genomic diagnostics

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Breast & Ovarian Cancer

Specialist Guide for Genetic Testing

Genomic testing for inherited breast & ovarian cancer

Approximately 5-10% of breast cancers are due to inherited genetic variants and at least 20% of ovarian cancers are also thought to be hereditary. Genomic testing of *BRCA1, BRCA2* and other cancer susceptibility genes can be used to identify patients and relatives with an increased lifetime risk of these cancers due to inherited pathogenic variants, and select patients who may respond to PARP inhibitor therapy.

MBS rebated testing for genes associated with hereditary breast and ovarian cancer is available when patients meet criteria and when requested by a specialist medical practitioner.

Identifying patients at risk using multi-gene testing

A hereditary predisposition to breast and ovarian cancer is caused by autosomal dominantly inherited pathogenic variants in a growing number of genes that are crucial for normal cellular function, DNA repair and genomic stability. Next generation sequencing based tests, such as BraOVO and BraOVO Plus, can be used to detect pathogenic variants in multiple genes in a single test.

	Breast Cancer	Ovarian Cancer	Other Cancers
BRCA1, BRCA2, PALB2	■	■	■
RAD51C, RAD51D	■	■	
PTEN, CDH1, STK11, TP53, ATM	■		■
BARD1, CHEK2	■		
MLH1, MSH2, MSH6, PMS2, EPCAM		■	■
BRIP1		■	

Table 1: Genes analysed in the BraOVO and BraOVO Plus gene panels and associated cancer types.

While *BRCA1* and *BRCA2* account for the largest proportion of pathogenic variants detected in patients with inherited breast and ovarian cancer, pathogenic variants in other genes including *ATM, BARD1, BRIP1, CHEK2, PALB2, PTEN, RAD51C* and *RAD51D* are also important contributors to increased risk. Breast and ovarian cancers can be a component of other cancer syndromes caused by pathogenic variants in *CDH1, PTEN, STK11, TP53* genes and genes associated with Lynch syndrome (*MLH1, MSH2, MSH6, PMS2* and *EPCAM*) and therefore these genes are suitable inclusions in diagnostic testing for breast and ovarian cancer patients.

Lifetime risk of breast and ovarian cancer varies by gene. *BRCA1* and *BRCA2* variants have high penetrance, resulting in a high lifetime risk of cancer. The lifetime risk of breast cancer increases from 12% to up to 72%, and lifetime risk of ovarian cancer increases from 0.9% to up to 44%, for women with pathogenic variants in *BRCA1* or *BRCA2*. Penetrance of other genes included in diagnostic testing varies, with cancer risks of 2-fold to greater than 4-fold that of the general population depending on the gene. Gene-specific cancer risk management guidelines are available accordingly. These can be found at www.eviq.org.au

When to consider genomic testing for hereditary breast and ovarian cancer

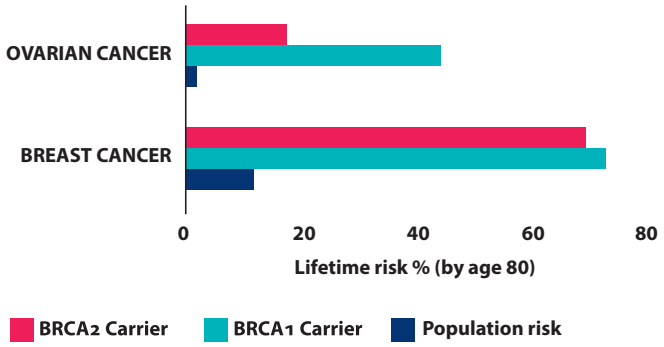

Figure 1: Lifetime risk of breast and ovarian cancer for BRCA gene carriers (adapted from eviQ.org.au)

Genomic testing in breast and ovarian cancer can be clinically useful in two main settings. **Diagnostic** testing is performed after a diagnosis of cancer, and **predictive** testing is performed in unaffected individuals to determine the future risk of cancer.

Awareness of inherited cancer susceptibility can alter medical management. Detection of pathogenic variants in genes causing hereditary breast and ovarian cancer can assist in the following ways:

- Confirms genetic susceptibility in patients with a personal history of cancer
- Provides genotype-specific information on prognosis and lifetime risk of cancer
- Directs genotype-specific therapy, including use of PARP inhibitors in patients with *BRCA1* or *BRCA2* variants
- Directs genotype-appropriate surveillance and consideration of prophylactic risk-reducing surgery and medications
- Guides testing of at-risk (asymptomatic) family members
- Assists couples with reproductive decision-making.

Diagnostic testing is currently recommended for individuals suspected to carry a pathogenic variant based on:

- clinical features, including age at diagnosis and tumour pathology
- family history of cancer and ethnicity
- risk assessment (>10% estimated risk of carrying a pathogenic variant) using a validated prediction tool.

Testing should also be considered for males with breast

cancer, as up to 20% of males with breast cancer may carry an underlying genetic variant. Women with ovarian cancer being considered for PARP inhibitor therapy should be tested for *BRCA1* and *BRCA2* germline or somatic pathogenic variants.

Predictive testing for individuals without a personal history of cancer is usually performed by testing for a specific variant previously detected in a family member. However, when family variant information is unavailable or unknown, testing may still be appropriate. Predictive testing is best performed in consultation with appropriately qualified specialists, such as clinical geneticists, genetic oncologists, or familial cancer clinics who can provide appropriate pre- and post-test genetic counselling.

Risk prediction models

Risk prediction models can be used to calculate the likelihood of carrying a variant in selected cancer risk genes. These are evidence-based tools that can assist in determining whether genomic testing should be performed. Likelihood of carrying variants in other cancer risk genes is typically assessed based on clinical features.

Risk calculator	Source	Background
Manchester Score Available online at: eviq.org.au	Medical Genetic Unit, St. Mary's Hospital, Manchester.	Simple, manual scoring system to estimate chance of identifying pathogenic variants in *BRCA1* and *BRCA2* gene.
BOADICEA Available online at: canrisk.org	Cambridge University – Centre for Cancer Genetic Epidemiology.	Web-based tool to predict the likelihood of carrying pathogenic variants in *BRCA1, BRCA2, CHEK2, ATM* and *PALB2* genes.
Penn II Risk Model Available online at: pennmodel2.pmacs.upenn.edu/penn2	University of Pennsylvania.	Ten questions used to predict probability of carrying a *BRCA1* or *BRCA2* pathogenic variant.

Test*	Description	Detail**
BraOVO (*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, PALB2, PTEN, RAD51C, RAD51D, STK11* and *TP53*).	Multi-gene test that analyses 13 breast & ovarian cancer susceptibility genes.	These genes all have medical management guidelines available. This test is bulk-billed for patients who fit the MBS criteria under Medicare item 73296 or 73295.
BraOVO Plus (*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, PALB2, PTEN, RAD51C, RAD51D, STK11 TP53, MLH1, MSH2, MSH6, PMS2 & EPCAM*).	Expanded multi-gene test that analyses 18 breast & ovarian cancer susceptibility genes.	These genes all have medical management guidelines available. This test is bulk-billed for patients who fit the MBS criteria under Medicare item 73296, 73295 or 73354.
Targeted Variant Testing "Familial Cancer Test".	For specified familial or ethnic specific variants for breast or ovarian cancer.	Testing of patients with a known familial pathogenic variant. This is bulk-billed under Medicare item 73297 or 73357.
Comprehensive *BRCA1* and *BRCA2* Screen.	*BRCA1* and *BRCA2* sequencing and copy number variant analysis.	Testing of patients to determine eligibility for PARP inhibitor treatment. This is bulk-billed under Medicare item 73295.
Germline assessment for tumour BRCA1 or BRCA2 pathogenic variants.	For specific BRCA1 or BRCA2 variants identified by tumour testing.	Testing of patients with a BRCA1 or BRCA2 variant to determine if it is inherited or only in the tumour tissue. This is bulk-billed under Medicare item 73302.

** All genes are assessed for sequence level and copy number changes*
***Private Pay is available for all panels where patients do not fit the MBS criteria.*

Genetic Counselling

Genetic counselling is of benefit to all patients undergoing cancer gene testing. It involves discussing benefits, limitations and possible outcomes from genetic testing. Genetic counselling can be provided by the referring specialist or a qualified genetic counsellor.

For patients eligible for MBS Item Numbers 73296 and 73295, Genomic Diagnostics can facilitate pre-test counselling through our genetic counselling partners at no cost to the patient. Please ensure the appropriate box is ticked on the request form if this service is required. Where the patient is not eligible for testing under these item numbers, Genomic Diagnostics can facilitate referral to a genetic counsellor at an affordable cost to the patient.

Patients who are found to have any form of pathogenic variant should also be offered post-test genetic counselling as there may be implications for other family members.

How to Order

STEP 1: Patient Consultation:

- Use the Genomic Diagnostics Cancer Genetics Specialist request form
- Tick the relevant boxes for Test Requested and Medicare eligibility and indicate clinical condition
- Ensure that the patient understands the implications of undergoing gene testing. If genetic counselling has been completed, ensure Patient Consent section on the reverse of the Cancer Genetics request form is signed.

STEP 2: Prepare for Collection

- If the patient is not eligible for Medicare, prepayment via genomicdiagnostics.com.au is required
- Patient notes their receipt number on the request form.

STEP 3: Sample collection

- Patient attends collection centre with signed request form
- Blood collected
- HBOC testing performed.

STEP 4: Result Discussion

- Results are returned using your preferred method
- Arrange appropriate genetic counselling if a pathogenic variant is detected.

Determining eligibility for MBS funded testing

MBS rebated testing for genes associated with hereditary breast and ovarian cancer is available when patients meet criteria and when requested by a specialist medical practitioner.

Item descriptors are available at: https://www.mbsonline.gov.au/

Private pay options are available for patients who do not qualify for MBS rebated testing. Prepayment is required. Please refer to genomicdiagnostics.com.au for current pricing.

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