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

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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.

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, BRIPI, 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.

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

<table>
<thead>
<tr>
<th>Reference Test</th>
<th>%LOH</th>
<th>11-gene panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>myChoice HRD**</td>
<td>Commercial</td>
<td>SCOTROC</td>
</tr>
<tr>
<td>%LOH Correlation</td>
<td>0.847</td>
<td>0.87</td>
</tr>
<tr>
<td>PPA (42)</td>
<td>64.9%</td>
<td>82.5%</td>
</tr>
<tr>
<td>PNA (42)</td>
<td>96.6%</td>
<td>95.8%</td>
</tr>
<tr>
<td>PPA (33)</td>
<td>51.0%</td>
<td>62.7%</td>
</tr>
<tr>
<td>PNA (33)</td>
<td>98.7%</td>
<td>75.0%</td>
</tr>
</tbody>
</table>

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.

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