Genomic Diagnostics

LEADING THE WAY TO IMPROVE HEALTH

Breast and Ovarian Cancer

GENETIC TESTING FOR GENERAL PRACTITIONERS

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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 targeted therapy.

Genomic Diagnostics offers MBS rebated testing for genes associated with hereditary breast and ovarian cancer for patients who meet criteria and when requested by a specialist medical practitioner. Testing can also be facilitated for patients who wish to access testing through their general practitioner (GP).

Identifying patients at risk using multi-gene testing

A small proportion of breast and ovarian cancer is hereditary, occurring due to pathogenic DNA variants that increase the lifetime risk of developing cancer. This predisposition is inherited in an autosomal dominant manner, such that there is a 50% chance of susceptibility of breast and ovarian cancer being passed from parent to child. The pathogenic variants occur in several genes that are crucial for normal cellular function, DNA repair and genomic stability, thereby increasing the opportunity for accumulation of DNA variants that promote abnormal and uncontrolled cellular growth and division.

The best known of these genes are *BRCA1* and *BRCA2*. Variants in these two genes occur in approximately 1 in 400 people but are more common in certain ethnic groups. Variants in other genes are also important contributors to a predisposition to breast, ovarian and other cancers but are much less common.

Next generation sequencing based tests, such as BraOVO,

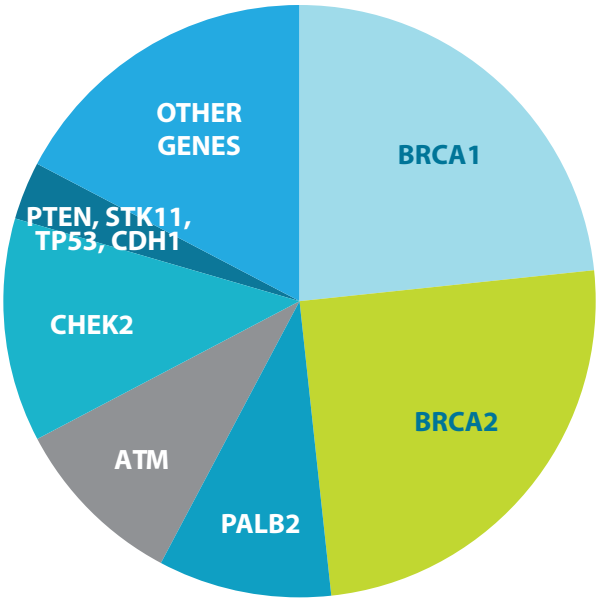

Figure 1: Relative frequencies of pathogenic variants in patients with breast cancer (adapted from Buys et al, 2017)

can be used to detect pathogenic variants in each of these genes in a single test.

In patients with **inherited breast cancer,** *BRCA1* and *BRAC2* account for the largest proportion of pathogenic variants, while variants in *PALB2, ATM, CHEK2* and *BARD1* are also seen. Breast cancer is a component of other cancer syndromes caused by pathogenic variants in *CDH1, PTEN, STK11* and *TP53* genes. These syndromes are rare and account for up to 5% of inherited breast cancer.

In most cases of **hereditary ovarian cancer,** pathogenic variants in *BRCA1* and *BRCA2* genes are responsible. However, variants in *BRIP1, RAD51C* and *RAD51D* account for 10% of these cancers, and variants in the mismatch repair genes (*MLH1, MSH2, MSH6, PMS2* and *EPCAM*) account for another 10%.

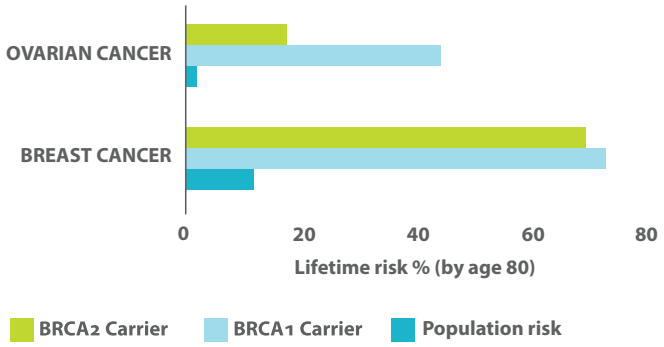

Figure 2: Lifetime risk of breast and ovarian cancer for BRCA gene carriers (adapted from eviQ.org.au)

Lifetime risk of breast and ovarian cancer varies by gene. *BRCA1* and *BRCA2* variants are associated with 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 for breast cancer, while variants in *ATM, CHEK2* and *BARD1* are considered moderate risk. Women with pathogenic variants in mismatch repair genes (MLH1, MSH2, MSH6, PMS2 and EPCAM) have a lifetime risk of up to 17% for ovarian cancer. Pathogenic variants in *BRIP1, RAD51C* and *RAD51D* are also considered high risk for ovarian cancer.

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 in individuals who have been diagnosed with cancer. Testing is usually offered to individuals suspected to have an inherited pathogenic variant based on age, sex, tumour pathology, family history and ethnicity. The probability of a pathogenic variant can be calculated using risk prediction tools such as the Manchester Score, BOADICEA, and Penn II Risk Model, that take these factors into account.

Predictive testing is performed in unaffected individuals with no previous diagnosis of cancer to determine their future risk. Traditionally, this is performed by testing for a specific variant previously detected in a family member. However, when family variant information is unavailable or unknown, testing using a gene panel may be appropriate.

Awareness of inherited cancer susceptibility can alter medical management. While the specifics of this can be gene dependent, the detection of pathogenic variants in genes causing hereditary breast and ovarian cancer can assist in the following ways:

- Confirms genetic predisposition in patients with a personal history of cancer
- Provides information on prognosis and lifetime risk of cancer
- Directs surveillance and consideration of prophylactic risk-reducing surgery and medications
- Guides testing of at-risk, unaffected family members
- Assists couples with reproductive decision-making

Detection of *BRCA1* and *BRCA2* variants, either inherited or occurring in tumour tissue, is also important in determining eligibility for PARP (poly (ADP-ribose) polymerase) inhibitor therapy currently listed on the PBS for selected patients with ovarian or prostate cancer.

Access to testing

The use of genomic testing for hereditary breast and ovarian cancer in patient care is clinically complex and has significant medical and personal implications for both the individual being tested and their extended family. It is best performed in consultation with appropriately qualified specialists, including oncologists, breast/ovarian cancer specialists or familial cancer clinics who can provide appropriate pre- and post-test genetic counselling for the patient and their family.

Current MBS items for genomic testing in this setting will only fund testing of patients with a high probability of having a pathogenic variant, based on strict criteria. This funding is also limited to requests made by non-GP specialists.

While MBS funded testing cannot be requested by general practitioners, GPs have an important role in assisting their patients to access testing. Most commonly this is through referral to an appropriate specialist. However, in circumstances where access to specialists is limited, GPs may request testing directly, supported by qualified genetic counsellors, and at a cost to the patient.

Genetic Counselling

Genetic counselling is essential to all patients undergoing cancer gene testing. Pre-test counselling involves discussing benefits, limitations and the possible consequences of the genetic testing to be performed. Post-test genetic counselling allows further discussion of these topics in the context of the returned result, and implications for other family members. Genomic Diagnostics facilitates pre- and post-test counselling through our genetic counselling partners at an affordable cost to the patient.

Testing Options Available

Genomic Diagnostics offers a range of testing options dependent on clinical indications and source of referral. Testing-only options are available on non-GP specialist request, while GPs can request a package of genomic testing with mandatory pre- and post-test genetic counselling. These options should be explored with patients to determine the most appropriate course of action for their personal circumstances.

Test	Description	Detail	GP referral	Non-GP specialist referral
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 testing is only available as a package with pre- and post-test genetic counselling, with an out-of-pocket cost to the patient.	✓ This test is bulk billed for patients who fit the MBS criteria under Medicare item 73296.
Targeted Variant Testing "Familial Cancer Test"	For specified familial or ethnic specific pathogenic variants for breast or ovarian cancer.	Testing of patients with a known familial variant.	-	✓ This test is bulk billed for patients who fit the MBS criteria under Medicare item 73294.
Comprehensive *BRCA1* and *BRCA2* Variant Screen	*BRCA1* and *BRCA2* analysis.	Testing of patients to determine eligibility for PARP inhibitor treatment.	-	✓ This test is bulk billed for patient who fit the MBS criteria under Medicare item 73295.
BraOVO Plus (*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, PALB2, PTEN, RAD51C, RAD51D, STK11 TP53, MLH1, MSH2, MSH6, PMS2 & EPCAM*	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.

How to Order

STEP 1: Patient Consultation:

- Use the dedicated Genomic Diagnostics Cancer Genetics Request form – GP Only (non MBS)
- Ensure that the patient understands the implications of undergoing gene testing
- Discuss the process for undertaking testing with the patient including the requirement for genetic counselling and the costs involved
- Patient signs consent on the Cancer Genetics Request form

STEP 2: Prepare for Collection

- Patient prepays for their BraOVO test and genetic counselling package via gdpay.com.au
- Patient notes their receipt number on the request form along with the amount paid

STEP 3: Sample collection

- Patient attends collection centre with signed request form
- Blood collected

STEP 4: Pre-Test Genetic Counselling

- Genetic counsellor contacts patient to arrange a time for pre-test counselling to occur
- Pre-test genetic counselling occurs discussing benefits, limitations and possible outcomes of the BraOVO test
- An appointment time is set for post-test genetic counselling

STEP 5: Testing Occurs

- Testing occurs
- Report is issued to GP and genetic counsellor

STEP 6: Post-Test Genetic Counselling and Result Discussion

- Results are provided to patient during post-test genetic counselling session and implications and next steps discussed
- Summary letter is sent back to referring general practitioner

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