

Comments by Expert Reviewer 1

Comment 1 : My only suggestions for improvement would be to include more detail on the sensitivity/specificity of each of the molecular diagnostic tests discussed, and to consider inclusion of a table to summarize the markers discussed, with a comment on the quality of evidence currently available.

Response : We are grateful to the expert reviewer's comments and we agree to the comments on this point. We have added a table that summarized the sensitivity and specificity of the detection of the discussed biomarkers in detecting carcinoma and adenoma. (Table 2, page 38)

Comments by Expert Reviewer 2

Comment 1 : It is not sure whether the same markers can be used to detect adenomas and cancers, and even if it can detect neoplasia in different sites in the colon, please discuss.

Response : We are grateful to the expert reviewer's comments and we agree to the comments on this point. We have added a table that summarized the sensitivity and specificity of the detection of the discussed biomarkers in detecting carcinoma and adenoma. (Table 2, page 38)

Comment 2 : TP53 is mentioned as a marker but with no relation to CRC, and I doubt anyone would suggest this to be a good and specific marker for colon cancer. Please discuss or remove as you see fit.

Response : We have removed this part from the text.

Comment 3 : Please discuss the current evidence for detecting adenomas/cancers by various fecal tests, be it occult blood or occult genes. What are the evidence, the costs and the current sensitivity/specificity for such testing?

Response : This information is summarized in a newly added table 2 on page 38.

Comment 4 : The section on methods used for molecular testing is good. What about immunohistochemistry for MSI testing/screening? Any role compared to the mentioned PCR methods? Please discuss.

Response : This information is added on Page 13, line 10 to line 19.

Comment 5 : I would suggest to address the features and role of hereditary syndromes (HNPCC, FAP) in a separate paragraph, and then discuss CRC on the basis of sporadic cases if that is your intention. Some aspects of hereditary clinical and molecular features may not apply to the sporadic, symptomatic screening setting, so this needs to be highlighted.

Response : This information is added on Page 10, line 7 to line 17.

Comment 6 : Maybe include a few words on the "rules and roles" of developing novel biomarkers - what about testing, validating etc the biomarker panels, any suggested guidelines that should be followed etc?

Response : This information is added on Page 17, line 15 to Page 18, line 2.

Comment 7 : Figures 1 and 2 is overly simplified and should better be combined to demonstrate the true complexity of CRC development and different classifications.

Response : We address the reviewer's queries as follows: We agree to the expert reviewer's comments on this point but we intended to keep them. As for figure 1, we intended to make the sequence simple and stick to the markers discussed in the text. In order to avoid misunderstanding of the true complexity of CRC development, we have added comments in the figure legends to remind the readers that this is a simplified presentation of CRC tumourigenesis. The true carcinogenesis progress of CRC is much more complicated.

Comment 8 : p. 7: a typo for MSI (is written MIS) p. 7 and ff: greek letters (beta, alpha etc) are marked as squares in the document, may be due to the typesetting, please correct.

Response : We have corrected the typo.

Comments by Expert Reviewer 3

Comment 1 : The authors seem to focus on methodological principles rather than clinical implication. They should explain the clinical benefits for the field of action. This must be revised.

Response : We are grateful to the expert reviewer's comments. This information is added on Page 10, line 18 to Page 11, line 8.

Comment 2 : While the authors discuss about clinical biomarkers such as CEA in the “Summary” section, they didn’t show any comments on it in the text. The summary is completely different to the contents of body text. They should properly address the status quo of clinical biomarkers in the text.

Response : This information is added on Page 10, line 18 to Page 11, line 8.

Comment 3 : As the review for diagnostic and prognostic markers are mixed in the text, readers will be confused. The authors should rewrite the text to make it clear.

Response : We address the reviewer’s queries as follows: The diagnostic and prognostic applications of each molecular marker are clearly mentioned in their respective paragraphs.

Comment 4 : Molecular Basis of Colorectal Cancer: 2nd sentence: Adenoma-carcinoma sequence was advocated by Dr Vogelstein’s team in Cell, 1990. Please correct the reference.

Response : We have corrected the reference.

Comment 5 : RAS family: Recent clinical trials have started to focus HRAS and BRAF as well as KRAS. Please address the state-of –the-art topics about these genes.

Response : This information is added on Page 12, line 5 to line 16.

Comment 6 : Figure Legends: At least, Figures 2 and 5 are not original, as far as I can confirm. The authors should note the original references in the legends.

Response : We address the reviewer’s queries as follows: We have replaced them with new figures.

Comment 7 : Itemization is treated roughly. For example, “Methods of miRNA Detection”, “Quantitative Reverse Transcription PCR”, “Microarray”, and “Lateral Flow Nucleic Acid Assay” should belong to “MicroRNA Markers” section in pp.14. Itemization should be carefully performed

Response : We address the reviewer’s queries as follows: This problem relates to the formatting of the text and we have made adjustment in itemization.

Comments by Expert Reviewer 4

Comment 1 : This is a timely review on colorectal cancer biomarkers. I congratulate the authors

Response : We thank the reviewer for his / her kind comment.

Comments by Expert Reviewer 5

Comment 1 : It is a very interesting topic for clinicians, oncologist, surgeons and gastroenterologist. It is very well written and should be published in WJG.

Response : We thank the reviewer for his / her kind comment.

Comments by Editor

Response : We have made adjustments in the formatting according to editor's comments.

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