Reviewer’s report

Title: Diagnostic yield and clinical utility of a comprehensive gene panel for hereditary tumor syndromes

Version: 0 Date: 15 Nov 2018

Reviewer: Florentia Fostira

Reviewer's report:

This is a very interesting article addressing a quite important aspect of hereditary cancer. Patients that have high probability of carrying germline mutations (early onset or multiple cancer diagnoses and/or strong family history) need to be thoroughly investigated in order to determine the phenotypic heterogeneity of causative variants in known genes, as well as to expand our perspective on novel associations.

A major advantage of this work is the validation of the comprehensive cancer-gene panel used, which was a combination of a commercial and a customized panel.

The manuscript is well-written. I have some comments:

1. I think that there are a couple of paragraphs that are lengthy and can be shortened. This will enable easy read-through of the manuscript.

   - More specifically, in the Patients and Methods section, the data collection paragraph can be shortened, keeping the basic in the section and transferring additional information in the supplementary files.

   - The Discussion section is also quite extensive. I am not sure if the detailed description of each case identified and described in the Results section needs to be discussed in detail. Moreover, I felt that the comparison with other studies, described in the last two paragraphs of the discussion is not needed, especially the details on MUTYH monoallelic/biallelic carriers. In the beginning of the last paragraph on page 17, the first sentence should be omitted, as it undermines the results of the current work.

2. A limitation of the study is the lack of evaluation for large genomic rearrangements in the tested genes. A comment in the discussion should be added, as some of the negative cases could be explained by such genetic events.
3. A comment should be added on the impact of rare variants that do not comply with the criteria the authors have set and might be causative.

4. In the variant filtering description, synonymous variants are not mentioned, so I assume that these have been filtered out? What if a synonymous variant causes aberrant splicing?

5. Maybe add in the abstract the number of "unsolved" cases you have been able to address.

6. Polymorphism is an obsolete expression; benign variant probably more appropriate

**Level of interest**

Please indicate how interesting you found the manuscript:

An article of importance in its field

**Quality of written English**

Please indicate the quality of language in the manuscript:

Acceptable

**Declaration of competing interests**

Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

No conflict to declare
I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal