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

Gordon B. Mills, MD, PhD; Michael Perry, BS; Alexander Gutiñ, PhD; Jerry S. Lanchbury, PhD; Robert Brown, PhD; Kirsten M. Timms, PhD

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
- SCOTROC trial (HGSOC only), N = 176
Mutation screening was also performed for 11 genes in the HR pathway (ATM, BARD1, BRCA1, BRCA2, BRI1, CHEK2, MRE11A, NBN, PALB2, RAD51C, RAD51D) for a subset of tumors from the SCOTROC trial (N = 153).

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

%LOH was calculated using the genomic profiling.

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 computed.
  - For comparisons to the 11-gene panel, samples were dichotomized 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 orange show samples with concurrent results from the myChoice GI score and %LOH. Data highlighted in orange show samples with discordant results. The myChoice GI score threshold is 33.

Table 1. Correlation between myChoice, %LOH, and the 11-gene panel in the commercial and SCOTROC cohorts.

<table>
<thead>
<tr>
<th>Reference Test</th>
<th>myChoice HRD*</th>
<th>%LOH</th>
<th>11-gene panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial</td>
<td>SCD ROC</td>
<td>SCD ROC</td>
<td>SCD ROC</td>
</tr>
<tr>
<td>PPA (42)</td>
<td>0.847</td>
<td>0.87</td>
<td>not evaluated</td>
</tr>
<tr>
<td>PNA (42)</td>
<td>64.9%</td>
<td>82.6%</td>
<td>46.0%</td>
</tr>
<tr>
<td>PPA (33)</td>
<td>96.6%</td>
<td>59.8%</td>
<td>96.1%</td>
</tr>
<tr>
<td>PNA (33)</td>
<td>51.0%</td>
<td>62.7%</td>
<td>36.8%</td>
</tr>
<tr>
<td>%LOH</td>
<td>98.7%</td>
<td>75.0%</td>
<td>97.6%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>myChoice HRD</th>
<th>%LOH</th>
<th>11-gene panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPA</td>
<td>90.1%</td>
<td>100%</td>
</tr>
<tr>
<td>PNA</td>
<td>85.3%</td>
<td>75%</td>
</tr>
<tr>
<td>%LOH</td>
<td>n/a</td>
<td>65.9%</td>
</tr>
<tr>
<td>11-gene panel</td>
<td>n/a</td>
<td>92.6%</td>
</tr>
</tbody>
</table>

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.

Email questions to klimms@myriad.com