found—should be presented to the family as an 'inconclusive' result. Indeed, a *BRCA1/2* mutation may have been missed by the standard molecular techniques or the family may carry a mutation in another, yet undiscovered breast cancer susceptibility gene. The interpretation here is also complex because, depending on the family history, the post-test probability will either be reduced (but not to the general population level) or remain unchanged. In the latter case, decisions regarding clinical management would likely be based on the familial risk assessment.

The interpretation of a test result and its implications in terms of familial risk and personal management options are not straightforward,

26. An index case is an affected family member who first draws attention to a pedigree.

in view of the complexity and degree of uncertainty associated with some of these results. Interpretation of test results and estimation of post-test probabilities need to consider the pedigree information, the analytical and clinical validity of the technique used, and the penetrance and nature of the detected mutation. Services need to be in place to support patients and families adequately. Qualified personnel and ample time have to be dedicated to providing this information and to allow an opportunity for questions and clarifications.

9 CONCLUSION

In the process of reviewing the literature for this report, important limitations in the evidence have been found. Major problems are the lack of a consensual definition of HBOC and the quality of the study designs and reporting of data, which are not up to epidemiological standards for molecular test evaluation studies. The variability in the study population selection criteria and in the testing protocols for molecular testing complicates the synthesis of the evidence. This variability is particularly striking in the literature on prevalence, penetrance and clinical validity. Current knowledge in areas such as the distribution of *BRCA1/2* mutations is dependent on the evolution of molecular techniques and testing criteria. Both prevalence and penetrance have been studied more thoroughly in high-risk families and in some founder populations than in families at moderate or low risk. Residual uncertainties and gaps in current knowledge have implications regarding decision making for individuals and families, for health-care providers and for policy makers.

Among the conditions put forward by the American Society of Clinical Oncology for molecular testing in cancer genetics in general, the evidence was reviewed with respect to the assessment of prior (pre-test) risk based on family history and on the informativeness of test results for the post-test updating of the risk assessment. As far as current practices are concerned, the majority of families considered eligible for testing in cancer genetics clinics (typically families with two or three affected individuals) are not found to carry a *BRCA1/2* mutation. Such a result is considered inconclusive and the residual risk of cancer remains higher than that of the general population. Providing precise post-test probabilities to these families is, however, difficult because good data on clinical negative predictive value are lacking. Another inconclusive test result which represents a challenging task for geneticists and genetic counsellors and does not substantially alleviate a family's anxiety, is the discovery of a variant of unknown clinical significance. This situation is relatively frequent, possibly almost as frequent as a positive test finding, but may be resolved over time as new knowledge about these variants accrues. In practice, for the very high risk families, the pre-test (prior) risk will not be substantially modified by an inconclusive test result.

Testing primarily benefits families in which a *BRCA1/2* mutation has been discovered. For unaffected relatives who undergo testing and are found not to carry the mutation present in the family, breast cancer risk drops from a high prior probability to a post-test risk comparable to that in the general population. Unaffected relatives in whom a mutation is identified, on the other hand, have a substantially higher cancer risk than that of the general population. In addition, individuals with breast or ovarian cancer in whom a *BRCA1/2* mutation is identified are at increased risk of developing a second cancer. For families in which a *BRCA1/2* mutation is identified, both positive and negative test results have implications for clinical management, either in the sense of a 'demedicalization' or of increased requirements for surveillance, prevention or prophylactic measures. A review of the effectiveness of these interventions did not fall within the purview of this report.

Consequently, a balanced view of benefits and risks, and formal recommendations with respect to the use of *BRCA1/2* mutation testing, cannot be presented at this time. It is, however, already apparent that the balance of benefits and risks will be heavily dependent on the prior risk assessment and that the knowledge base to derive decisions is stronger for high-risk families than for populations at lower risk. In the subsequent AETMIS report, the forthcoming evidence from other systematic reviews on issues such as the analytical validity of molecular tests, the psychosocial consequences of testing, and the effectiveness of available interventions will be integrated with our further analysis of the economic and organizational issues surrounding cancer genetic services.

APPENDIX A

LITERATURE SEARCH

Searches of the following databases were completed to the end of June 2004: PubMed, Cochrane Library, Dialog® OneSearch® on MEDLINE®, CANCERLIT®, EMBASE®, Biosis Previews®, and PASCAL. In addition, PubMed, CANCERLIT®, and EMBASE® were searched from July to end of December, 2004. A preliminary investigation revealed extensive literature, particularly on prevalence and penetrance, subsequent to the cloning of *BRCA1* and *BRCA2* in 1994 and 1995, respectively. The following strategies were therefore used:

1) The literature search for primary research articles was restricted to January 1999 onwards. An additional search for review articles published from 2001 to 2002 was conducted, and the reference lists of these articles were examined to identify key primary research articles published before 1999.

2) For the risk assessment chapter, review articles published from 2001 and 2002 were used to describe models developed before 1999. Contact was also made with clinical practice experts in cancer genetics from Québec, Ontario, and British Columbia to confirm that the models and tools most often used in clinical care were included in this chapter.

3) Clinical practice guidelines on test indications were examined from 1996 onwards, as the clinical use of *BRCA* genetic testing was first discussed in guidelines in that year. Guidelines listed in the Inherit BRCA database [INHERIT BRCAs, 2001] were examined.

4) For the clinical validity chapter, besides studies on mutation prevalence, articles on the performance of molecular tests for *BRCA1/2* were also examined to identify studies on large genomic rearrangements and non-coding mutations.

Grey literature was identified by searching the INAHTA (International Network of Agencies for Health Technology Assessment) websites, other health agency websites, clinical trial registries, clinical practice guideline databases, websites of relevant societies and associations (for conference abstracts), and other specialized databases.

STUDY SELECTION CRITERIA

The selection criteria used for each topic are listed below.

Prevalence and penetrance

The selection criteria for material on prevalence and penetrance were the following:

1) Primary research study published since 1999.

2) Sample size ($n \geq 100$) for samples selected for family history.
   - Families could be a mixture of breast cancer only, ovarian cancer only, or breast-ovarian families, or the sample could be entirely made up of one of these groups.
   - No sample size cut-off was used for Canadian studies of this type.

3) Sample size ($n \geq 500$) for samples not selected for family history.
   - These were usually persons affected with cancer, and selection for age at onset/diagnosis was allowed.
   - No sample size cut-off was used for Canadian studies or for studies of this type from Iceland (due to the small number of studies available for the Icelandic population).

- ‘Key’ articles (i.e., frequently cited primary research) published before 1999 were identified using 33 review articles from January 2001 to June 2002 and using reference lists from primary research articles which met the selection criteria. For key articles which studied persons unselected for family history, the sample size cut-off was lowered to at least 100 persons.
- For samples not selected on the basis of family history nor age at onset/diagnosis, the sample size cut-off was lowered to at least 100 persons if the study sample was from USA, United Kingdom or France (the two last countries being major founding regions for the Canadian and American populations).

4) For key articles on Ashkenazi Jewish persons, testing for all 3 frequent *BRCA1/2* founder mutations was necessary (i.e., *BRCA1* 185delAG, *BRCA1* 5382insC, *BRCA2* 6174delT).

5) Abstracts were excluded, due to the large number of peer-reviewed primary research articles in this area, except for those presented at a recent large genetics conference (American Society of Human Genetics, Toronto, October 2004).

Review articles and additional primary research articles that were suggested by a genetics expert were used in the discussion of variability of penetrance and in the section on other cancers. These issues were not the primary focus of the systematic review on prevalence and penetrance.

Risk assessment

No sample size restrictions were used as criteria for this topic. To be included in the data extraction, a primary research study (published since 1999) had to develop and/or test predictive risk models (these models were developed using *BRCA1/2* mutation testing or estimates of *BRCA1/2* prevalence/penetrance and cancer incidence). Simulation studies and segregation analyses used to develop explanatory models and purely methodological papers were excluded.

Testing indications

No sample size restrictions were used as criteria for material on testing indications. Guidelines were selected that specifically mentioned indications for *BRCA* genetic testing or referral to family cancer clinics, clinical geneticists, genetic counsellors, etc.; some of these also discussed clinical management (management details were not summarized). Recommendations for referral to different levels of specialized care (within which a decision to test for mutations may or may not be made) were included since these also gave an idea of the risk levels in use in clinical practice.

Clinical validity

No sample size restrictions were used as criteria for clinical validity material. A search was carried out for primary research on the prevalence of *BRCA1/2* mutations or on *BRCA* mutation testing methods that potentially contained information on the distribution of susceptibility mutations. Due to the relative scarcity of material, abstracts were not excluded in the search for this topic.

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