

29 October 2019

Dear Sirs,

Thank you very much for your message communicating the outcome of the editorial review of my manuscript No 51399 entitled **"Biomarkers for detecting colorectal cancer non-invasively: DNA, RNA or proteins?"**.

Having carefully examined comments of the five reviewers, I have substantially revised the manuscript, taking into account reviewers' recommendations.

The order of reviewers was changed a few times during the editorial process, so I am going to follow the order used in the Peer-Review Report from the website of the journal.

I would now like to address specific comments of the reviewers:

Reviewer 1:

This reviewer assessed the manuscript positively and has not presented any critical comments.

Reviewer 2:

(1) "Early detection" of colorectal cancer is certainly one of the topics this paper addresses (alongside colorectal cancer screening). This theme was present in the original text, but it is further enhanced in the revision.

(2) Although method non-invasiveness and cost-efficiency are, indeed, highlighted as the key criteria defining the applicability of discussed approaches to CRC screening, other features of the compared methods are considered as well. Examples of disadvantages mentioned in the text include excessive technical complexity, inconveniences related to sample collection and preparation, needs for expensive equipment, lengthy sequences of laboratory steps etc.

(3) Re-arranging tables according to sensitivity/specificity values would be difficult since sensitivity/specificity combinations used by different authors are often arbitrary (some authors report higher sensitivities at the expense of specificities and *vice versa*). Moreover, biomarker panels are placed in the tables after single biomarkers, and this order would have to be altered if reviewer's suggestion is accepted. I would also like to clarify that the figure was prepared by myself, so there is no question about getting any permission.

(4) I believe that there are no discrepancies between the abstract and the main text in the revised version of the paper.

Reviewer 3:

I agree with the reviewer that the manuscript might be too long for an editorial. In my original submission letter, I suggested that the Editors can choose to regard it either as an editorial or a review. I have not changed my opinion.

I do not entirely agree with the reviewer regarding the required changes in the abstract since my personal opinion is that FIT combined with colonoscopy is the best existing option for colorectal cancer screening. The reviewer seems to regard Cologuard as an equally valid test (it may be popular in the USA), but I believe that this test is prohibitively expensive. Nevertheless, both Cologuard and EpiProColon are mentioned in the revised version of the Abstract.

I agree with the reviewer that the provided tables may be too large, but abundant information presented in them may be useful for readers with specific interest in some areas.

The recommendation to polish the language of the paper is accepted, and I sincerely hope that presentation style has been improved in the revision. Several typing errors were removed as well

Reviewer 4:

This reviewer assessed the manuscript positively and has not presented any critical comments.

Reviewer 5:

The only critical point of this reviewer is his invitation to express my own opinion regarding CRC screening. I have extended the concluding section of the manuscript and hope that my view can now be seen more clearly.

I believe that the revised version of the manuscript reflects my answers presented above.

In addition, I carefully followed editorial recommendations regarding manuscript format and preparation of additional materials (provision of Audio core tip and my only illustration in the original PowerPoint format).

I have also scrutinized reference list and made a few corrections. Specifically, I have added previously missing PMID & DOI information to reference 58 and modified references 39, 43, 70 & 121 (previously marked "in press" and now published). I have also checked reference 12, but it is still "in press".

All my changes are highlighted in yellow in the revised version of the manuscript.

I hope that the revised version of the manuscript will be found suitable for publication.

Yours sincerely,

Dr Alexandre Loktionov