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Reply to Dr. Witjes regarding universal tumor genomic sequencing as a prescreen for germline genetic testing in patients diagnosed with ovarian cancer

Jenny Lin, Melissa K. Frey *

Weill Cornell Medicine, United States

We would like to thank Dr. Witjes and her colleagues for their interest in our paper and for taking the time to elaborate on the promises of universal tumor genomic sequencing as a prescreen for germline genetic testing.

We are in agreement that *BRCA1/2* tumor genomic sequencing as a prescreen for germline genetic testing has many potential advantages; however, we wish to highlight that the data specifically regarding this approach in patients with ovarian cancer remain sparse and further studies are necessary. Our review noted high study heterogeneity that resulted in a quality of evidence that was low based on the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework, indicating that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change this estimate (Lin et al., 2021).

As Dr. Witjes mentioned, Vos et al. (2019) reported that 77.6% of patients received tumor genomic profiling and 86.3% of patients with aberrant tumor *BRCA1/2* testing chose to pursue genetic counseling and germline testing. However, 22.4% of patients did not undergo genomic profiling and only 22% of these patients were subsequently referred for germline testing; Vos et al. did not specifically report reasons for lack of tumor or germline testing. These results suggest that reflex tumor *BRCA1/2* testing is promising with high uptake.

With limited published experience in ovarian cancer, we can also examine this approach to genetic assessment in other malignancies. Clark et al. (2019) describe the development and implementation of a novel algorithm for referral of patients for germline testing following tumor genomic sequencing for several tumor types. Among patients undergoing tumor genomic profiling, 5% had somatic findings triggering referral for genetic testing. Implementation of the proposed automatic referral pipeline resulted in 74% germline confirmation. However, only 41% of patients referred for germline testing successfully completed this recommended testing. Reasons cited by patients for not pursuing germline testing included: poor patient health or death (30%), lack of follow-up (30%), and patient refusal (30%). This study highlights the promise of tumor testing with reflex germline testing; however, the authors also emphasize that such pipelines must be accompanied by patient and provider education and an improved infrastructure for referrals for germline testing. Additional studies on tumor genomic profiling with the inclusion of such interventions are needed as low levels of germline confirmatory testing represent a critical missed opportunity for patients.

Although reflex *BRCA1/2* tumor testing as a prescreen for germline genetic testing is promising, further research is needed to determine its efficacy as well as cost-effectiveness in the ovarian cancer patient population. The literature remains scarce and we are eager to see future studies that report on such findings. The current American Society of Clinical Oncology (ASCO) guidelines recommend that all women with epithelial ovarian cancer receive germline genetic testing for *BRCA1/2* and other ovarian cancer susceptibility genes, with the further recommendation that those without germline pathogenic or likely pathogenic *BRCA1/2* variants receive somatic tumor testing (Konstantinopoulos et al., 2020).

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CRediT authorship contribution statement

Jenny Lin: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Melissa K. Frey:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources,

* Corresponding author at: Assistant Professor, Division of Gynecologic Oncology.
E-mail address: mkf2002@med.cornell.edu (M.K. Frey).

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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