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 the rate of missed germline pathogenic variants. This still seems a high value, due to the possible impact on missed cascade genetic screening.

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.

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REFERENCES

- 1 Konstantinopoulos PA, Norquist B, Lacchetti C, *et al.* Germline and somatic tumor testing in epithelial ovarian cancer: ASCO guideline. *J Clin Oncol* 2020;38:1222–45.
- 2 Moore K, Colombo N, Scambia G, *et al.* Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med* 2018;379:2495–505.
- 3 Mafficini A, Simbolo M, Parisi A, *et al.* BRCA somatic and germline mutation detection in paraffin embedded ovarian cancers by next-generation sequencing. *Oncotarget* 2016;7:1076–83.
- 4 Gori S, Barberis M, Bella MA, *et al.* Recommendations for the implementation of BRCA testing in ovarian cancer patients and their relatives. *Crit Rev Oncol Hematol* 2019;140:67–72.
- 5 Capoluongo E, Scambia G, Nabholz J-M. Main implications related to the switch to BRCA1/2 tumor testing in ovarian cancer patients: a proposal of a consensus. *Oncotarget* 2018;9:19463–8.
- 6 Minucci A, Mazzucato G, Marchetti C, *et al.* Detecting germline rearrangements of BRCA1 by next generation tumor sequencing. *Mol Biol* 2020. In press.
- 7 D'Indinosante M, Marchetti C, Caricato C, *et al.* BRCA tumor-testing in a tertiary referral center: are we missing something or not? Presented at the Society of Gynecologic Oncology's 51th Annual Meeting on Women's Cancer 2020.
- 8 Kwon JS, Tinker AV TA, Karsanc A, *et al.* Costs and benefits of tumor testing for BRCA mutations in high-grade serous ovarian cancer as a companion diagnostic for PARP inhibitor treatment. Presented at the Society of Gynecologic Oncology's 50th Annual Meeting on Women's Cancer. Honolulu, HI, 2019.