

Performance of a 52-gene NGS panel combined with shallow WGS for accurate HRD analysis.

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Background: Homologous recombination deficiency (HRD) is a pivotal biomarker for predicting response to PARP inhibitors in multiple cancers. This study evaluates the analytical performance of a 53-gene somatic NGS panel combined with low-pass whole genome sequencing (shallow WGS, sWGS) for HRD assessment. **Methods:** In the present study, 36 FFPE tissues from ovarian cancer patients were analyzed for 52 genes implicated in DNA repair pathways, along with sWGS for the evaluation of tumor genomic instability (GI). Libraries were generated with the KAPA HyperPlus Kit (Roche) and sequenced in duplicate using the Avity sequencing instrument (Element Bioscience) and the DNBSEQ-G400 NGS platform, subsequent to conversion for compatibility with MGI chemistry. HRD positivity was defined as either the presence of pathogenic BRCA1/2 mutations or high GI. Data analysis was performed using the SeqOne platform. The performance of the sWGS assay in detecting GI was initially assessed using the OncoScan CNV assay for 15 samples, as well as 4 reference materials with known HRD status. The efficacy of sWGS was also evaluated by comparing its agreement with the GI scores obtained from the validated HRD test (Myriad MyChoice) in 21 samples. **Results:** A 93% agreement was observed between the sWGS assay and OncoScan, demonstrating strong concordance. Additionally, the assay accurately evaluated the HRD status in all 4 reference samples with known values. The results obtained were highly similar between the two sequencing platforms. In addition, shallow NGS achieved >95% overall percentage agreement (OPA) with the validated HRD test for genomic instability score (Table 1). 5 of the 6 samples with discordant GI findings between Myriad and OncoScan aligned with the Myriad results when analyzed with sWGS. This implies that sWGS has the potential to resolve the discrepancies that were observed with OncoScan, thereby indicating its reliability as a robust alternative for HRD analysis. **Conclusions:** The assay demonstrated robust performance in detecting HRD-associated genomic signatures, supporting its applicability in clinical use. The reliability of the NGS assay for clinical use is guaranteed by its high concordance (95%) with the validated test, which entails the incorporation of shallow WGS for HRD analysis. Research Sponsor: None.

Concordance between Myriad MyChoice and shallow WGS.

		Validated HRD Test					
		HRD +	HRD -	PPV	NPV	OPA	r
Shallow WGS HRD	HRD +	13	0	100%	88%	95.24%	0.9014
	HRD -	1	7				p< .00001