GENETIC TESTING IN BREAST CANCER

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HIGHLIGHTING THE IMPORTANCE OF NEXT GENERATION SEQUENCING

Breast cancer is the most-frequently diagnosed cancer worldwide and is a leading cause of cancer-related death. It is a genetically complex and heterogeneous disease with familial clustering identified more frequently than with other malignancies. The application of next generation sequencing (NGS) on breast cancer has been associated with tremendous advances in the understanding of the disease. NGS can assist with screening for familial predisposition and can identify pathogenic sequence variants (mutations) that have an important predictive role in the implementation of targeted therapy.

What is the difference between Somatic and Germline genetic testing?

Somatic genetic testing:

- Identifies pathogenic variants found within the tumour itself, and are not inherited.
- The tumour develops from genetic damage in an individual cell during a person's life and is associated with lifestyle and environmental factors (e.g. cigarette smoke).
- The test is performed on tumour tissue or circulating tumour DNA in a liquid biopsy.
- Tumour testing can provide information on recurrence risk, prognosis and treatment options (Table 1).

Germline genetic testing:

- Identifies pathogenic variants that are hereditary and present in every cell from the time of conception (Table 2).
- The test is usually performed on EDTA blood.
- Testing can be performed on patients with or without cancer, and is best undertaken in conjunction with genetic counselling for the individual/family.
- Testing allows for risk evaluation and may identify patients who have the option of risk- reducing medical and surgical strategies.

Fast Facts

- Ampath offers a range of tests for germline and somatic breast cancer testing.
- NGS has advanced the treatment of many malignancies through the application of a precision medicine approach.
- Although still in its infancy, new actionable targets offer an improved outcome for breast cancer patients.

QUERIES?

- Contact the NGS laboratory at 012 678 0645 or email ngs@ampath.co.za
- For genetic counselling, email geneticsclinic@ampath.co.za

What if a pathogenic *BRCA1/BRCA2* variant has been identified on tumour tissue?

BRCA1/BRCA2 NGS testing on tumour tissue cannot distinguish between a somatic and germline (inherited) pathogenic variant. If the pathogenic variant frequency in the tumour tissue is high (~50%), then germline confirmatory testing, accompanied by genetic counselling, is suggested. If the variant frequency is low, then this likely represents a somatic variant (and is likely present within the tumour only with no additional testing required).

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Table 1: Summary of targetable genomic alterations in breast cancer

Target / Biomarker	Tests	Mnemonic	Approved therapy
ERBB2 amplification *(HER2)*	• Oncomine™ Precision Assay • HER2 Fluorescence in Situ Hybridisation	OPANGS HER2 FISH	Trastuzumab, Pertuzumab, Lapatinib, Neratinib
BRCA1/BRCA2	• *BRCA1/BRCA2* gene sequencing	ONCOBRCA	Olaparib
PIK3CA	• *PIK3CA* NGS • Oncomine™ Precision Assay	EGFRASSEQ OPANGS	Alpelisib
NTRK fusions	• Oncomine™ Precision Assay	OPANGS	Larotrectinib, Entrectinib

Table 2: Summary of available tests for breast cancer testing

Mnemonic	Included genes	Indications	Specimen
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 and • Peutz-Jeghers syndrome	EDTA blood (At least 5ml)
ONCOBRCA	Full *BRCA1* and *BRCA2* genes (including copy number variants/MLPA analysis)	• Hereditary breast/ovarian cancer syndrome	EDTA blood (At least 5ml)
		• Somatic BRCA testing on tumour tissue	FFPE tissue (4-6 Slides)
BRCAFDR	Common South African *BRCA1* and *BRCA2* variants only	• Targeted testing for patients from Afrikaner and/or Ashkenazi Jewish ancestry	EDTA blood (At least 5ml)
ATMNGS	*ATM* gene	• ATM related cancers (e.g. breast, prostate, pancreas) • Testing for suspected ataxia-telangiectasia (Autosomal recessive inheritance)	EDTA blood (At least 5ml)
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 5ml)
PHARMA	Thirteen drug metabolising genes including *CYP2D6*	• CYP2D6 enzyme is involved in metabolising Tamoxifen • Genetic variation may lead to increased, decreased or absent enzyme activity	EDTA blood (At least 5ml)