Peer Review File

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Reviewer A

The authors have performed a systematic review on the role of ctDNA for the detection of MRD in resected NSCLC. This is a very important and "hot" topic.
The paper is well written, the methodology used is clearly described, and the conclusions are adequately discussed.
Reply: we are grateful to the reviewer for these positive comments.

Several modifications would improve this review:

Comment 1: *The concordance rates reported ranged between 6% and 45%. Is this related to the NGS strategy used (standard approach or personalized approach by first testing the tumors)?*
Reply: Thank you for this comment. The concordance rates were calculated independently from NGS strategy used in different studies. According to this suggestion, the percentages according to NGS approach were verified. Considering the absence of difference between the concordance according to different NGS approach, we did not perform any change in the revised version.

Comment 2: *It would be nice to indicate which strategy (standard or personalized) was used in Table 1 or 2.*
Reply: Thanks for the suggestion, we added the "NGS strategy" (standard or personalized) information in the Table 2.
Changes in the text: Table 2.

Comment 3: The clinical trials gathered in Table 3 are not all interventional studies. It would be interesting to separate observational and interventional studies.
Reply: Thanks for the suggestion, we specified the study type: 1 = interventional; 2 = observational in the Table 3.
Changes in the text: Table 3.

Comment 4: *During last ASCO were reported the results of the Dynamic trial (colorectal cancer), and their publication in the NEJM (PMID: 35657320). This is a great demonstration of the potential use of ctDNA in MRD. It would be nice to quote this important trial in the discussion.*
Reply: Thanks for the suggestion, we added this important trial in the discussion of the paper.
Changes in the text: Page 11, lines 261-263.

Reviewer B

Comment 1: *the introduction gives great example of the (minimal) success of adjuvant therapies, however, several measurements are used (absolute DFS and HR). Could the authors provide similar measurements for all these different treatments for ease of comparison? Especially as the 5-6% of absolute benefit in 5 years is something that few people seem to realize.*
Reply: We are grateful to the reviewer for this useful suggestion.
Changes in the text: We modified the text according to the suggestion, reporting HR for DFS for each adjuvant treatment described. Page 3, lines 65-68.

Comment 2: *reporting according to the PRISMA.*
Reply 2: We are grateful to the reviewer for the comment.

Changes in the text: We modified Figure 2, according to PRISMA.

Comment 3: *missing a quality assessment of the studies.*
Reply: We used the Newcastle–Ottawa Scale to assess the quality of the articles.
Changes in the text: We modified the text according to this suggestion. Page 6, lines 131-134 and Page 7, lines 168-169. Therefore, we added a supplementary table for assessing the quality of the included studies.

Comment 4: *Was any data missing? Were these requested from the original authors?*
Reply: We are grateful to the reviewer for the question. Only reported data was analyzed and no further data was required to the authors. Therefore, we did not perform any change in the revised version about this comment.

Comment 5: *sensitivity analyses (stratified for kind of treatment for example) could harmonize the populations somewhat, and be used to further support the hypothesis that ctDNA can be linked to recurrence.*
Reply: We are grateful to the reviewer for this comment. We did not perform a sensitivity analysis due to heterogeneity of included studies. In fact, available data from the studies did not allow us to carry out a sensitivity analysis.

Comment 6: *missing an image showing the compounded results.*
Reply: for the same reason described above, a meta-analytic synthesis of the data was not possible and therefore we did not report a relative image.

Some small English changes. Some small adjustments for the paper itself. Missing quality assessment for a good systematic review.
Reply: English has been checked throughout the manuscript.

Reviewer C

Comment 1: Interesting topic with little structuring of the studies and a lot of heterogeneity in the studies shown in the review.
Reply: We are grateful to the reviewer for these positive comments.

Post-revision Review Comments

The authors have corrected their manuscript according to the reviewer comments.
However, the reviewers think there are a number of mistakes in Table 2. As the authors indicate in their manuscript (lanes 245-247), in the personalized approach, the patient's tumor is sequenced and the probes are designed to detect these variants in the patient's plasma.
In this table, the only study using such a personalized approach is Abbosh et al 2017 (ref 29).
Chen et al 2019 (31) analyzed the most commonly mutated oncogenic genes.
Ohara et al 2020 (33) used a deep sequencing approach (CAPP-Seq) technique, which can detect mutations in 197 genes.
Xia et al 2022 (not 2021, ref 38) used the same 769 gene panel for all samples. It was the analysis of the data generated that was based on a tumor-informed strategy.

Reply: Thanks for the observation. We double-checked the studies and agreed with the correction

proposed by the reviewer.
Changes in the text: We made the correction in table 2.