Peer Review File

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Reviewer A

Comment 1: In table 3, please remove blood and saliva assay from Tempus given this table displays various vendors providing tissue based genomic profiling and not including liquid biopsy.

Response 1: The Tempus HRD assay is primarily a tissue-based assay. The company required blood or saliva specimens to obtain normal cells (peripheral blood mononuclear cells or buccal mucosal cells) to perform germline testing. This is not a liquid biopsy/ctDNA assay. Because germline results are integral to this assay, we believe that this should not be removed from the table.

Comment 2: Please elaborate more on the trial results in table 4 and any potential implication for future trial design and biomarker study.

Response 2: An additional section has been added prior to the conclusion titled "Implications for Future Trial Design and Biomarker Discovery".
Changes in the text: see Page 12, line 233 to 246.

Comment 3: Please include a section to discuss trials in progress.

Response 3: Table 5 was added to address trials in progress.
Changes in the text: see Page 11-12, line 232 to 238.

Reviewer B

Comment 1: Including a section on limitations: Adding a dedicated section on limitations would help provide a more nuanced understanding of the study's scope and implications. The authors could discuss the limitations of the search strategy, data extraction, and statistical approaches used in the study.

Response 1: An additional section has been added to discuss the limitations.
Changes in the text: see Page 12, line 248 to 260.

Comment 2: Providing more detail on data extraction: To ensure accuracy in data extraction, the authors could provide more information on how discrepancies in data extraction were resolved. This would help readers evaluate the reliability of the data.

Response 2: Since this is a narrative literature review instead of a systematic analysis or a meta-analysis. The data extraction from different studies were more descriptive rather

than analytical. No major discrepancies in data extraction were noticed or needed to be resolved. We clarified further in the methodology section.
Changes in the text: see Page 4, line 71 to 72.

Comment 3: Providing more detail on study design: Providing more information on the study design, such as whether it was a randomized controlled trial, cohort study, or case-control study, would help readers better understand the context of the findings.

Response 3: The data abstracted included some laboratory studies, translational studies, retrospective translational studies and some clinical trials. Due to the heterogeneity of the data collected, no one method was used to summarize the data and the results are mostly descriptive to bring together common themes from these distinct types of studies.

Comment 4. Additionally, providing more detail on the inclusion and exclusion criteria used in the study would help readers evaluate the generalizability of the findings.

Response 4: Additional inclusion and exclusion criteria information added. Issues regarding selection of patients are also discussed further in the new Limitation section to help readers evaluate the generalizability of the findings.
Changes in the text: see Page 4, line 65 to 66 and Page 12, line 248 to 254.

Reviewer C

Comment 1: Nice review highlighting HRD and possible avenues of therapy for pancreatic adenocarcinoma.

Response 1: Thank you!

Reviewer D

Comment 1: I would like to congratulate the authors on the present review. It has offered a clinical point of view on a topic that remains little debated like the homologous recombination deficiency. If the BRCA mutations and their implications are known, everything about the HRD signature remains to be discovered. Tan and Hosein have summarized the diagnostic techniques esplorating HRD, and they have investigated potential biomakers even those less known in clinical practice (such as HRD score).

Response 1: Thank you!

Reviewer E

Comment 1: The authors describe “canonical mutations” in double strand DNA repair genes (p3, line 69). This term is not clear. Authors should distinguish pathogenic vs variant of unknown significance (VUS) and benign for BRCA and related genes.

Response 1: Thank you for pointing this out. All the mutations that we referenced in this review focused on pathogenic variants only. We substituted the “canonical” to “core” and emphasized the pathogenic variants in the modified manuscript. Core HRD mutations usually mean BRCA1 and BRCA2.
Changes in the text: see Page 4, line 74.

Comment 2: There is no distinction or discussion of whether mutations and genomic lesions in BRCA1 and BRCA2 may differ in their translational significance. Given reference #37 that specifies somatic BRCA2 and germline PALB2 carriers responded to PARP inhibitions compared to germ line and somatic BRCA1 cases, this should be addressed in the review. Is there a difference based on individual genes or does the difference reflect the nature of the mutations (e.g., pathogenic vs VUS, homozygous vs heterozygous) or some other clinical feature of the cases described in the manuscript?

Response 2: Thank you for the recommendation. Additional reference and explanation have been added to clarify the potential differences in behavior of BRCA1 versus BRCA2
Changes in the text: see Page 5-6, line 109 to 116.

Comment 3a: In Tables 1 and 2 The authors cite results from commercial platforms that associate increase mutational burden with BRCA loss. It is not clear how or why loss of homologous recombination would promote higher mutation burdens. Do these include single nucleotide variants or other classes of mutations?
Response 3a: BRCA1 and BRCA2 encode proteins that play a central role in the process of homologous recombination (HR) DNA repair. This DNA repair system is important in maintaining genomic stability. It therefore follows the defects in this pathway, which impairs the tumor cell’s inability to maintain DNA health, resulting in increased genomic instability. This phenomenon was very nicely characterized in the Sokol et al paper (reference 13) and summarized in the section “Frequency and Implications of HRD”.

Comment 3b: Do they discriminate BRCA1 and BRCA2 mutations and include only pathogenic variants in their analysis? This needs to be clarified.
Response 3b: Note that this manuscript only considers pathogenic variants as being influential. Variants of uncertain significance were not included. This has now been clarified in the Methods section.
Changes in the text: see Page 4, line 65 to 66.

Comment 3c: HRD genomes have increased numbers of copy number aberrations (CNAs). However, the role of CNAs in HRD positive pancreas cancer is not discussed. Is there a difference in the extent of HRD driven scars in pancreas compared to other cancer including breast and ovarian?

Response 3c: It is true that CNAs are increased in HRD-positive tumors. However CNAs are not clinically relevant biomarkers (unlike TMB and gLOH). This is why CNAs were not specifically addressed in this article.

Comment 3d: Can the authors predict if the same score to distinguish HRD based on genomic scars will distinguish HRD cases across tumor types?

Response 3d: The Sokol et al paper (reference 13) mentioned above was a pan-cancer analysis that showed similar trends in different tumor types, but the overall finding was the same across the board, i.e. biallelic BRCA1/2 alteration was associated with increased gLOH versus monoallelic or wild-type BRCA1/2; predicted germline or somatic mutations were both associated with elevated gLOH. Additional information was added to the manuscript to clarify this.

Changes in the text: see Page 5, line 98 to 99.