Lian-Sheng Ma
Science Editor, Company Editor-in-Chief, Editorial Office
Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: l.s.ma@wjgnet.com

**"Cell-free DNA liquid biopsy for early detection of gastrointestinal cancers: a systematic review" (Manuscript NO.: 65222, Systematic Reviews)**

Dear Mrs, MA, dear reviewers,

We would like to thank you for taking the time to read our manuscript, and for all the comments you have made.

Please find below our point-by-point answers.

**Reviewer #1**

I was glad to review this narrative systematic review, partially conducted in line with PRISMA checklist. The topic is interesting and appealing. English language would probably require some further minor polish. As for literature search method, the Authors only screened PUBMED database. It is advisable to screen more than one database when conducting a systematic review (i.e. EMBASE, Scopus). I wonder if the Authors decided to proceed as they did according to a specific motivation.

*We agree with you that including various databases in the search strategy is a relevant point, since it can provide more occurrences and improve the quality of the search. However, especially in the case of experimental studies as reported in our paper, some databases were for us less crucial. For instance, the Cochrane Library if more useful for systematic review covering clinical topics, since it offers more an evidence-based database than a bibliographic one* [1]*.*
*We searched EMBASE using an equivalent search strategy to the one in PUBMED ('liquid biopsy'/exp OR 'liquid biopsy' OR 'cell free DNA' OR 'circulating free DNA') AND ('early cancer' OR 'digestive system cancer') AND ('screening' OR 'diagnosis' OR 'detection') AND ('blood' OR 'plasma'). A total of 509 studies were identified, of which 5 duplicates were removed. Of the 504 studies remaining, 476 were removed after title and abstract screening, and 24 were further excluded after full text reading. Ultimately, 4 studies were suitable for inclusion, which had already been identified in our MEDLINE search.*
*Even though the search was limited to MEDLINE, we believe that our systematic review offers a report of the latest data in the field, providing for the clinician information about the current applications of this technology for the detection and screening of gastro-intestinal cancer.*

A very important part of the PRISMA checklist is reporting results: in the present systematic review there is not any assessment of risk of bias for each studied included in the analysis (i.e. item #18, item #21). The Authors should implement this part.

*Thank you for this relevant observation. According to your comment, we evaluated the risk of biais of each study using the ROBINS-I tool ("Risk Of Bias In Non-randomised Studies - of Interventions"). We added a paragraph describing this in the results section.*

As for reporting results, the Authors could have performed a pooled-analysis – when possible, in accordance to outcome measures, data availability and samples homogeneity – in order to obtain a unitary outcome indicator instead of describing, in a narrative-review fashion, other studies results independently (i.e. colorectal cancer). I think that a pooled/meta-analysis of presented results would add further value and novelty to the manuscript.

*Thank you for underlining this point. A meta-analysis could indeed improve the quality of the review. However, the population, methodology and reporting of results of included papers are too heterogeneous to clearly define outcomes for a meta-analysis.*

We would like to thank you again for giving us the opportunity to improve our manuscript and submit a revised version to your consideration.

We remain at your disposal for any further questions,
Best regards,

On behalf of the co-authors,

Ms Isabelle Uhe

References

1. Systematic Reviews - ITM. Accessed June 28, 2021. http://lib.itg.be/literature/writing/reviews.php