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.

- The myChoice HRD test is the only analytically- and clinically-validated, FDA-approved HRD test that includes *BRCA1/2* mutation status and three measures of genomic instability.

OBJECTIVE

- We compared the proportion of patients identified as candidates for PARP inhibitor use by three measures of HR deficiency: myChoice HRD, percent loss of heterozygosity (%LOH), and an 11-gene panel.

METHODS

MOLECULAR TESTING

- 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 SCOTROC trial (N = 153).

- The myChoice GI score incorporated three measures assessed using the genomic profiles [LOH, telomeric allelic imbalance (TAI), and large-scale state transitions (LST)].

- %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.
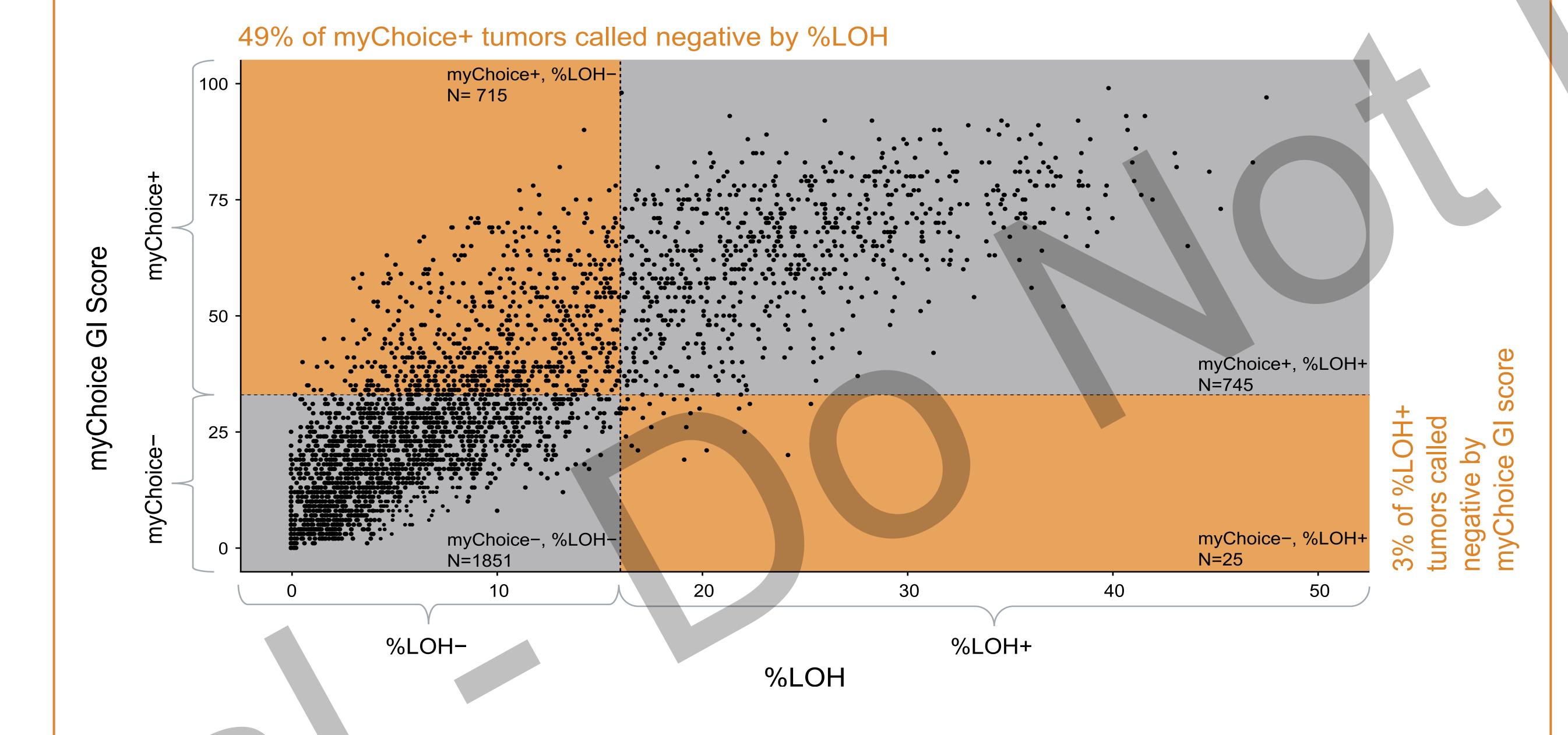
ANALYSIS

- 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 myChoice GI score were compared.
  - For comparisons to the 11-gene panel, samples were 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.
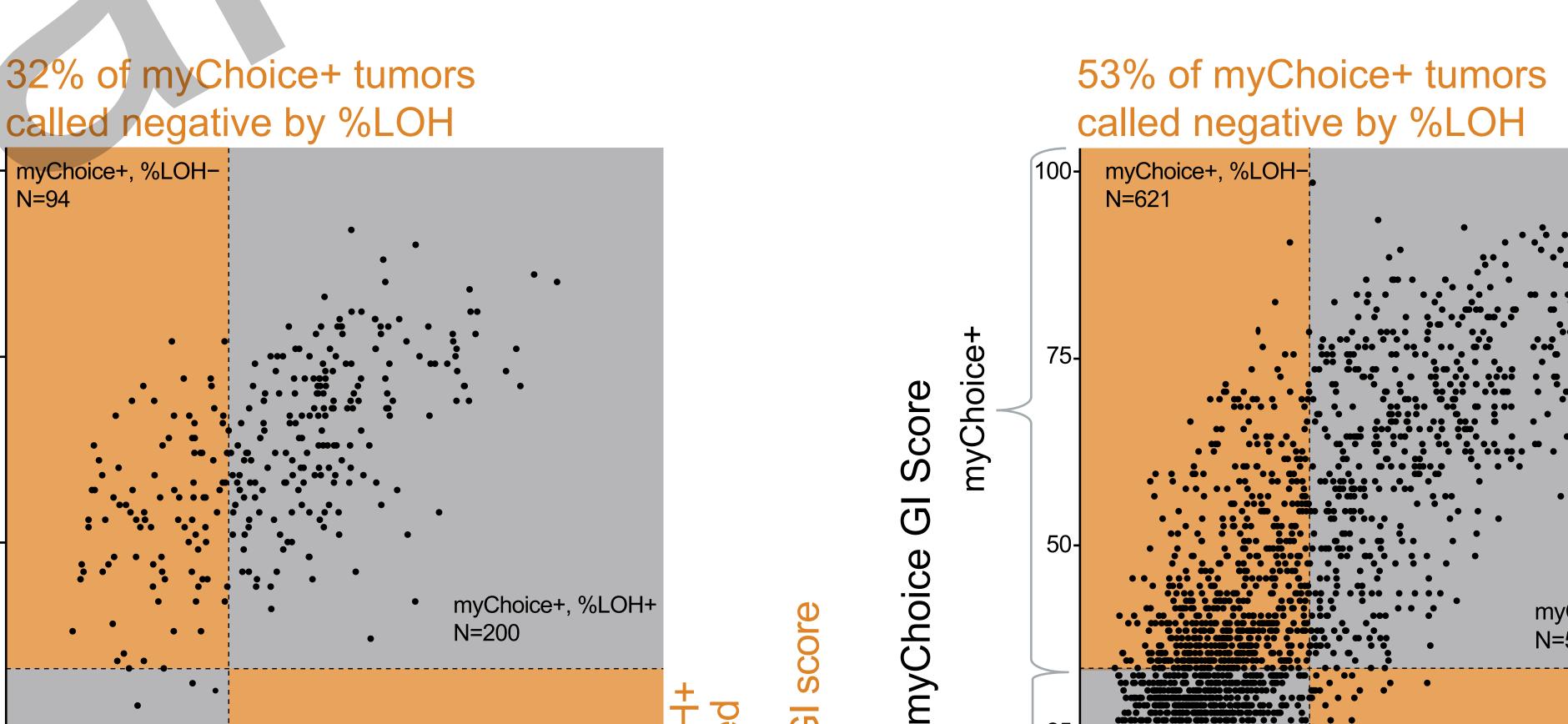
RESULTS

Figure 1. Correlation between myChoice GI score and %LOH

Data highlighted in grey show samples with concordant results from the myChoice GI score and %LOH. Data highlighted in orange show samples with discordant results. The myChoice GI score threshold is 33.
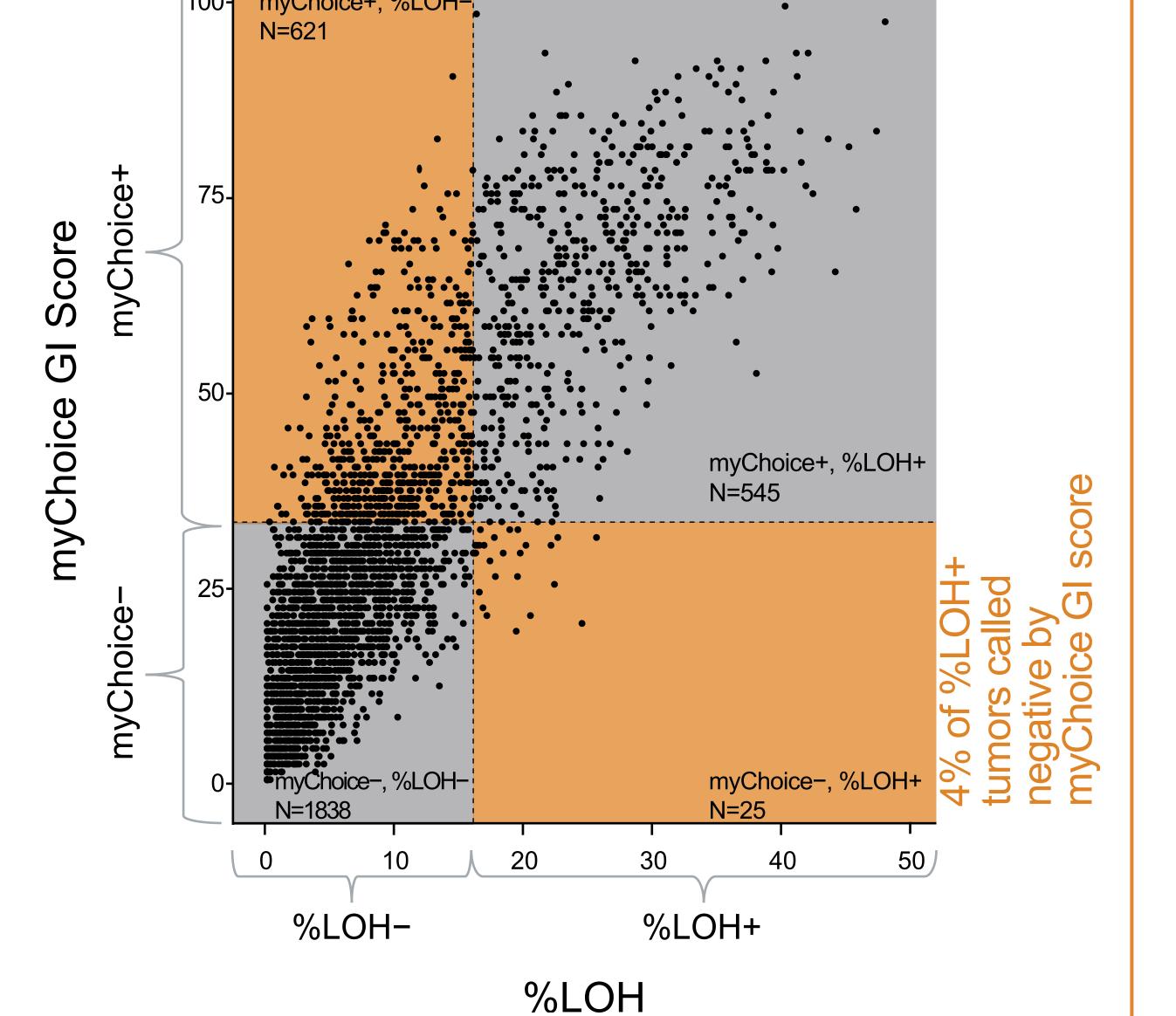

A. Full Commercial Cohort (N=3,336)

49% of myChoice+ tumors called negative by %LOH

myChoice+, %LOH− N= 715 | myChoice+, %LOH+ N=745 | myChoice−, %LOH− N=1851 | myChoice−, %LOH+ N=25

3% of %LOH+ tumors called negative by myChoice GI score

B. Subset of Samples with *BRCA1/2* Tumor Mutations (N=307)

32% of myChoice+ tumors called negative by %LOH

myChoice+, %LOH− N=94 | myChoice+, %LOH+ N=200 | myChoice−, %LOH− N=13 | myChoice−, %LOH+ N=0

0% of %LOH+ tumors called negative by myChoice GI score

C. Subset of Samples with Wild-Type *BRCA1/2* (N=3,029)

53% of myChoice+ tumors called negative by %LOH

myChoice+, %LOH− N=621 | myChoice+, %LOH+ N=545 | myChoice−, %LOH− N=1838 | myChoice−, %LOH+ N=25

4% of %LOH+ tumors called negative by myChoice GI score

Table 1. Correlation between *myChoice, %LOH, and the 11-gene panel in the commercial and SCOTROC cohorts.*
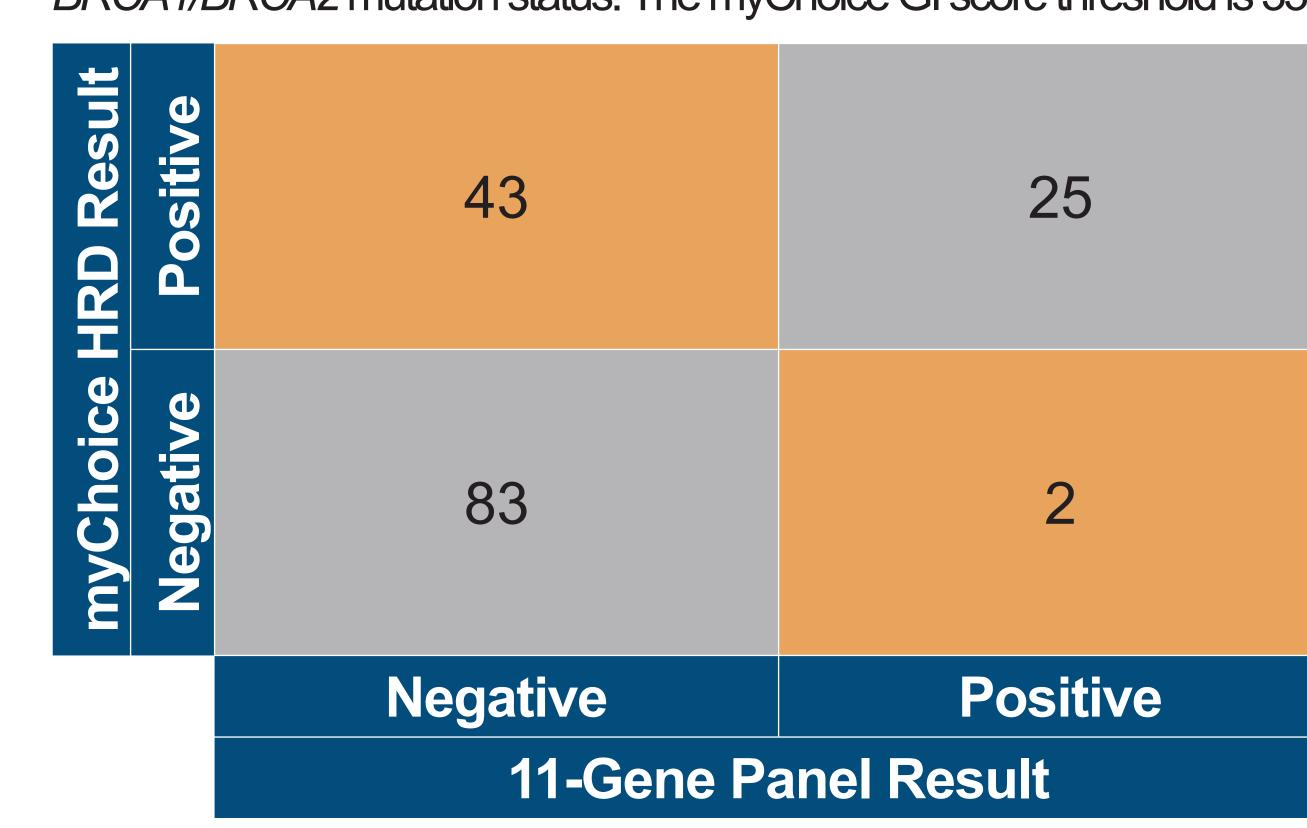
Reference Test		myChoice HRD*		%LOH		11-gene panel
		Commercial	SCOTROC	Commercial	SCOTROC	SCOTROC
myChoice HRD	Correlation	--	--	0.847	0.87	n/a**
	PPA (42)	--	--	64.9%	82.5%	46.0%
	PNA (42)	--	--	96.6%	95.8%	96.1%
	PPA (33)	--	--	51.0%	62.7%	36.8%
	PNA (33)	--	--	98.7%	75.0%	97.6%
%LOH	Correlation	0.847	0.87	--	--	not evaluated
	PPA	90.1%	100%	--	--	not evaluated
	PNA	85.3%	75%	--	--	not evaluated
11-gene panel	Correlation	n/a	n/a**	not evaluated		--
	PPA	n/a	92.6%	not evaluated		--
	PNA	n/a	65.9%	not evaluated		--

*Using the threshold score at 33. **Could not be calculated because positive results by the 11-gene panel were not continuous.
NOTE: For comparisons to the 11-gene panel, *BRCA1* and *BRCA2* tumor mutation status were also considered for the myChoice.

Table 2. Comparison of myChoice HRD and 11-gene panel results in the SCOTROC cohort (N=153).

myChoice HRD accounted for the myChoice GI score and tumor *BRCA1/BRCA2* mutation status. The myChoice GI score threshold is 33.

myChoice HRD Result	11-Gene Panel Result	
	Negative	Positive
Positive	43	25
Negative	83	2

- Correlations, PPA, and PNA between myChoice, %LOH, and the 11-gene panel indicate a high concordance, but not equivalence (Table 1).

- Nearly half of patients identified as positive by myChoice HRD would have been missed by %LOH in the commercial cohort (Figure 1).
  - This 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 myChoice HRD (Figure 1).

CONCLUSIONS

- These data show that tests used to evaluate HR deficiency in published and ongoing clinical trials are not equivalent, and they 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.