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Oncomine Solutions for assessment of homologous recombination deficiency (HRD)

Homologous recombination deficiency (HRD) is becoming a hot new biomarker in precision oncology clinical research. Under normal conditions, errors during homologous recombination are repaired in the homologous recombination repair (HRR) pathway. Errors in the HRR pathway, such as loss-of-function or deleterious mutations in the associated genes, lead to higher levels of genomic instability—the HRD phenotype. HRD has been shown to be relevant in certain tumors, such as ovarian or prostate cancer, and it's intensively studied in clinical research.

HRD can be assessed using three main strategies:
1. Detection of genetic causes, such as germline or somatic mutations of HRR genes; **2.** Including *BRCA1* and *BRCA2* evaluation of genomic scaring representing genomic instability: such as analysis of the genome-wide loss of heterozygosity (LOH), measuring telomeric allelic imbalance or examining large-scale transition of chromosomal break: **3.** A combination of 1 and 2.

Oncomine™ Solutions, powered by Ion Torrent™ sequencing technology and Ion AmpliSeq™ chemistry, provide a set of tools for HRD assessment using all three strategies. The low sample input requirement assures that more, and smaller, samples can be tested. A high degree of automation, as well as a complete bioinformatics solution including reporting, means that Oncomine Solutions are easily implemented in your laboratory.

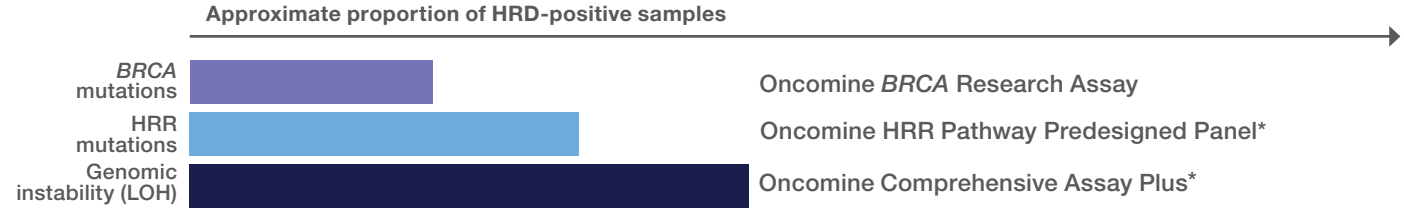

Figure 1. Approximate proportion of samples with HRR deficiency in ovarian cancer samples using different Oncomine Solutions. Based on published data[1,2,3,4] and design/panel content of the different types of Oncomine Solutions.

1. Neff RT et al. *Ther Adv Med Oncol.* 2017;9(8):519-531.
2. Pennington KP et al. *Clin Cancer Res.* 2014;20(3):764-775.
3. Konstantinopoulos PA et al. *Cancer Discov.* 2015;5(11):1137-1154.
4. Cancer Genome Atlas Research Network. *Nature.* 2011;474(7353):609-615.

Oncomine Solutions for HRD assessment include:

- **Ion Torrent™ Oncomine™, BRCA Research Assay**—100% exon coverage across both genes, *BRCA1* and *BRCA2*, with high uniformity; >99% confidence in detecting 5% somatic variants, detection of exon- or gene-level deletions/duplications
- **Ion Torrent™ Oncomine™ HRR Pathway Predesigned Panel**—a 28-gene panel containing *BRCA1* and *BRCA2* and additional HRR pathway genes, plus non-HRR genes such as *KRAS* and *PIK3CA* important for ovarian, breast, prostate, and pancreatic cancer research
- **Ion Torrent™ Oncomine™ Comprehensive Assay Plus**—a comprehensive assay for all HRR gene mutations, as well as measuring genomic instability, assessing LOH at both the gene and sample level, and identifying mutational signatures

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Detection of HRR Pathway genes mutations

The significant role of HRR genes in maintaining genome stability and tumor suppression has been studied extensively, especially in the *BRCA1* and *BRCA2* genes. In recent years, it has been demonstrated that alterations in the BRCAness pathway, including HRR genes, may increase the risk. The mutation status of HRR genes is now considered a potential biomarker for precision oncology. Figure 2 shows the HRR pathway genes covered by different Oncomine assays.

All Oncomine assays for HRD assessment use the same tried-and-tested amplicons as the Oncomine *BRCA* Research Assay with 100% exon coverage across both genes with high uniformity; and >99% confidence in detecting 5% somatic variants. The included software algorithm also detects large indels and whole-gene deletion or duplication events, uniquely empowering laboratories to detect all classes of mutations in one next-generation sequencing (NGS) workflow, removing the need to employ multiple technologies. (Figure 3)

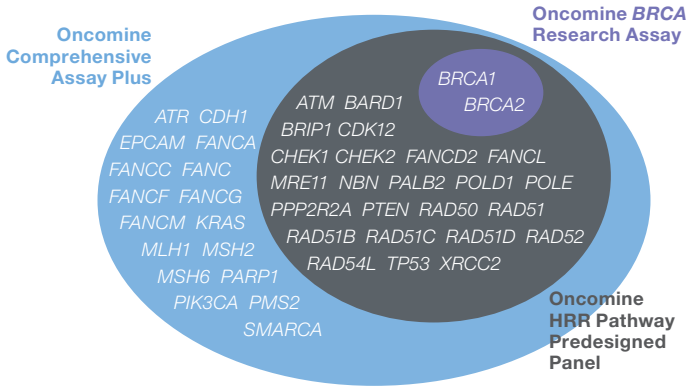

Figure 2. HRR pathway genes contained by different Oncomine assays.

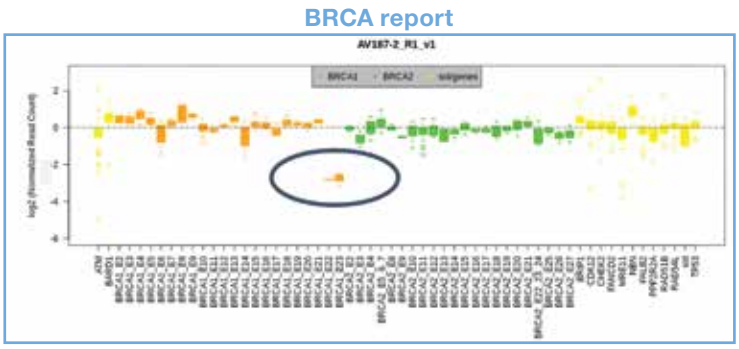

Figure 3. Exon Deletion detection by Oncomine BRCA Research Assay.

Genomic instability measurement

The Oncomine Comprehensive Assay Plus measures gene level as well as also sample level LOH. Figure 4 demonstrates the LOH assessment at both sample level (A) and gene level (B) compared with the Applied Biosystems™ OncoScan™ assay as an orthogonal test using the same FFPE samples. Test sample set consists of FFPE samples from various solid tumor tissue types.

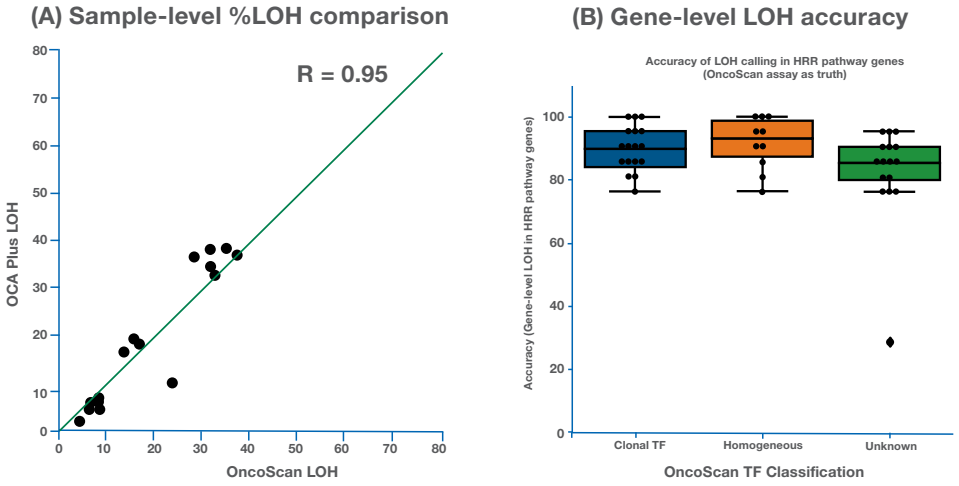

Figure 4. (A) The Oncomine Comprehensive Assay Plus sample-level %LOH estimates (y-axis) correlate favorably with the orthogonal test (x-axis), the OncoScan assay, on the same FFPE samples. Pearson Correlation (R) is shown as measure of correlation. **(B)** This graph shows gene-level LOH accuracy comparing 21 genes in HRR pathway (accuracy defined as proportion of these 21 genes that have LOH in both OncoScan and Oncomine Comprehensive Assay Plus assays), with 89% mean accuracy across clonal samples.

Find out more at **oncomine.com**

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