Reviewer’s report

Title: Targeted capture-based NGS is superior to multiplex PCR-based NGS for hereditary BRCA1 and BRCA2 gene analysis in FFPE tumor samples

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Reviewer: Matthias Nees

Reviewer's report:

The language used on this manuscript is good but not flawless; especially in the beginning of the text, there are a few grammar issues including e.g. the endings of words (singular/plural). Otherwise, grammar and sentences are okay and acceptable. However, at least one round of additional proofreading is necessary/recommended.

The abstract in particularly is well written and concise, the main message - despite complex patient cohorts analyzed - comes easily across and also appeals to readers not specifically or directly involved in this research.

The same applies to introduction, which summarizes the field of BRCA1/2 biology, genetic research and treatment options in a few short paragraphs; very expertly written in my opinion.

The technical issues introduced in this manuscript are of very real and practical nature, due to the poor and highly variable quality of DNA in paraffin-embedded tissues. The manuscript as such is therefore relevant for the field and should attain significant attention. Moreover, it is written in a very Hands-on, practical and clear fashion that should be particularly useful for those who adapt, optimize and utilize such laboratory methods in daily clinical practice.

Concerning the methods themselves, one may wonder if the originator of the PCR panels (Illumina) has actually compared these or related methods carefully themselves, and if any relevant publications (maybe in the form of posters, short communications, white papers etc) from Illumina exist that would corroborate the findings described here? (This would be interesting for practical reasons again).

The figures are somewhat difficult to interpret for non-experts in the field, in particular the combined data from 5 or 13 patients in the PCR Panel (Figure 1B, and Suppl. Figure 1B). It is not entirely clear what the red arrows indicate (or description in figure legend is insufficient to clarify). Would the example of just one or 2 exemplary patient data give a more clear representation of the typical differences between the 2 approaches? And illustrate the strength and Advantage of the targeted capture-based NGS?

It might be more conclusive if 1 or 2 concrete examples that typically affect the quality of genetic testing (and everyone fears) were shown as examples - similar to figure 2, but indicating
broader genetic areas. In particular, when based on highly fragmented DNA, from 1 or 2 selected patient samples as discussed in the text. It could be considered if such selected examples might illustrate the power and advantages of the 2 methods more impressively than current figure 1, and suppl. figure 1

Small issues:
There are several small typos or inconsistencies in lines 90 - 92:
90 ….for example in cases where the index patient IS deceased or with suspicion of
91 mosaicism. In addition, testing of tumor tissueS aids interpretation of variants of unknown
92 significance (VUS) with regard to the identification of a possible second hit, represented as
93 loss-of-heterozygosity (LOH) or a second pathogenic somatic variant
line 100: reference inserted wrongly: (respectively[10]-13)
line 104: diagnostic algorithms need to be complemented

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.
Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.
Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.
Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.
I am able to assess the statistics
Quality of written English
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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