

Office of Population Health Genomics

Paper:
ACCE Review Summary
Breast and Ovarian Cancer
(BRCA1/BRCA2)

Purpose: To evaluate genetic testing for BRCA1/2 in
Australia using the ACCE framework

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ACCE REVIEW – Breast and Ovarian Cancer (BRCA1/BRCA2)

The Centre of Disease Control (CDC) in the United States has been working on a review of BRCA1/2 genetic testing using the ACCE framework comprising of Analytic validity, Clinical validity, Clinical utility and Ethical, legal and social issues. Comprehensive documents are currently being developed by the CDC. This documentation is in draft form at this time and is available for comment on the following website: <http://www.cdc.gov/genomics/gtesting/ACCE/fbr.htm>

Following is an early draft of an ACCE review summary of genetic testing for BRCA1/2 for the Australian context.

The CDC documents, as well as the National Health and Medical Research Council's (NHMRC) document, *Clinical Practice Guidelines - Familial Aspects of Cancer: A Guide to Clinical Practice (1999)* and the National Breast Cancer Centre's (NBCC) *Advice about familial aspects of breast cancer and epithelial ovarian cancer: A guide for health professionals* have provided extensive information for this document.

This document has been authored by Suzy Maxwell, with contributions from Assoc Prof Ted Edkins and Dr Ian Walpole.

Disorder / Setting

<p>Breast and ovarian cancer statistics</p> <p>What is the specific clinical disorder?</p>	<ul style="list-style-type: none"> Breast cancer Australia 2001: 11 791 [1] 2 954 deaths [1] 1-5% breast cancers are due to an autosomal dominant inheritance of a mutated gene [2] . Ovarian cancer Australia 2001: 1 295 [1] 857 [1] 												
<p>Characteristics of hereditary breast and ovarian cancer</p> <p>What are the clinical findings?</p>	<ul style="list-style-type: none"> Early onset of breast and ovarian cancer <i>Physical findings associated with breast cancer are relatively specific and well understood. Information about this is widely disseminated. Many cases of breast cancer are diagnosed at an early stage. Physical findings associated with ovarian cancer are not apparent in the early stages. Many cases of ovarian cancer are diagnosed at a late stage. Diagnosis is by biopsy/pathologic examination. Histologic grading and tumour staging is standardised [3]</i> 												
<p>Genetic mutation</p> <p>What DNA tests are associated with this disorder?</p>	<ul style="list-style-type: none"> Autosomal dominant trait Genes involved [2] <table border="1" data-bbox="627 1324 1881 1428"> <thead> <tr> <th>Gene</th> <th>Location</th> <th>Comment</th> <th>Available</th> </tr> </thead> <tbody> <tr> <td>BRCA1</td> <td>17q</td> <td>About 60% of inherited breast cancer</td> <td>Yes</td> </tr> <tr> <td>BRCA2</td> <td>13q</td> <td>About 20% of inherited breast cancer</td> <td>Yes</td> </tr> </tbody> </table> 	Gene	Location	Comment	Available	BRCA1	17q	About 60% of inherited breast cancer	Yes	BRCA2	13q	About 20% of inherited breast cancer	Yes
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	<ul style="list-style-type: none"> • Other genes have been identified that have a link to breast cancer development. However, this ACCE review is primarily concerned with BRCA1 and BRCA2. • Hereditary Non-Polyposis Colorectal Cancer (HNPCC) genes are also associated with ovarian cancer. For information about these genes please see the HNPCC ACCE review. • <i>BRCA1 and BRCA2 are large genes with thousands of mutations [3].</i> • <i>Most BRCA1/2 mutations are unique, so that each family with a defined history of breast/ovarian cancer tends to have its own mutation [3].</i> • <i>Due to the size and complexity of the genes, expensive and time-consuming gene sequencing is often necessary [3]</i> • <i>Once a family mutation is known, less expensive targeted testing can be performed [3]</i> • <i>Ongoing studies are helping to resolve some of the variants of unknown clinical significance [3]</i>
<p>Screening process</p> <p>What is the clinical setting in which the test is to be performed?</p> <p>Are screening questions used?</p> <p>Is it a stand-alone test, or one in a series?</p> <p>Are tests run in parallel or in series?</p>	<ul style="list-style-type: none"> • The NHMRC recommends that a <i>family history is taken, asking about any cancer in all first and second degree relatives, male or female, on both the maternal and paternal sides of the family, and age of diagnosis [2].</i> • Preliminary screening questions are required as BRCA1/2 mutations are uncommon (>1 per 1000) [2], and gene sequencing costs are high. Guidelines have been developed as to risk levels and who should be offered genetic testing. • Clinics assess detailed information about a woman’s family history of cancer before providing risk information, a risk estimate of carrying a mutation, strategies to reduce cancer risk, information about genetic testing (including the limitations) and early detection. [4] • Genetic testing should proceed only in the context of pre and post test genetic counseling. • Familial cancer clinics (FCCs) are the clinical setting in which testing occurs. In Australia there are currently only a few laboratories that offer BRCA1/2 testing. • Clinics assess and validate documented detailed information about a woman’s family history of cancer before providing risk information, an estimate of carrying a mutation, strategies to reduce cancer risk, information about early detection, genetic testing [4] • FCCs have recognised methods of assessing the threshold likelihood of ascertaining susceptibility gene mutations, before embarking upon testing.

Analytic Validity

<p>Analytic sensitivity</p> <p>Analytic specificity</p>	<ul style="list-style-type: none"> • External proficiency testing provides a way to determine analytic sensitivity • Based on data from the European Molecular Genetics Quality Network [5] <ul style="list-style-type: none"> ○ The overall error rate is 2.7 percent (95 percent CI 1.6 to 4.2%) ○ Analytic sensitivity is 97.1 percent (95 percent CI 95.2 to 98.5%) • Based on data from the American College of Medical Genetics and the College of American Pathologists Molecular Genetics Laboratory Survey [5] <ul style="list-style-type: none"> ○ The overall error rate is 0.0 percent (95 percent CI 0.0 to 4.6%) ○ The analytic sensitivity is 100 percent (95 percent CI 93.0 to 100%) ○ The analytic specificity is 100 percent (95 percent CI 96.0 to 100%)
<p>Quality control</p> <p>Is an external quality control program defined and externally monitored?</p> <p>Have repeated measurements been made on specimens?</p> <p>If appropriate, how is confirmatory testing performed to resolve false positive results in a timely manner?</p>	<ul style="list-style-type: none"> • The NHMRC's <i>Clinical Practice Guidelines - Familial Aspects of Cancer: A Guide to Clinical Practice</i> state that <i>all laboratories should be involved in a relevant quality assurance program, which should be administered by a body representing the expertise of both the Royal College of Pathologists of Australasia or the Human Genetics Society of Australasia</i> [2]. • The guidelines stipulate the issues that need to be addressed by a quality assurance program, including, but not limited to diseases and techniques, provision of samples, distribution of samples, genomic DNA from cell lines, RNA or PCR-amplified alleles [2]. • <i>Where there is insufficient demand in Australia to warrant creating a quality assurance program for a specific gene, a laboratory should seek to join a quality assurance program established overseas</i> [2]. • Having information about repeated measurements on the same specimen is important for determining the type and rate of errors in <i>BRCA1/2</i> testing [5] • A positive diagnostic mutation result is best confirmed by a second method of analysis. For predictive testing duplicate samples are used. • Confirmatory testing is additional testing to verify the finding of a mutation(s). It is likely to be useful because of occasional false positive test results [5] • HGSA is offering a BRCA QAP module in 2006/7
<p>Assay</p> <p>Is testing qualitative or quantitative?</p> <p>What range of patient specimens have been tested?</p>	<ul style="list-style-type: none"> • BRCA1/2 testing is qualitative • Result categories are: <ul style="list-style-type: none"> ○ Positive for a deleterious mutation ○ Negative for a deleterious mutation

<p>How often does the test fail to give a useable result?</p> <p>How similar are results obtained in multiple laboratories using the same, or different technology?</p>	<ul style="list-style-type: none"> ○ Genetic variant (suspected deleterious, favour polymorphism, and uncertain significance) ○ Specific variant/mutation not identified [5] <ul style="list-style-type: none"> ● BRCA1/2 testing can be done on blood for diagnostic testing and use RNA from PHA-stimulated white blood cells. This will pick up more mutations than through exon-by-exon sequencing. MPLA is also required for BRCA1/2 testing. ● When analytic failures do occur, repeating the analysis will often yield useable results [5] ● Types of failures and their associated rates are rarely reported [5]
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Clinical Validity

<p>Clinical specificity</p>	<ul style="list-style-type: none"> ● The reliability of questionnaires on family history of breast/ovarian cancer has not been validated. Specificity estimates range from 83-95% [6]
<p>Clinical sensitivity</p> <p>Are there methods to resolve clinical false positive results in a timely manner?</p>	<ul style="list-style-type: none"> ● The reliability of questionnaires on family history of breast/ovarian cancer has not been validated. Sensitivity estimates range from 93-99% [6] ● <i>Clinical false positives are defined as individuals who carry a BRCA mutation and have none of the associated cancers nor will develop one of these cancers during their lifetime [6]</i> ● <i>As with most pre-symptomatic DNA testing, there are no methods to resolve clinical false positives among those identified with a mutation conveying increased susceptibility [6].</i> ● <i>If an individual has a mutation and has not developed an associated cancer by the time of testing, estimates of cancer risks can be given based on age and family [6].</i> ● <i>Preventive/risk-reducing measures can then be considered. However, there is currently no way of determining whether an individual will develop cancer later in life [6]</i>
<p>Prevalence</p> <p>What is the prevalence of the disorder in individuals with a positive family history?</p> <p>Has the test been adequately validated on all populations to which it may be offered?</p>	<ul style="list-style-type: none"> ● The NHMRC categorises breast cancer risk into three main categories based on the extent of family history [4]. For details see the NHMRC document. <ul style="list-style-type: none"> ○ <i>At or slightly above average risk</i> Coverage: over 95% of the female population ○ <i>Moderately increased risk</i> Coverage: Less than 4% of the female population Risk: between 1 in 8 and 1 in 4 ○ <i>Potentially high risk</i> Coverage: Less than 1% of the female population

	<p>Risk: Between 1 in 4 and 1 in 2 (individual risk may be higher or lower if genetic tests are known)</p> <ul style="list-style-type: none"> • The NHMRC categories ovarian cancer into three main categories based on the extent of family history [2] <ul style="list-style-type: none"> ○ <i>At or slightly above average risk / Moderately increased risk</i> Coverage: More than 99% of female population Risk: Between 1 in 100 and 1 in 30 ○ <i>Potentially high risk</i> Coverage: Less than 1% of the female population Risk: Between 1 in 30 and 1 in 3. Individual risk may be higher or lower if genetic test results are known. • <i>BRCA1/2</i> mutations responsible for susceptibility to breast and ovarian cancer may vary by ethnicity. However mutation testing via direct sequencing is believed to reliably identify all mutations that are detectable by this methodology, regardless of race/ethnicity if done from RNA via cDNA. [6]
<p>Predictive values</p> <p>What are the positive and negative predictive values?</p> <p>What are the genotype/phenotype relationships?</p>	<ul style="list-style-type: none"> • According to the NHMRC guidelines <i>failure to detect a genetic alteration does not automatically imply a low or reduced risk of developing breast cancer. Negative genetic tests are meaningful only when the genetic alteration in the family is already known and an individual family member is found not to carry that specific high-risk alteration in her or his constitutional DNA</i> [2] • While there has been much research in the area of genotype/phenotype relationships of breast/ovarian cancer, results have not had an impact on the clinical management of the mutation carriers' disease [6].
<p>Penetrance</p> <p>What are the genetic, environmental or other modifiers?</p>	<ul style="list-style-type: none"> • <i>Of women with a mutated BRCA1 gene, clinical disease may develop in about 50% by age 50 and 80% by age 70, based on data from large extended breast cancer kindreds. The risk of ovarian cancer in carriers is thought to be up to 20% by age 50 and 60% by age 70. There is also limited evidence that carriers may have an increased risk of colon cancer and that male carriers may have an increased risk of prostate cancer. However, there is considerable uncertainty in these estimates of risk, and they may need to be modified when population based studies are published.</i> [2] • Other factors are likely to play a role in the development of breast and ovarian cancer including; <ul style="list-style-type: none"> ○ Age ○ Hormonal factors <ul style="list-style-type: none"> ▪ Early age of menarche ▪ Nulliparity ▪ Late menopause ▪ The use of Hormone Replacement Therapy (it has not been evaluated in women at high risk of hereditary breast cancer) ▪ Tamoxifen

- Oral Contraceptive Pill use
 - Obesity
 - Alcohol consumption
 - Physical activity
 - Risk reducing surgeries (oophorectomy, mastectomy)
- The role of non-genetic modifiers in women with BRCA1/2 mutations is largely unknown [6].

Clinical Utility

Natural history

If applicable, are diagnostic tests available?

- A study by Boyd et al aimed to determine whether hereditary ovarian cancers have distinct clinical and pathological features compared with sporadic (nonhereditary) ovarian cancers. The study found that *although BRCA-associated hereditary ovarian cancers in [the studied] population have surgical and pathological characteristics similar to those of sporadic cancers, advanced-stage hereditary cancer patients survive longer than nonhereditary cancer patients. Age penetrance is greater for BRCA1-linked than for BRCA2-linked cancers in this population.* [7]
- Some findings suggest that there are differences in the natural history of disease between BRCA1 breast cancers, BRCA2 breast cancers and sporadic cases [8-12].
- For identifying and diagnosing breast/ovarian cancer once it has occurred [13]
 - Clinical breast exam and mammography are screening tests aimed at identifying breast cancer
 - Measurement of CA125 and ultrasound are screening tests aimed at identifying ovarian cancer
 - Histologic examination of tissue/fluid samples is the diagnostic test for both breast and ovarian cancer

Costs and benefits

Is there an effective remedy, acceptable action, or other measurable benefit?

Is there general access to that remedy or action?

What are the financial costs associated with testing?

- According to the NHMRC guidelines *failure to detect a genetic alteration does not automatically imply a low or reduced risk of developing breast cancer. Negative genetic tests are meaningful only when the genetic alteration in the family is already known and an individual family member is found not to carry that specific high-risk alteration in her or his constitutional DNA* [2].
- A meaningful negative test result (as described above) puts an individual at a population risk of developing breast/ovarian cancer. Standard population screening programs apply.
- The NHMRC have developed guidelines as to the management of individuals with a suspected or confirmed BRCA mutation. These are available on pages 57-60 in the document *Clinical Practice Guidelines - Familial Aspects of Cancer: A Guide to Clinical Practice* [2].
- Surveillance options include mammography, breast self examination, clinical examination, transvaginal ultrasound and CA-125 measurement.
- Risk reducing strategies include prophylactic surgery (oophorectomy, mastectomy) and chemoprevention.

<p>What are the economic benefits associated with actions resulting from testing?</p>	<ul style="list-style-type: none"> • Barriers to surveillance and prophylactic surgery include time and distance. • Financial costs associated with testing include counselling and test intensive surveillance and surgery. See reference [14] for more detailed information • Cost-effectiveness analysis of genetic testing for BRCA1/2 (based on decision analytic model) [14] <ul style="list-style-type: none"> ○ Intervention group genetic test (for individuals with a first degree relative with a known mutation) mutation positive – intensive surveillance & prophylaxis mutation negative – population surveillance ○ Control group no genetic test (for individuals with a first degree relative with a known mutation) Control group 1) intensive surveillance and prophylaxis Control group 2) population surveillance ○ For each woman who had genetic testing for breast cancer: <ul style="list-style-type: none"> ▪ Compared to control group 1; BRCA 1 intervention provided total savings of \$1 795 and delayed the onset of breast cancer by 6 months; BRCA2 intervention provided total net savings of \$1 681 and the cancer onset was delayed by 3 months ▪ Compared to control group 2, BRCA 1 intervention incurred a \$3 055 total net cost but delayed the onset of breast cancer by 5.1 years (\$601 per cancer free year gained); BRCA 2 intervention incurred \$3 389 net cost for gain of 3.2 cancer-free years, (\$1 070 per cancer free year gained). ○ For each woman who had genetic testing for ovarian cancer: <ul style="list-style-type: none"> ▪ Compared to control group 1, provided total net savings of \$980-\$1 008 for BRCA1/2 intervention with no change in effectiveness; ▪ Compared to control group 2, BRCA1 intervention incurred a \$1 630 total net cost but delayed the onset of ovarian cancer by 3.5 years (\$2 159 per cancer free year gained). 		
<p>Quality assurance What quality assurance measures are in place?</p>	<p><i>Organisation</i> National Association of Testing Authorities NHMRC Human Genetics Society of Australasia</p>	<p><i>Service area</i> Laboratory practices Clinical practice General/laboratory practices</p>	<p><i>Quality assurance/guidelines</i> Accreditation www.nata.com.au Guidelines Policy - Presymptomatic and predictive testing for genetic disorders Training & professional development</p>
<p>Health risks What health risks can be</p>	<ul style="list-style-type: none"> • Health risks associated with increased surveillance include repeated radiation exposure (transvaginal ultrasound) and false positive screening tests that may result in biopsies or exploratory surgery. 		

<p>identified for follow-up testing and/or intervention?</p>	<ul style="list-style-type: none"> • Tamoxifen use is a risk factor for venous thromboembolism [13] • Prophylactic surgery complications include for [13]; <ul style="list-style-type: none"> ○ Mastectomy: hematoma, seroma, pain, infection, tissue necrosis, death (on rare occasions) ○ Breast reconstruction: capsular contracture, implant rupture, infection, death (on rare occasions) ○ Oophorectomy: infection, bleeding, urinary tract and bowel injury. • Endocrine changes induced by oophorectomy are associated with adverse effects on the lipid profile, increased incidence of coronary artery disease and osteoporosis [13]
<p>Evaluation What guidelines have been developed for evaluating program performance?</p>	<ul style="list-style-type: none"> • Evaluation of program performance is integrated into NATA accreditation/control control programs – see quality assurance above
<p>Facilities What facilities/personnel are available or easily put in place?</p>	<ul style="list-style-type: none"> • There are a number of specialised familial cancer clinics (FCC) throughout Australia which genetic counselling and testing services. These may be site-specific clinics or general familial cancer clinics.
<p>Education What educational materials have been developed and validated and which of these are available? Are there informed consent requirements?</p>	<ul style="list-style-type: none"> • Within Australia the NHMRC, the Cancer Councils and genetic services provide breast and ovarian cancer educational materials for both health professionals and consumers. Some examples of this information are listed below. <ul style="list-style-type: none"> ○ For health professionals NHMRC: Clinical practice guidelines, Familial aspects of cancer: A guide to clinical practice NBCC: Advice about familial aspects of breast cancer and epithelial ovarian cancer: A guide for health professionals. ○ Consumers GSWA: Breast and ovarian cancer in the family NBCC: Do you have breast cancer in your family? • The Human Genetics Society of Australasia Policy statement on <i>Presymptomatic and predictive testing for genetic disorders</i> states that <i>a test should only be performed on an individual who has made an informed voluntary decision to have the test.</i>[15]. • The policy includes how and what information should be provided to consumers, the requirement for consumers to read, understand and sign a consent document, and issues pertaining to individuals unable to consent.

<p>Monitoring</p> <p>What methods exist for long term monitoring?</p>	<ul style="list-style-type: none"> Local efforts have been mainly through Registry data collection. Registry evaluation of surveillance compliance Collaborative studies in association with kConFab In Western Australia there is a pilot program underway to follow-up consumers (and family) action taken as a result of testing ie including surgical prophylactic interventions
<p>Ethical, Legal and Social Issues</p>	
<p>Psychosocial</p> <p>What is known about stigmatization, discrimination, privacy / confidentiality and personal/family social issues?</p>	<ul style="list-style-type: none"> There is a growing body of literature regarding the psychological implications of genetic testing for cancer susceptibility. This literature has been reviewed in the journal article ‘Psychological impact of genetic testing for cancer susceptibility: An update of the literature [16]’, which found: <p><i>Most studies on the psychological impact of genetic testing amongst individuals who have never been affected by cancer demonstrate that non-carriers derive significant psychological benefits from genetic testing, while no adverse effects have been observed amongst carriers. These benefits are more clear-cut for HNPCC, compared to hereditary breast/ovarian cancer, reflecting differences in risk management options. The few studies available on individuals affected with cancer indicate that the impact of genetic testing is mediated and amplified by their former experience of cancer.</i></p> Meiser (2005) also identified that ‘more empirical data are needed on the broader impact of genetic testing on those with inconclusive results or results with uncertain significance’.
<p>Discrimination (insurance)</p>	<ul style="list-style-type: none"> Due to legislation requiring health insurance premiums be based on a community rating and not individual risk, genetic testing cannot have an impact on health insurance in Australia. Life insurance and income protection coverage may be affected by the availability of genetic information. The implications that genetic testing for cancer susceptibility has on life and income insurance in Australia is described in the paper, ‘<i>Cancer in the Family and genetic testing: implications for life insurance [17]</i>’. This paper found that although there is certainly potential for discrimination as a result of genetic testing, the incidence of this occurring is largely unknown. Under the code of practice for insurers, individuals cannot be required to have a genetic test, but are required to disclose any information regarding past genetic tests, or of any results (if known) of any other family members’ genetic test results [17]. As such there are implications. Pre-test counselling should include information on the possible implications of genetic testing on insurance for both themselves and other family members.
<p>Privacy [18]</p> <p>Are there legal issues regarding consent, ownership of data and/or samples, patents, licensing, proprietary</p>	<ul style="list-style-type: none"> The Commonwealth Privacy Act 1988 protects the privacy of individuals who have genetic testing. The Act sets standards as to the collection of personal information, storage and security, record keeping, access, alteration of records, and use and disclosure of the information. The release of genetic information is only through the consent of the individual tested, with one exception being the release of information for law

<p>testing, obligation to disclose, or reporting requirements? What safeguards have been described and are these safeguards in place and effective?</p>	<p>enforcement purposes.</p> <ul style="list-style-type: none"> • Further guidelines and recommendations can be found in the following documents. <ul style="list-style-type: none"> ○ <i>National Statement on Ethical Conduct in Research Involving Humans – Part 16 Human Genetic Research</i> [19] ○ <i>National Statement on Ethical Conduct in Research Involving Humans – Part 18 Privacy of information</i> [19] ○ <i>NHMRC Guidelines for genetic registers and associated genetic materials</i> [20] ○ <i>NHMRC Guidelines under Section 95 of the Privacy Act 1988</i> [21] ○ <i>Australian Law Reform Commission – Joint reference on genetic information: Essentially Yours: The protection of human genetic information in Australia</i> [22].
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