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Better Testing, Better Treatment

HRD in ovarian cancer: defined today, evolving for the future

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Background

Homologous recombination repair (HRR) gene mutations result in homologous recombination deficiency (HRD) associated with increased risk of high-grade serous ovarian cancer (HGOC) and subsequent response to PARP inhibitors (PARPi). Traditionally, HRD has been determined by testing for germline and/or somatic *BRCA*1/2 mutations. Today, a growing number of HRR gene mutations are known to result in HRD and genomic instability, thus being a suitable target for PARPi. Therapy response to PARPi is highest in *BRCA*-mutant and second highest in HRD+/non-*BRCA*-mutant HGOC. Today, no standard HRD testing methods exist, causing confusion for physicians and leading to poor outcomes for missed PARPi eligible patients. Thus, there is need to understand HRD testing utilization and methods in HGOC to inform best practices and optimize HRD testing in the clinic.

Methods

We assessed the testing landscape for determining HRD status in ovarian cancer using a data set of 8,400 newly diagnosed and metastatic ovarian cancer patients in the US from Q3-2018 through Q2-2019 identified from Diaceutics' proprietary Global Diagnostic Index (GDI). Analysis of real-world *BRCA*1/2- and NGS-associated testing data and laboratory profile mapping exercise of 82 US labs was carried out using Diaceutics proprietary methods and data sources to evaluate *BRCA*1/2 and/or HRD germline/somatic testing rates, test availability, and test panel HRR gene composition.

Results

Overall, germline mutation testing rates were 3x greater than somatic testing rates. Excluding *BRCA*1/2, 67 labs offered comprehensive solid tumor NGS panels capable of measuring HRD with varied HRR gene target composition. Across 34 labs, 5 HRR genes were commonly found on panels: *PALB2, ATM, BARD1, BRIP1,* and *CHEK2*. Three labs currently offering panels explicitly intended for HRD determination only include *BRCA*1/2 and at least one genomic instability marker (loss of heterozygosity, large-scale state transitions, or telomeric allelic imbalance).

Discussion

Lack of standardized HRD panels and low testing rate identifying patients with somatic mutations in *BRCA*1/2 and other HRR genes are leading to poorer outcomes for missed patients eligible for PARPi's. As clinical evidence linking HRD status with PARPi efficacy grows in ovarian as well as prostate and pancreatic cancer, Diaceutics recommends organizations such as ASCO, CAP, or AMP establish defined universal HRD testing panels, including relevant somatic/germline HRR genes and *BRCA*1/2 as well as genomic instability markers, and educate stakeholders, aiding harmonization and, ultimately, better treatment outcomes.