Comparison of genomic instability test scores used for predicting PARP activity in ovarian cancer

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BACKGROUND

- Clinical trials have explored the utility of various genomic instability (GI) scores or gene panels to assess deficiencies in the homologous recombination (HR) DNA repair pathway and support PARP inhibitor use in ovarian cancer.
- These tests may include the identification of pathogenic variants in genes within the HR pathway, genomic markers of instability, or a combination of the two. However, these methods of assessing homologous recombination deficiency (HRD) may not be equivalent.
- myChoice HRD is the only analytically- and clinically-validated, FDA-approved HRD test that includes *BRCA1/2* mutation status and three measures of genomic instability.
- We compared the proportion of patients identified as candidates for PARP inhibitor use by three measures of HR deficiency: myChoice genomic instability (GI) score, percent loss of heterozygosity (%LOH), and an 11-gene panel.

METHODS

- Whole-genome SNP analysis was used to reconstruct ovarian tumor genomic profiles for two cohorts:
  - Clinical laboratory cohort, N=3,336
  - SCOTROC4 trial (HGSOC only), N=176
- Mutation screening was also performed for 11 genes in the HR pathway (*ATM, BARD1, BRCA1, BRCA2, BRIP1, CHEK2, MRE11A, NBN, PALB2, RAD51C, RAD51D*) for a subset of tumors from the SCOTROC4 trial (N=153).
- The myChoice GI score incorporated three measures assessed using the genomic profiles [LOH, telomeric allelic imbalance, and large-scale state transitions]. %LOH was calculated using the genomic profiles. The HR gene panel was assessed via the mutation status of the 11 tested genes in the HR pathway.
- Samples were considered positive if:
  - The myChoice GI score was above the threshold (threshold scores of 42 and 33 were assessed)
  - %LOH was above the threshold (16%)
  - A pathogenic variant was identified in one of the 11 HR genes.
- The correlation between positive results from %LOH, the 11-gene panel, and the myChoice GI score were compared.
  - For comparisons to the 11-gene panel, samples were also considered positive by the myChoice test if there were tumor mutations in *BRCA1* and *BRCA2* (to reflect the clinically available test offering).
- Percent positive agreement (PPA) was calculated as the proportion of positive test results from one test that were also positive by another test. The percent negative agreement (PNA) was similarly calculated.

RESULTS

- Correlations, PPA, and PNA between myChoice, %LOH, and the 11-gene panel indicate high concordance, but not equivalence (Table 1).
- Nearly half of patients identified as positive by the myChoice GI score would have been missed by %LOH in the commercial cohort (Includes 32% of tumors with *BRCA1/2* mutations and 53% of tumors with wild-type *BRCA1/2).*
- In contrast, only 3% of patients identified as positive by %LOH would have been missed by the myChoice GI score.

Table 1. myChoice, %LOH, and 11-gene panel correlation

Reference Test		%LOH		11-gene panel
		Commercial	SCOTROC	SCOTROC
myChoice GI Score	Correlation	0.847	0.87	n/a*
	PPA (42)	64.9%	82.5%	46.0%
	PNA (42)	96.6%	95.8%	96.1%
	PPA (33)	51.0%	62.7%	36.8%
	PNA (33)	98.7%	75.0%	97.6%

Reference Test		myChoice HRD**	
		Commercial	SCOTROC
%LOH	Correlation	0.847	0.87
	PPA	90.1%	100%
	PNA	85.3%	75%
11-gene panel	Correlation	not eval	n/a**
	PPA	not eval	92.6%
	PNA	not eval	65.9%

NOTE: myChoice HRD includes *BRCA1* and *BRCA2* tumor mutation status.

*Could not be calculated because positive results by the 11-gene panel were not continuous.

**Using 33 as the threshold score.

CONCLUSIONS

- Tests used to evaluate HR deficiency in published and ongoing clinical trials are not equivalent, and should not be considered interchangeable in predicting PARP inhibitor response in clinical practice.
- %LOH missed between 32% and 53% of tumors that were positive by the myChoice GI score, even when the subset of samples with *BRCA1* or *BRCA2* tumor mutations was assessed.
- The consistency of the data between mutant and wild-type tumors suggests that %LOH may miss up to half of patients who are appropriate candidates for PARP inhibitors.