BRCA1 and BRCA2, Homologous Recombination Repair (HRR) and Homologous Recombination Deficiency (HRD) Testing

Compiled by: Dr Kusha Kalideen

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The efficient and error-free process of DNA repair is essential to maintain genomic integrity in cells. The most critical DNA damage that occurs is a double-stranded break which simultaneously affects both DNA strands. Double-stranded breaks are repaired by two distinct pathways: a high-fidelity pathway (known as the homologous recombination repair (HRR) pathway) and an error-prone pathway (known as the non-homologous end-joining pathway).

Tumours with defects in the DNA repair pathways, particularly the HRR pathway, are vulnerable to poly ADP ribose polymerase (PARP) inhibitors. When cells have lost the ability to repair double-stranded breaks with high fidelity (for example through a germline or somatic mutation), the cells revert to using the error-prone repair pathway. This error-prone pathway results in an accumulation of unrelated double-stranded breaks, creating genomic instability and culminating in cell death.

Genomic instability resulting from a deficient HRR pathway is known as Homologous Repair Deficiency (HRD). HRD has been associated with several tumour types, including breast, ovarian, prostate, and pancreatic cancers.

Targeted therapies based on PARP inhibitors have shown clinical efficacy with prolonged survival in patients whose cancers exhibit a high degree of genomic instability.

Biomarker tests for PARP inhibitors can be categorised into three approaches based on how they detect the presence of HRD in tumour cells:

1. Evaluating tumour mutation status by gene sequencing of BRCA1 and BRCA2
2. Evaluating tumour mutation status by gene sequencing of a panel of specified genes (HRR genes) known to cause HRD
3. Investigating the degree of genomic instability (HRD)

BRCA1 and BRCA2 testing

BRCA1 and BRCA2 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 (Garidshar et al. 2016; NDoH 2018).

Genes Tested: BRCA1 and BRCA2

HRR testing

Homologous Recombination Repair (HRR) genes are involved in the repair of double-stranded DNA breaks. Mutations within the HRR genes may lead to a loss of optimal function, resulting in a deficiency in the repair of damaged DNA. The most common HRR genes are BRCA1 and BRCA2.

Genes Tested: HRR genes, including BRCA1 and BRCA2

HRD Testing

A measure of genomic instability is assessed by identifying chromosomal aberrations (genome scars). These genome scars are changes in the genome because of a dysfunctional HRR pathway. The result of HRD testing is a genomic scar score (GSS), also referred to as the HRD score. The GSS is the unweighted sum of three independent DNA-based measures of genomic instability in tumour tissue, namely loss of heterozygosity (LOH), telomeric allelic imbalance (TAI) and large-scale transitions (LST).

Clinical application

Prognostic and predictive biomarker for PARP inhibitor therapy and platinum-based chemotherapy.

Availability of testing

BRCA, HRR and HRD tests are available at Lancet Laboratories.

Contact us for further information on molecularoncology@lancet.co.za.

Sample requirements: 1x FFPE block

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