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Response to Tomao, Panici, and Tomao

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Tomao et al. highlight the importance of the new tumor DNA BRCA1/2 testing workflow for tailored therapeutic strategy and state critical elements that may affect the quality of the workflow. They raise three concerns: first, a quality assessment protocol for the tumor test should be in place to ensure test validity and reliability; second, patients and clinicians should be satisfied with the workflow; and third, epithelial ovarian cancers should be selected based on histotype.

Their concerns give us the opportunity to emphasize aspects that are essential for safe clinical implementation of the workflow. First, the tumor test needs to undergo a rigid validation to ensure adequate detection of clinically relevant variants. We have chosen a technique with unique molecule identifiers that are used to quantify the number of analyzed template molecules at each position to determine the quality of the formalin-fixed, paraffin-embedded (FFPE) material and the sensitivity of our analysis. Our single-molecule molecular inversion probe-based targeted next-generation sequencing approach uses overlapping single-molecule molecular inversion probes on both the plus and minus strand to ensure detection of single and multiple nucleotide variants at each position and is able to recognize formalin-induced artifacts. The assay has been thoroughly validated for use in FFPE material and is combined with multiplex ligation-dependent probe amplification to detect exon deletions in BRCA1 (1). Analyses of ascites were considered to be valid in cases with a sufficient amount and percentage of neoplastic cells given the assumption that especially homogeneously BRCA1/2-mutated tumors would benefit from PARP inhibitors.

Second, although the observed overwhelming satisfaction of patients and clinicians was based on interviews and questionnaires with a limited number of participants, more than 70% of the invited ovarian cancer patients participated. Moreover, these findings are supported by our experiences from daily clinical practice over the last 4 years from the day since we have been implementing this workflow. There is wide support for a tumor DNA BRCA1/2 testing workflow both from the national and international communities (2).

Third, because current guidelines advise BRCA1/2 germline testing in all epithelial ovarian cancer cases irrespective of subtype, these subtypes were also included in the universal tumor test workflow (3). Compared to the overall yield of BRCA1/2 pathogenic tumor variants of 17% (51 of 305), the yield was 20% (38 of 193) higher in high-grade serous ovarian cancer. We note that the yield was still 12% (13 of 112) in the remaining subtypes, of which germline variants were detected in 4 of 11 evaluated cases.

We agree that to modify the clinical practice, it is essential that the test on FFPE tumor material as a prescreen be equally reliable as genetic predisposition testing on DNA derived from peripheral blood lymphocytes and be able to detect somatic alterations. Provided that the universal tumor DNA testing workflow is implemented by a multidisciplinary team of experts active in the clinical-care pathway, including an experienced laboratory specialist in cancer genetics, the workflow has shown to be a valid and reliable clinical workflow to prescreen for genetic predisposition testing and to stratify for PARP inhibitor therapy.

Notes

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