TEST IN FOCUS

GENETIC TESTING IN BREAST CANCER (*BRCA1* AND *BRCA2* TESTING)

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BACKGROUND

Breast cancer is the most frequently diagnosed cancer worldwide and a leading cause of cancer-related deaths.[1] It is a genetically complex and heterogeneous disease with familial clustering identified more frequently than with other malignancies. *BRCA1/2*-associated hereditary breast and ovarian cancer syndrome is an autosomal dominant inherited disorder with germline mutations in *BRCA1* and *BRCA2* genes causing an increased risk for developing breast and other cancers (especially before the age of 50 years).[2]

WHO SHOULD GET TESTED?

Patients who are concerned about a harmful variant in the *BRCA1* and *BRCA2* gene should discuss their concerns with a genetic counsellor. The genetic counsellor will discuss the benefits and challenges of genetic testing and indicate the most appropriate genetic test (Table 1).[3]

The National Comprehensive Cancer Network (NCCN) has criteria for the testing of *BRCA1* and *BRCA2* genes, as well as several other genes (including *TP53, PTEN*, *CDH1* and *PALB2*) associated with an increased risk of breast and/or ovarian cancer. The NCCN recommends genetic testing for high-penetrance breast and/or ovarian cancer susceptibility genes to be considered in the following situations:[4]

1. Individuals with any blood relative with a known harmful (pathogenic/likely pathogenic) variant in a cancer susceptibility gene.

2. Individuals with a personal history of cancer, specifically:
   - Breast cancer with at least one of the following:
     - Diagnosed at or before the age of 45 years.
     - Diagnosed at 46 to 50 years with:
       - Unknown or limited family history.
       - A second breast cancer diagnosed at any age.
       - One or more close relatives with breast, ovarian, pancreatic or prostate cancer at any age.
     - Triple negative breast cancer diagnosed at or before the age of 60 years.
     - Breast cancer at any age with:
       - Ashkenazi Jewish ancestry.
       - One or more close relative(s) diagnosed with breast cancer at or before the age of 50 years.
       - One or more close relative(s) diagnosed with ovarian, pancreatic and/or metastatic or intraductal prostate cancer.
       - Three or more total occurrences of breast cancer in a patient and/or blood family relative.
   - A male patient diagnosed with breast cancer at any age.

3. Individuals diagnosed with ovarian cancer, specifically:
   - Epithelial-derived primary ovarian carcinoma diagnosed at any age.
   - Fallopian tube and primary peritoneal carcinomas.

4. Individuals diagnosed with exocrine pancreatic (ductal adenocarcinoma) at any age.

5. Individuals with prostate cancer with:
   - Metastatic prostatic cancer diagnosed at any age.
   - Intraductal prostatic adenocarcinoma diagnosed at any age.

6. To assist with therapy decision making (e.g. HER2 negative metastatic breast cancer).

WHAT DO *BRCA1* AND *BRCA2* GENETIC TEST RESULTS MEAN?

There are three possible results from *BRCA1/2* testing. The findings should be conveyed with the assistance of a genetic counsellor:

- **Positive/detected/pathogenic/likely pathogenic:** The tested person has inherited a harmful variant and is at increased risk of developing certain cancers.
- **Negative/not detected:** The tested person has not inherited a harmful *BRCA1/2* variant and has a cancer risk similar to an individual in the general population.
- **Variant of uncertain significance (VUS):** The tested person has a variant, but it is not known whether this specific genetic change is harmful (it is uncommon in the population or has not previously been associated with cancer).

TABLE 1: TESTING OF BREAST AND/OR OVARIAN CANCER SUSCEPTIBILITY GENES

Test mnemonic	Targets	Test indications	Specimen	Turnaround time (from being received in the laboratory)
BREAST	*BRCA1, BRCA2, PTEN, TP53, CDH1, PALB2, RAD51C, RAD51D, STK11*	Germline testing for inherited cancer syndromes associated with an increased susceptibility to breast and other cancers Syndromes/phenotypes detected by this panel include: • Hereditary breast/ovarian cancer syndrome • Cowden syndrome • Li-Fraumeni syndrome (TP53-associated) • CDH1-associated cancers • PALB2-associated cancers • Peutz-Jeghers syndrome	EDTA blood (At least 5 ml)	6 weeks
ONCOBRCA	Full *BRCA1* and *BRCA2* genes (including copy number variants/ MLPA analysis)	• Hereditary breast/ovarian cancer syndrome	EDTA blood (At least 5 ml)	6 weeks
		• Somatic *BRCA* testing on tumour tissue	Formalin fixed tissue	6 weeks
BRCAFDR	Common South African *BRCA1* and *BRCA2* variants only	• Targeted testing for patients from Afrikaner and/or Ashkenazi Jewish ancestry	EDTA blood (At least 5 ml)	6 weeks
ATMNGS	*ATM* gene	• ATM-related cancers (e.g. breast, prostate, pancreas) • Testing for suspected ataxia-telangiectasia (autosomal recessive inheritance)	EDTA blood (At least 5 ml)	6 weeks
DNAMUT	Specific gene testing of a known pathogenic familial variant	• Specific to a previously identified familial pathogenic variant • Must provide a copy of the report that specifies the gene and variant	EDTA blood (At least 5 ml)	6 weeks

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