**BRCA status assessment in epithelial ovarian cancer and the challenge of tumor testing**

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We read with great interest the recently published ASCO guidelines regarding the need for genomic testing in patients with epithelial ovarian cancer.1 The authors made a notable effort to further the field as it pertains to germline and somatic mutations in patients with epithelial ovarian cancer and to personalize its management. Nevertheless, we were rather surprised that women diagnosed with epithelial ovarian cancer should have germline BRCA (gBRCA) genetic testing, while reserving tumor tissue DNA (tBRCA) sequencing only for those with negative gBRCA.

The authors stated that “up to 5% of germline mutations will be missed if using tumor somatic mutation results” and that “missing a germline mutation has grave implications for family members”. Although we fully agree with the last sentence, we believe that some issues need to be discussed. The authors’ reference to 5% of gBRCA pathogenic variants in tBRCA negative cases is taken from the SOLO1 study, where all patients were either gBRCA or tBRCA mutants.2 Seventeen samples showed discordances; in particular, 12 of 341 (3.5%) were tBRCA wild-type and five (1.5%) had a tBRCA variant of unknown significance. If we do not consider a variant of unknown significance as tumor test missing, but rather as a different variant interpretation, we can conclude that 3.5% is necessary and stressful double-test procedures.

In the SOLO1 trial, formalin-fixed, paraffin-embedded tissue was used for tBRCA testing. Formalin-fixed, paraffin-embedded quality, different DNA extraction protocols, and level of DNA integrity testing may influence the quality of the extracted DNA, muddying sequencing and subsequent analysis.3 More recently, fresh frozen tissue has been proposed as an alternative procedure.4 5 This tissue handling seems to minimize damage to nucleotides, allowing extraction of high-quality DNA, enabling the identification of gBRCA large genomic rearrangements in tumor tissue.6 Indeed, 10 of 12 tBRCA wild-type samples were due to large genomic rearrangements, reported by Myriad test but not detected by Foundation Medicine Kit.

We admit that a fresh-frozen, tissue-based BRCA testing approach is not simple to offer, as it is strictly related to hospital organization, depending on close cooperation among surgeons, pathologists, and the molecular testing team. With this regard, in 456 patients with high-grade serous carcinoma, we found that commitment of all professionals enables fresh-frozen, tissue-based BRCA testing to identify up to 32% of patients with the tBRCA mutation (including those with germline large genomic rearrangements), ruling out 6% of women who would have been missed if only gBRCA testing had been performed.7

Lastly, it remains unclear which is the most cost-effective approach.8 According to the ASCO guidelines,1 all patients with epithelial ovarian cancer with no gBRCA mutation will require tumor testing to unmask the presence of a somatic mutation. If we assume approximately 20% of cases of high-grade serous epithelial ovarian cancer harbor a gBRCA mutation, roughly 80% will undergo tBRCA testing, with a tBRCA mutation found in no more than 15% of cases. As a consequence, 65% of patients with epithelial ovarian cancer will receive a needless and expensive double-test procedure.

In our view, broadening of the BRCA-tested population should be pursued, while reducing expensive, unnecessary and stressful double-test procedures. If fresh tissue is the way, then we should persevere and improve our laboratory technical skills for BRCA testing interpretation, as well as our commitment toward an effective in-house ‘BRCA testing approach.

**To cite:** Marchetti C, Minucci A, Pietragalla A, et al. Int J Gynecol Cancer Published Online First: [please include Day Month Year]. doi:10.1136/ijgc-2020-001670

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Received 27 May 2020
Revised 29 May 2020
Accepted 2 June 2020

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; internally peer reviewed.

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**Contributors** All authors have read and approved the manuscript. All authors consistently contributed to the manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Check for updates**

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Commentary

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