

Whole exome sequencing provides Loss of Heterozygosity (LoH) data comparable to that of Whole Genome Sequencing

Elizabeth Evans¹, Jhalak Dholakia¹, Jim Abraham², Jian Zhang², Matt Oberley², Premal Thacker³, Thomas Herzog⁴, David Spetzler², Rebecca C. Arend¹

¹University of Alabama at Birmingham, Birmingham, AL; ²Caris Life Sciences, Phoenix, AZ; ³Washington University School of Medicine, St. Louis, MO; ⁴University of Cincinnati, Cincinnati, OH.

Background:

- Genomic scars assay measured by SNP (single nucleotide polymorphisms) -based tests are increasingly used clinically to identify patients more likely to benefit from PARP inhibitors (PARPi) in ovarian cancer.
- We aim to leverage the extensive SNP coverage built into a WES platform to accurately measure genomic loss of heterozygosity (LOH) and homologous recombination deficiency (HRD).
- We assessed the validity of WES compared to the whole genome sequencing (WGS) in identifying LOH.
- HRD was correlated with clinical outcome in PARPi-treated ovarian cancer patients.

Methods:

- Whole Exome Sequencing (WES) was performed at Caris Life Sciences (Phoenix, AZ) on genomic DNA isolated from microdissected FFPE tumor sample using the Illumina NovaSeq 6000 sequencers and covers over 2.7 million SNPs throughout the genome, with approximately 250,000 SNPs spanning intragenic/intronic regions.
- WES performed on a total of 99 patient tumor samples (90 epithelial ovarian carcinoma, 9 breast adenocarcinoma) were compared to OncoScan copy-number microarray WGS (Thermo Fisher Scientific.)
- Separately, a total of 138 ovarian tumors previously tested with Myriad myChoice were sequenced using WES and calculated for Caris HRD score.
 - Caris HRD score incorporates BRCA1/2 mutation status and Genomic Scar Score (GSS) measured by WES. A positive score means:
 - BRCA1/2 pathogenic or likely pathogenic mutations or
 - Genomic Scar Score (GSS) >= 42
 - GSS = LOH (Loss of Heterozygosity) + LST (Large-scale State Transition)
 - For genomic LOH calculation, 22 autosomal chromosomes were split into 552 segments and the LOH of SNPs within each segment was calculated. 99% of segments were at least 5Mb in length; segments excluded from the calculation included those spanning >= 90% of a whole chromosome or chromosome arm and segments.
- Real-world overall survival (rwOS) information was obtained from insurance claims data and calculated from start of PARPi treatment to last day of contact for a cohort of ovarian cancer patients.

Results:

Figure 1: Confusion matrix (left) and correlation (right) for Caris LOH call vs. Oncoscan (CHLA) for 99 tumors.

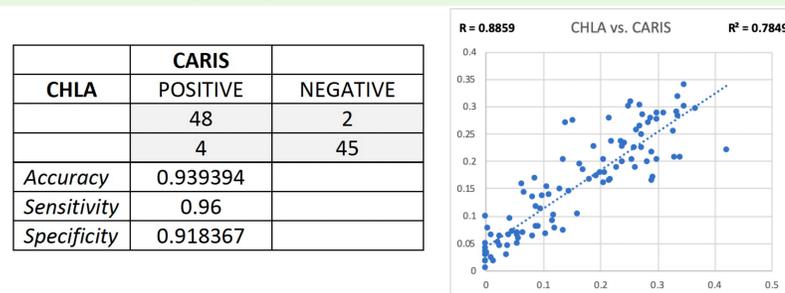


Table 1: Concordance of Caris HRD score and Myriad myChoice score

• **138** Cases with Myriad Results and WES

- Inconclusive
 - Myriad 8.1%
 - Caris 8.1%

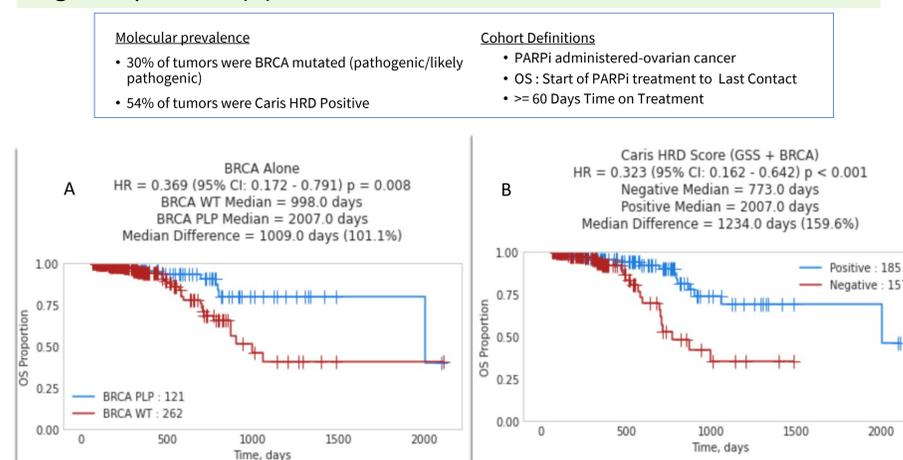
	PPV	NPV	Sensitivity	Specificity
	0.96	0.99	0.96	0.99

• Discordant Cases Near Inconclusive Zone

- 0-38: Negative
- 38-46: Inconclusive
- 46+: Positive
- 1 FP – Caris GS Score = 47
- 1 FN – Caris GS Score = 35

		Myriad HRD	
		Positive	Negative
Caris HRD	Positive	24	1
	Negative	1	103

Figure 2: Real world OS in PARPi-treated BRCA1/2 mutated vs. wild type ovarian cancer patients (A) and Caris HRD Score positive vs. negative patients (B).



Conclusions:

- Built on a WES platform with a >2.7M SNP coverage spanning the genome, Caris HRD score shows high concordance with the Myriad myChoice score with similar rate of inconclusive results. When compared to WGS, WES provides LOH information comparable to that of WGS.
- Real World Evidence shows BRCA mutation alone is inferior to Caris HRD Score in identifying patients most likely to benefit from PARPi treatment.
- GSS is correlated with overall survival in PARPi-treated ovarian cancer patients; a cutoff of 42 was associated with a HR of 0.268 with a p value of <0.001 and was determined as an optimal cutoff.

Figure 3: Caris Genomic Scar Scores (GSS) are associated with Overall Survival: (A) Correlation of GSS and OS (Pearson's r=0.238; p=0.000024); (B) rwOS in GSS positive vs. negative (cutoff: >= 42) PARPi-treated ovarian cancer patients

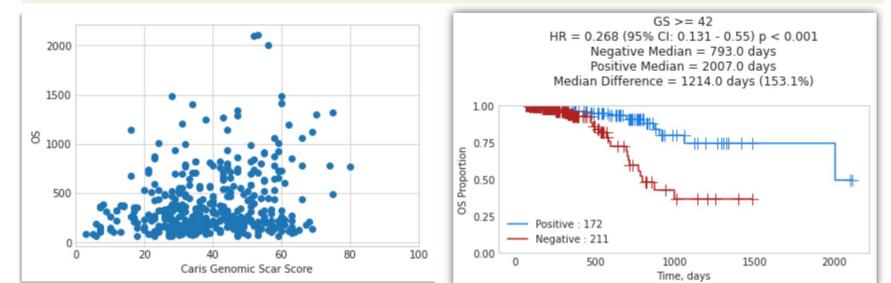


Figure 4: rwOS in GSS positive vs. negative PARPi-treated ovarian cancer patients at cutoffs of >=28, >= 32, >= 36, >= 56, >= 58 and >= 60.

