AMPATHCHAT no. 93

THE ABC OF HRD:
INTRODUCING THE ONCOMINE™ COMPREHENSIVE ASSAY PLUS HRD SUB-PANEL

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INTRODUCTION

Homologous recombination deficiency (HRD) refers to the inability of a cell to effectively repair DNA double-strand breaks (DSB) through the homologous recombination repair (HRR) pathway. This deficiency is often due to mutations in key HRR genes such as *BRCA1*, *BRCA2*, *RAD51*, and *PALB2*, among others, and leads to genomic instability and an increased accumulation of DNA damage. Cancers with HRD are particularly sensitive to treatments that induce DNA damage, such as platinum-based chemotherapies and poly (ADP-ribose) polymerase (PARP) inhibitors. The efficacy of PARP inhibitors has been demonstrated across various malignancies, including ovarian, breast, pancreatic, and prostate cancers, where HRD is prevalent.

BRCA, HRR, AND HRD: ROLES AND RELEVANCE IN CANCER

Two pathways are responsible for the repair of DSBs: Homologous recombination and Non-Homologous End-Joining (NHEJ), (see Figure 1 below). While NHEJ is more straightforward, it comes at the expense of error prone repair. Homologous recombination repair is the more precise pathway, with multiple genes involved, including *BRCA1* and *BRCA2*, *ATM*, *PALB2*, *RAD51*, and others. Mutations in any of these genes may result in the phenotype of homologous recombination deficiency (HRD).

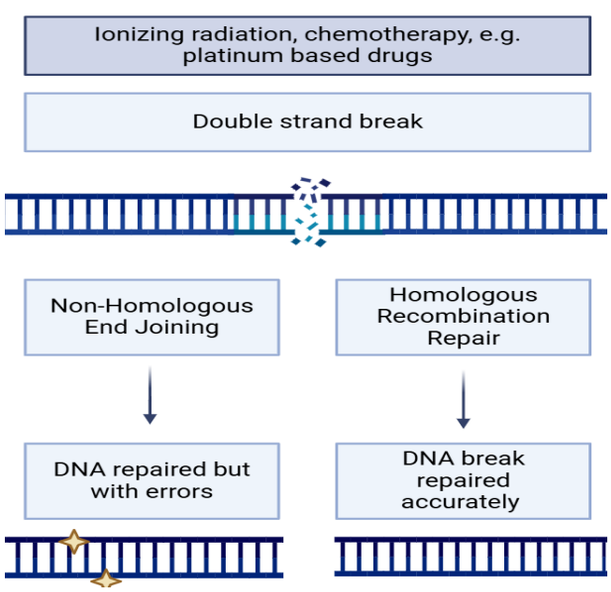


FIGURE 1: DNA DOUBLE STRANDED BREAK REPAIR PATHWAY

As affected tumour cells are no longer able to rely on the HR pathway for repair, "genomic instability or "genomic scarring", resulting from reliance on the error prone NHEJ pathway, is a telltale sign for identifying tumours with HRD, irrespective of the underlying aetiology.

MEASURING HRD

The HRD phenotype is defined by mutations in the genes involved in the HRR pathway ("causes") and/or genomic scarring/instability ("consequences"), (see Figure 2 below). Potential causes of HRD can be identified by sequencing genes involved in the HRR pathway. Testing for the consequences of an impaired HRR pathway is performed by probing the genome for evidence of genomic abnormalities.

These signatures of instability include:

- Loss of heterozygosity (LOH): intermediate size regions (>15 MB and < whole chromosome)
- Telomeric imbalances (TAI): number of regions with allelic imbalance which extend to the sub-telomere but not cross the centromere.
- Large-scale transitions (LST): chromosome breaks (translocations, inversions, or deletions)

DETERMINING OF HRD STATUS

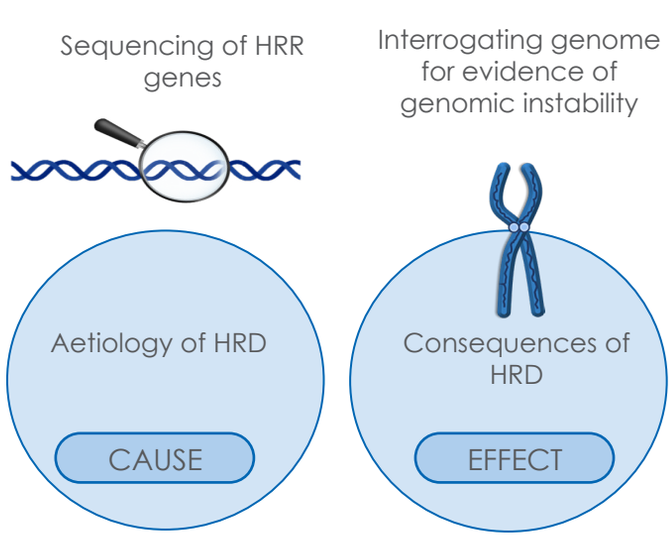
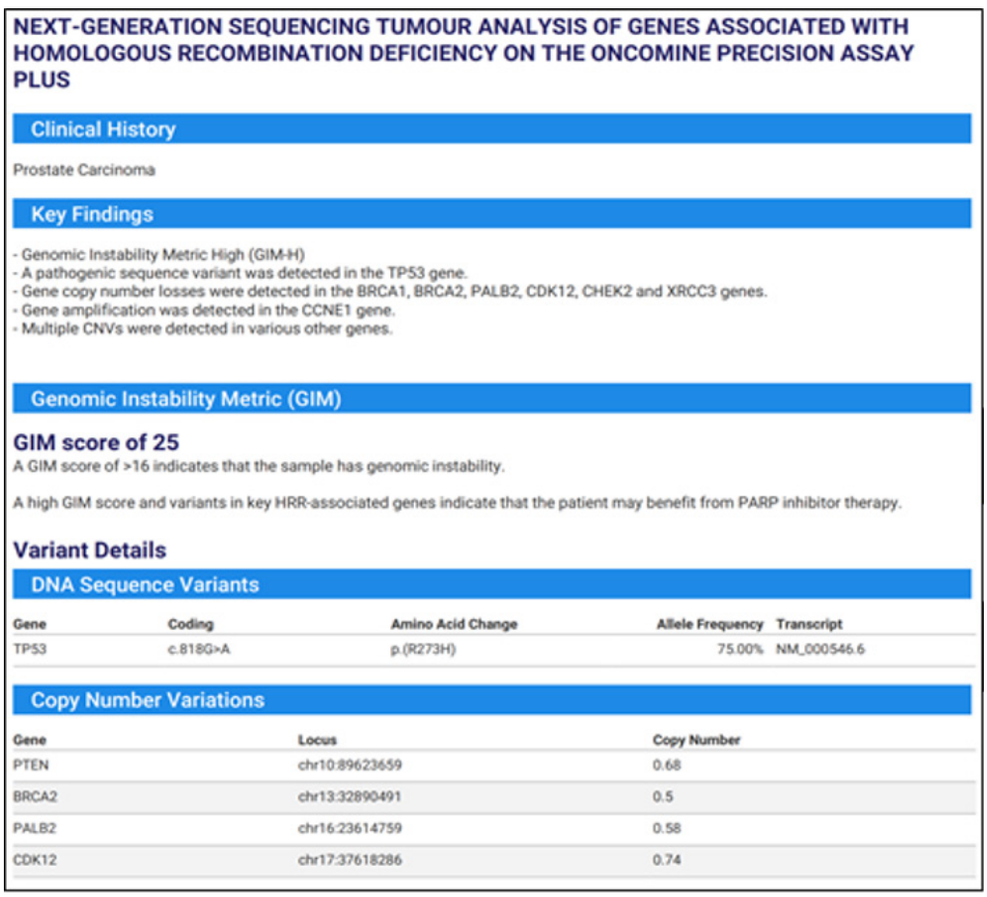


FIGURE 2: TWO COMPONENTS OF AN HRD REPORT

The Oncomine™ Comprehensive Assay Plus enables detection of HRR gene mutations that may cause HRD, as well as reporting the consequences, i.e., genomic scarring, through the Genomic Instability Metric (GIM). The GIM is a quantitative metric that summarizes unbalanced copy number changes found on genome probing. An example of a typical laboratory report is shown in Figure 3 below highlighting the report components, including the GIM score.



NEXT-GENERATION SEQUENCING TUMOUR ANALYSIS OF GENES ASSOCIATED WITH HOMOLOGOUS RECOMBINATION DEFICIENCY ON THE ONCOMINE PRECISION ASSAY PLUS

Clinical History

Prostate Carcinoma

Key Findings

- Genomic Instability Metric High (GIM-H)
- A pathogenic sequence variant was detected in the TP53 gene.
- Gene copy number losses were detected in the BRCA1, BRCA2, PALB2, CDK12, CHEK2 and XRCC3 genes.
- Gene amplification was detected in the CCNE1 gene.
- Multiple CNVs were detected in various other genes.

Genomic Instability Metric (GIM)

GIM score of 25

A GIM score of >16 indicates that the sample has genomic instability.

A high GIM score and variants in key HRR-associated genes indicate that the patient may benefit from PARP inhibitor therapy.

Variant Details

DNA Sequence Variants

Gene	Coding	Amino Acid Change	Allele Frequency	Transcript
TP53	c.818G>A	p.(R273H)	75.00%	NM_000546.6

Copy Number Variations

Gene	Locus	Copy Number
PTEN	chr10:89623659	0.68
BRCA2	chr13:32890491	0.5
PALB2	chr16:23614759	0.58
CDK12	chr17:37618286	0.74

Reflects any HRD related genomic effects

Reflects any sequence or copy number variants in HRR

FIGURE 3: EXAMPLE OF AN ONCOMINE™ COMPREHENSIVE HRD REPORT

CONCLUSION

Homologous recombination repair deficiency testing plays an essential role in identifying HR-deficient cancers which can be targeted with appropriate therapies like PARP inhibitors and platinum-based chemotherapies. Testing can be requested in isolation or as part of the Oncomine™ Comprehensive Assay Plus.

TEST INFORMATION

Test mnemonic	**HRD**
Clinical indication	Oncology patients, particularly: • Prostate carcinoma • Ovarian carcinoma • Endometrial carcinoma
Genes tested	*ABRAXAS1, ATM, ATR, BARD1, BLM, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, MRE11, NBN, PALB2, PARP1, POLD1, POLE, PPP2R2A, PTEN, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RNASE2A, RNASE2B, RNASE2C, RPA1, TP53, XRCC2, XRCC3*
Specimen type	Formalin Fixed Paraffin Embedded Tissue (FFPE): • 6-8 normal slides (not charged) with 10 micron thick unstained recuts
Turnaround time	14 working days

For more information, contact ngs@ampath.co.za

REFERENCES AVAILABLE ON REQUEST

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