

Cover Letter in Response to Reviewer's Comments to *The World Journal of Gastroenterology*

Re manuscript number 02441109 entitled 'Biomarkers in the Diagnosis of Pancreatic Cancer – Are we closer to finding the golden ticket?'

The authors would like to firstly thank you for the time taken to review the submitted manuscript and the comments made. Please find below a point-by-point response to questions in **blue type presented by the reviewers** (reviewer's comments in italics).

This work by O'Neill et al. aims at providing a comprehensive review of biomarkers for Pancreatic Cancer. The Manuscript is generally well-written and basically summarizes a plethora of candidates having been or being scientifically evaluated. Partly the manuscript is hard to read, especially in the first part where blood/serum protein biomarkers are merely listed one after another without any conceivable order. I have a couple of comments and issues which I suggest to address before consideration for publication: Core Tip Section: I would tone down the wording "Ca19-9 is not recommended..." since this could generate misunderstandings. As the authors state elsewhere Ca19-9 is widely used, its strengths and limitations should briefly appear in the core tip section as well.

The authors thank the reviewer for the kind comments regarding the presented manuscript. In response to the reviewer's statements, the manuscript has been amended to reflect the recommendations in the core tip section where wording regarding CA19-9 has been changed.

Abstract: Consider to provide a more concrete outlook at the end of the abstract including the current state/most promising biomarker candidates (or panels)

A more concrete outlook has been provided at the end of the abstract which highlights the current promise associated with miRNA panels and circulating tumour cells in the detection of PC.

Table 1: add the references as in the other tables – for consistency. Think about grouping protein biomarkers according to type/family/function, e.g. growth factors, cyto-/chemokines, glycolipids/-proteins, adhesion molecules,...etc. this would really help to and give a sense of order and overview.

The manuscript has been amended to have the references included in Table 1. Additionally, the protein biomarkers in serum have been amended to be separated into subgroups. The authors thank the reviewer for the suggestion.

Blood/Serum protein biomarkers: as mentioned for Table 1 – I would strongly suggest to somehow group the markers with subheadings to make the reading experience more smooth

The manuscript has been amended to reflect the changes in the text order with a change in the structure of table 1. Serum proteins biomarkers have now been ordered into multiple categories. It is such a complex topic with over 300 markers reviewed so it was not easy to present them in

References: the number of refs provided is huge. I think a good number of them are not strictly necessary – in the case where more than one or two are used to cite previous work. But of course this should be handled according to the editors' assessment and the journals policy.

The authors have not changed the number of references included as they believe this is reflective of the number of biomarkers included in the review and the work we did on reviewing them. Future researchers can use our paper to research markers hence appropriate and detailed references are important . If however there are changes suggested by the editors, the authors will make the appropriate changes.

Conclusions section: I am missing a part that gives an outlook (as I mentioned for the abstract section above), informing about and summarizing the most promising biomarker candidates based on the collated list in the provided work. Further, a point should be made, that very likely a biomarker PANEL will be necessary to achieve strong sens. and spec. relations. And again, calling Ca19-9 "inappropriate" is sounding too shallow and should be reworded (e.g. "limited") making it's strengths and shortcomings more clear.

The conclusion has been amended reflect the comments made by the reviewer. Comments regarding CA19-9 have been rectified as per the reviewer's suggestions.

Further, I have a number of additional comments and found many typo, syntax, and vocab issues which all are highlighted by the track change function in the attached file-copy. Those should be addressed.

The authors thank the reviewer for this and have made the appropriate changes.

We hope that you find the submitted manuscript acceptable for publication. Thank you once again for your consideration.

Yours sincerely,

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