Author’s response to reviews

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

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Comments to the Reviewers

We thank the referees for their careful review and the constructive remarks which helped us to improve the manuscript and to correct some inaccuracies. We followed the suggestions and recommendations as described below and give point-by-point descriptions on how we dealt with the different comments. The changes in the text are highlighted via 'tracked changes'.

REVIEWER # 1 wrote:
No comments.

REVIEWER #2 wrote:
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.

1. Our comment

   As recommended, we shortened the patients / data collection paragraph and transferred more detailed information and the description of the structural POLD1 analysis into the supplement (see pages 5-8). We agree with the reviewer that the discussion is quite long, however, we used the cases to discuss some more general issues regarding multigene panels and feel that these points might be relevant. Nevertheless, we now shortened this part in a modest way, in particular by removing and summarizing detailed information (see especially pages 14-16). As suggested, we also removed the sentence on page 17 and reduced the comparison with other studies (see pages 18-19).

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. Our comment

   As recommended, we added a comment in the discussion (page 18).

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.
3. Our comment

We added a comment in the discussion (page 18).

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?

4. Our comment

We thank the referee for this comment. We absolutely agree, that synonymous variants can be pathogenic, mainly due to aberrant splicing. Indeed, we considered synonymous variants, if they are rare (MAF of $\leq 0.001$) and located in the first or last three bases of an exon, but this was not clarified in the manuscript and thus, we now added this information in the methods section (page 8, first paragraph). However, the exclusion of synonymous variants is a common strategy to reduce the high number of rare variants to those which are most likely pathogenic / causative. As suggested, we now pointed out in the discussion, that due to the exclusion of synonymous variants in general, it cannot be ruled out that a pathogenic variant was overlooked although we suppose, that the likelihood is quite low (page 18).

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

5. Our comment

In the abstract we mentioned the percentage of most interesting and probably causative variants in group U (17%) and the number of patients (2%) with variants in genes that can be considered as causative (PMS2, PTEN, POLD1). These two numbers more or less represent the range of the diagnostic yield of the study with pre-screened patients. We feel that it would be very difficult to provide a precise number of solved cases and thus we would prefer to mention in the abstract this range only and refer to a more detailed description in the results and discussion sections, if the referee agree.

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

6. Our comment

We followed the suggestion and replaced the expression “polymorphism” by benign variant.