BRCA gene mutation testing

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WHAT IS BRCA?

The BRCA1 and BRCA2 genes are tumour suppressor genes involved in DNA repair pathways. Loss of function of these genes are associated with an increased risk of breast and ovarian cancer. Pathogenic or likely pathogenic mutations within the BRCA genes result in inactivation or truncation of the resulting protein, thus impairing the DNA repair pathway.[2,4]

BENEFITS OF BRCA TESTING

Genetic testing of the BRCA1 and BRCA2 genes are recommended in certain disease phenotypes for both preventative and therapeutic management. For hereditary breast and ovarian cancer syndrome germline BRCA1 and BRCA2 testing is widely recommended to identify patients at high risk of developing breast and ovarian cancer and implementing patient management strategies.

Germline and/or tumour testing (see Table 1) has been recommended for those patients in whom platinum-based chemotherapy or treatment with poly ADP ribose polymerase inhibitor (PARPi) is considered. Further details on the patient phenotypes in which testing is recommended is available in Table 2.

Table 1. Overview of germline and tumour testing for BRCA1 and BRCA2[3,7]

	GERMLINE TESTING	TUMOUR TESTING
Source	Mutations present in every cell	Mutation present only in certain cells (DNA damage caused by errors in cell division or environmental factors)
Inheritance	Can be passed on to the next generation	Cannot be passed on to the next generation
Benefit	- Non-invasive - Identify increased risks of certain cancers - Identify family members at risk - Identifies cancer patients who will benefit from platinum-based chemotherapy or PARPi	- Identify driver genes in cancer - Potential to guide therapeutics - Identifies up to 50% more females with a BRCA mutation - Identifies cancer patients who will benefit from platinum-based chemotherapy or PARPi
Limitation	Does not identify patients with only somatic mutations	- May miss large genomic rearrangements - Tumour heterogeneity is a factor - Fragmented DNA may cause drop-out of regions in sequencing

SOUTH AFRICAN PERSPECTIVE

The South African Department of Health has, in 2018, released clinical guidelines for breast cancer control and management. Referral to genetic services and testing are suggested for patients with breast cancer diagnosed before the age of 40 years, and ovarian cancer diagnosed before the age of 60 years. The guideline recommends testing of, at a minimum, the BRCA1, BRCA2 and TP53 genes by means of next generation sequencing.[4] Unfortunately, no comment on tumour tissue testing for BRCA1 and BRCA2 has been made.

For germline BRCA1 and BRCA2 testing, there are generally three testing arms, all of which have advantages and disadvantages (see Table 2):

(a) founder mutation testing

(b) full gene sequencing of BRCA1 and BRCA2

(c) multi-gene panels including BRCA1 and BRCA2

Table 2. Overview of the testing workflow available for BRCA1 and BRCA2 testing in South Africa[5,6]

	FOUNDER MUTATION TESTING	BRCA1 AND BRCA2 FULL GENE SCREEN	MULTI-GENE PANELS
SAMPLE TYPE	Germline	Germline and Tumour	Germline and Tumour
METHODOLOGY	Sanger sequencing	Next Generation Sequencing	Next Generation Sequencing
ADVANTAGE	Cost-effective	More comprehensive screen of BRCA1 and BRCA2 than founder mutation testing	Comprehensive screen of all genes involved in hereditary breast and ovarian cancer/ inherited cancer/ homologous recombination
DISADVANTAGE	Not suitable for all patients, may miss other pathogenic variants. If negative, full gene screen of BRCA1 and BRCA2 should be considered.	- Costly - Only two genes involved are assessed. There is a likelihood of missing variants in closely associated genes. If negative, multi-gene panels should be considered.	Costly

WHAT DOES A POSITIVE BRCA1 AND BRCA2 TEST RESULT MEAN?

A positive test confers an increased risk of developing cancer. The test provides only an indication of increased cancer risk. It does not tell patients whether they will actually develop cancer and if so, when. NOT ALL women with a harmful mutation will develop cancer.

HOW TO REFER YOUR PATIENT FOR BRCA TESTING

Full BRCA1 and BRCA2 sequencing as well as inherited cancer panels are available through Lancet Laboratories, done in conjunction with genetic counselling.

Lancet Laboratories offers genetic counselling with a clinical geneticist who will determine if testing is indicated and explain to your patient how the test is done, what the results mean, and the risks associated with the result.

If you have a patient who requests BRCA testing, or for whom BRCA testing is indicated, he/she should email genetics@lancet.co.za to book a counselling session with our clinical geneticist. The counselling can be done telephonically. The clinical geneticist will assist with determining the appropriate testing and will guide the patient through the testing process.

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