Genomic Diagnostics

LEADING THE WAY TO IMPROVE HEALTH

Breast and Ovarian Cancer

CLINICIAN GUIDE FOR GENETIC TESTING

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Genomic testing for inherited breast and 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 high and moderate risk 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 several genes that are crucial for normal cellular function, DNA repair and genomic stability. Next generation sequencing based tests, such as BraOVO, can be used to detect pathogenic variants in multiple genes in a single test.

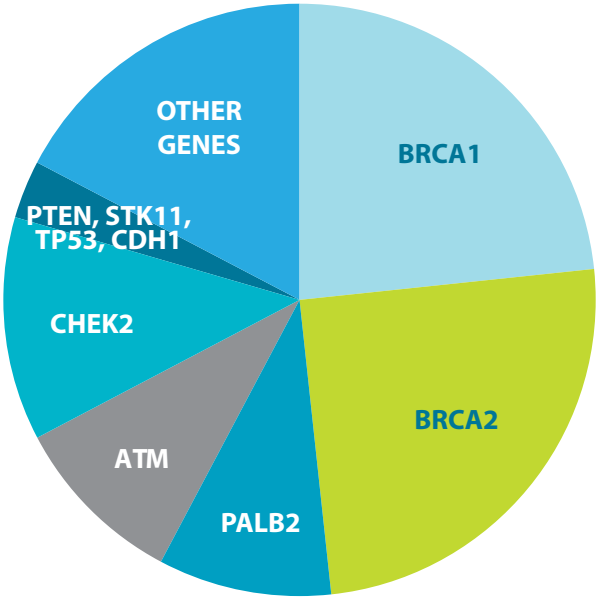

Figure 1: Relative frequencies of pathogenic variants in patients with breast cancer (adapted from Buys et al, 2017)

While *BRCA1* and *BRCA2* account for the largest proportion of pathogenic variants detected in patients with inherited breast cancer, pathogenic variants in other genes, including variants in *PALB2, ATM* and *CHEK2*, are also important contributors to an increased risk. Breast cancer is a component of other cancer syndromes caused by pathogenic variants in *CDH1, PTEN, STK11* and *TP53* genes. These syndromes account for up to 5% of inherited breast cancer.

Pathogenic variants in *BRCA1* and *BRCA2* genes are responsible for most cases of hereditary ovarian cancer, however variants in three other genes, *BRIP1, RAD51C* and *RAD51D,* are estimated to account for 10% of inherited ovarian cancers.

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*.

Pathogenic variants in *PALB2, CDH1, PTEN, STK11*, and *TP53* are also considered high risk (greater than 4-fold that of the general population) for breast cancer, while variants in *ATM* and *CHEK2* are considered moderate risk (2 to 4-fold).

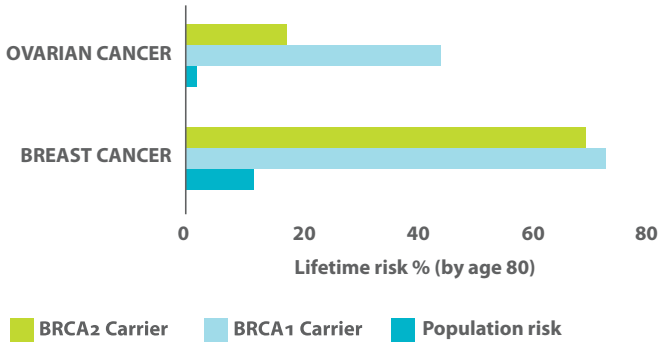

Figure 2: Lifetime risk of breast and ovarian cancer for BRCA gene carriers (adapted from eviQ.org.au)

When to consider genomic testing for hereditary breast and ovarian cancer

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	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.

Testing Options Available

Test	Description	Detail
BraOVO (*ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, PALB2, PTEN, RAD51C, RAD51D, STK11* and *TP53*)	Multi-gene test that analyses 12 high risk & moderately high risk breast & ovarian cancer susceptibility genes.	These high-risk genes all have medical management guidelines available. This test is bulk-billed for patients who fit the MBS criteria under Medicare item 73296.
Targeted Mutation Testing "Familial Cancer Test"	For specified familial or ethnic specific mutations for breast or ovarian cancer.	Testing of patients with a known familial mutation. This is bulk-billed under Medicare item 73297.
Comprehensive *BRCA1* and *BRCA2* Mutation 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.

All genes are assessed for sequence level variants. BRCA1, BRCA2 and PALB2 genes are also assessed for copy number changes.

Genetic Counselling

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

For patients eligible for MBS Item Number 73296, Genomic Diagnostics can facilitate pre-test counselling through Genetic Counselling Australia 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 this item number, 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 referred for post test genetic counselling as there may be implications for other family members.

References

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How to Order

STEP 1: Patient Consultation:

- Use the Genomic Diagnostics Cancer Genetics 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.

Medicare item 73295 – diagnostic testing for eligibilty for olaparib

The Comprehensive BRCA1 and BRCA2 Mutation Screen qualifies for this rebate.

MBS Item Descriptor

Detection of germline *BRCA1* or *BRCA2* gene mutations, in a patient with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer with high grade serous features or a high grade serous component, and who has responded to subsequent platinum-based chemotherapy, requested by a specialist or consultant physician, to determine whether the eligibility criteria for olaparib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

Medicare item 73296 – diagnostic testing in women with breast or ovarian cancer

The BraOVO test qualifies for the use of this rebate.

MBS Item Descriptor

Characterisation of germline gene mutations, requested by a specialist or consultant physician, including copy number variation in *BRCA1* and *BRCA2* genes and one or more of the following genes *STK11, PTEN, CDH1, PALB2,* or *TP53* in a patient with breast or ovarian cancer for whom clinical and family history criteria, as assessed by the specialist or consultant physician who requests the service using a quantitative algorithm, place the patient at >10% risk of having a pathogenic mutation identified in one or more of the genes specified above.

Medicare item 73297 – predictive familial cancer test

The Predictive Familial Cancer Test qualifies for the use of this rebate.

MBS Item Descriptor

Characterisation of germline gene mutations, requested by a specialist or consultant physician, including copy number variation in *BRCA1* and *BRCA2* genes and one or more of the following genes *STK11, PTEN, CDH1, PALB2,* or *TP53* in a patient who is a biological relative of a patient who has had a pathogenic mutation identified in one or more of the genes specified above, and has not previously received a service under item 73296.

Diagnostic testing in women with breast or ovarian cancer who do not qualify for a Medicare rebate

Choose either the BRCA1 and BRCA2 comprehensive test or the BraOVO test. Prepayment is required.

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For more information, contact us at info@genomicdiagnostics.com.au

1800 822 999 **genomicdiagnostics.com.au** **PO Box 250, Heidelberg West, VIC 3081**

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