

Paired Somatic and Germline Genetic Testing for Ovarian Cancer Patients: Observations, Benefits and Implications for Treatment

Daniel Chen, Patrick Reineke, Negar Ghahramani, Ashley Deckman, Erica Wellington, Monalyn Umali Salvador, Lucia Guidugli, Melissa Pronold, Holly LaDuca, Michelle Jackson

Background: Germline and somatic genetic testing have traditionally been offered separately; however, the clinical applications of these tests are now converging with continued FDA approval of targeted therapies for both germline and somatic mutation carriers. This study aims to describe the findings of a paired testing (germline and somatic) approach among ovarian cancer (OC) patients.

Methods: Study participants consisted of 95 consecutive OC patients undergoing paired testing at a clinical diagnostic laboratory. Eleven OC predisposition genes in the homologous recombination (HR) repair pathway were targeted by capture-based NGS: *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*, and *RAD51D*. Paired analysis of sequence data from both tumor (minimum of 20% neoplastic cellularity) and blood specimens was performed to differentiate variants of somatic vs. germline origin. Customized NGS pipelines and/or microarray were used to detect gene copy number variants. Additional test results included hypermethylation analysis of *BRCA1* and *RAD51C* promoter regions by methylation-specific PCR, when available.

Results: In total, 41 patients (43.2%) were eligible for PARP-inhibitor therapy based on the presence of a germline (n=3, 7.3%), somatic (n=34, 82.9%) or germline and somatic (n=4, 9.8%) *BRCA1* or *BRCA2* pathogenic mutation. Of 38 (40.0%) patients with somatic alterations, 3 (7.9%) had sequencing mutations, 32 (84.2%) had whole gene deletions of *BRCA1* and/or *BRCA2*, and 3 (7.9%) had both alteration types. Somatic whole gene deletions of *BRCA1* or *BRCA2* were often accompanied by gains or losses of other genes in the tumor. Twenty-nine patients (30.5%) were germline and tumor *BRCA1/2*-negative, but tested positive for germline or somatic pathogenic mutations in other HR genes or tumor promoter methylation in *BRCA1* or *RAD51C*.

Conclusion: Our findings highlight the benefits of paired testing over germline and/or somatic testing alone, such as concurrent confirmation of germline mutations and maximizing detection of patients who would benefit from therapy. Further research is needed to determine the impact of paired testing on healthcare costs and patient outcomes.