Author’s response to reviews

Title: Evaluation of a 27-gene inherited cancer panel across 630 consecutive patients referred for testing in a clinical diagnostic laboratory

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Bryony A Thompson, PhD
Associate Editor, Hereditary Cancer in Clinical Practice
Huntsman Cancer Institute, USA and University of Melbourne, Australia
Dear Dr. Thompson,

We thank the reviewers for their appreciation of our manuscript and the constructive comments provided. We have attempted to respond to each comment (quoted verbatim) below. We hope this will sufficiently resolve any doubts/clarifications and allow for a final acceptance of the manuscript in its edited form. All changes to the edited manuscript have been tracked as requested in the author instructions. The revised manuscript also conforms to the journal style.

Response to Reviews

Reviewer #1: I applaud the work of the authors of this paper who have written an excellent analysis of the findings of hereditary cancer testing using a 27-gene panel. The writing was clear and the analysis understandable. However, I have a few comments to consider for revision.

1) In the paper you group participants by personal and family history of either Lynch Syndrome or HBOC. Considering ovarian cancer is a common clinical feature of both, how did you group the patients that have that personal and/or family history? It seems, based on Table 2, that these participants were counted twice (as both HBOC and Lynch Syndrome). It may be helpful to expand further on the personal and family history features of these participants or to perhaps leave room for a third category of those who have personal and/or family history of both HBOC and Lynch Syndrome.

Response: As described in the methods (lines 108-110 of the original submission), patients with ovarian cancer were counted in both HBOC and Lynch syndrome categories, which, as the reviewer points out, is a common clinical feature of both. Table 2 was specifically intended to describe the number of patients from each phenotype group who carry a DV among the 14 genes on our panel. As correctly pointed by the reviewer, in Table 2, these patients were counted twice, once in HBOC and once in Lynch syndrome categories. Furthermore, in the additional file which describes the same patients as in Table 2, we provide the specific type(s) of cancer(s) found in each patient carrying a pathogenic variant, allowing the readers to distinguish those who had ovarian cancer versus those who had two different types of cancers that fit into each category.

Elsewhere in the manuscript, we utilize a third category, individuals with a personal/family history of both HBOC and LS. In Figure 1, we describe patients with a personal history of both HBOC and LS, which includes patients with ovarian cancer, as well as patients with two different types of cancers that fit into each category. Additionally, the same numbers have been provided for individuals with a family history of both HBOC and LS. In Figure 3, which describes the positive, negative and VUS rates for personal/family history category, we also show a category for patients who have a personal history of both cancers (Fig 3d), patients who have a family history of both cancers (Fig 3g), as well as a category for individuals with both a personal AND family history of both cancers (Fig 3j).

To clarify this further, we have added a statement in the text pointing readers to view the additional file for specific phenotypic data on the patient counts reported in Table 2 (lines 210-211, revised manuscript). In addition, we have included an explicit statement to this effect on
lines 110-112 (revised manuscript) and a foot note with superscript c has been included under Table 2.

2) Your paper highlighted the fact that the patient group was not enriched for adherence to the National Comprehensive Cancer Network (NCCN) criteria for either HBOC or Lynch Syndrome and rather they constitute a referral laboratory cohort. I question whether patients would have adequate insurance coverage for genetic testing if they do not meet NCCN criteria. This could be a bias in the participant group just based on the fact that many individuals who do not meet this criteria do not have insurance coverage for testing and choose not to pursue testing. I wonder if you could retrospectively look at the patient information that was collected to determine what percentage actually meet criteria for testing.

Response: We acknowledge the reviewer’s comment regarding the lack of information on the exact percentage of patients fulfilling the NCCN criteria in our cohort and mention this as one of the limitations in the discussion section. The 2 major studies that reported the positive rates in patients enriched for NCCN criteria were outcomes of collaboration between academic medical centers and diagnostic reference laboratories. This facilitated prospective patient recruitment at the academic medical center prior to data analysis. Within the scope of our study, a detailed assessment of each patient for adherence to the NCCN criteria for HBOC or LS testing could not be performed. To further address this concern, we have expanded the discussion section to emphasize the potential for such a bias while pointing to the higher non-BRCA and non-LS positive rates in our study (lines 380-385, revised manuscript).

Reviewer #2: This is an interesting article in its field. It corroborates the utility of multi-gene panels testing, and the need to go over traditional criteria.

1) This article has limits, as the authors said, as the lack of informations about personal and familial histories of cancer. How did they classified patients on Table 2 without these informations?

Response: As stated in the results, among the 630 cases referred for testing, 90% (n=565) had an indication for testing provided by the referring physician. The limitation about some patients who lacked detailed clinical information is mentioned in the discussion section of the manuscript. Table 2 was specifically intended to describe the number of patients from each phenotype group who carry a DV among the 14 genes on our panel. Patients lacking clinical data are noted with the superscript a, and mentioned in the footnote of the table. This small subset of patients were not counted in either category (personal or family history of cancer) since that information could not be obtained.

2) Furthermore, in Table 2, results were classified according to personal or family history of HBOC and/or LS. The authors could have mentionned the organ affected.

Response: In the methods section (lines 108-110 of the original submission), we state the criteria used to group patients into each category, and the affected organ site used for our ascertainment.
Furthermore, in the additional file which describes the same patients as in Table 2, we provide the specific type(s) of cancer(s) found in each patient carrying a pathogenic variant, allowing the readers to review the associated affected organ site in both personal and family history of cancer categories.

We hope this addresses each reviewer comment in sufficient detail.

Please contact me for any additional questions or concerns.

Sincerely,

Narasimhan Nagan, PhD, FACMG, DABCC
Corresponding author