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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 86466

Title: Diagnostic value of methylated branched chain amino acid transaminase 1/IKAROS family zinc finger 1 in plasma for colorectal cancer

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 01550341
Position: Peer Reviewer
Academic degree: MD, PhD
Professional title: Chairman, Full Professor
Reviewer's Country/Territory: Belgium
Author's Country/Territory: China

Manuscript submission date: 2023-06-20
Reviewer chosen by: Geng-Long Liu
Reviewer accepted review: 2023-08-08 10:44
Reviewer performed review: 2023-08-17 12:10
Review time: 9 Days and 1 Hour

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

There is quite some literature about using methylated BCAT1/IKZF1 as diagnostic marker in colorectal cancer, therefore this meta-analysis is of interest to the field. I do have some remarks/suggestions before this manuscript could be suited for publication:

- The conclusion might be somewhat overstated as a general sensitivity of 60% is still low for clinical use, especially since diagnostic sensitivity seems to decrease substantially in the early stages of CRC, as has been shown with other methylation markers as well. It is not clear whether all 6561 patients were included in the analysis of sensitivity at the different stages and what the clinical implication of this finding would be as early diagnosis seems not to be that effective. An additional paragraph about CRC stages could be added in the discussion. - This manuscript is written in a very statistical manner. Additional biological information in the introduction would welcome. For example o why did you choose to perform this meta-analysis specific on methylation of BCAT1/IKZF1, as there are a multitude of other markers available. o you mention that this has advantages over SEPT9, while a similar sensitivity. What is the proven sensitivity of SEPT9, as you state in the discussion that it is less sensitive then other

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current tests. o Does mutational status of tumors have an influence on methylation of BCAT1/IKZF1? o It is not clear for an unexperienced reader that you look into ctDNA o Could there be anything done in the future to increase the sensitivity of this test? o … - The meaning of some sentences is not clear/Minor mistakes. o First sentence of paragraph 3.5 o Paragraph 2.4: "if there is any significance, …" I suppose significance is not the correct term here. o 7th sentence discussion. Sensitivity is written with a capital. o Discussion: "Another one new method" is not a correct sentence -Quality of figure 3 and 4 needs to be improved. It currently is impossible to read and therefore could not be assessed.

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Reviewer's code: 02551692
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Chief Doctor, Director, Surgeon, Surgical Oncologist
Reviewer's Country/Territory: Italy
Author's Country/Territory: China

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Reviewer chosen by: Geng-Long Liu

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Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

1 / 1 ASSESSING THE DIAGNOSTIC VALUE OF METHYLATED BCAT1 AND IKZF1 IN PLASMA FOR COLORECTAL CANCER: A META-ANALYSIS The aim of this meta-analysis was to analyze and evaluate the diagnostic accuracy of DNA methylation markers, in particular BCAT1/IKZF1, in plasma for screening and postoperative follow-up of colorectal cancer (CRC). Colorectal cancer (CRC) is the most common malignancy and it's third for his percentage of death and recurrence; even in patients who have recived radical treatment the recurrence in about 25-40%. Due to this scenario the necessity of early diagnosis and treatment are the main content of secondary cancer prevention. Both the initial diagnosis and the diagnosis of relapse after radical treatment have a significant impact on the overall survival of patients. At present, although the diagnostic accuracy of CRC has greatly improved through the wide application of CEA testing, colonoscopy, and imaging examination, it's still necessary to explore more safe, convenient, economical, and accurate diagnostic methods. In order to that, in recent years liquid biopsy technology's value has increased rapidly in disease diagnosis and treatment. This method is becoming an important pathway to follow because of the

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process of tumor development, to its aggressiveness and the biological phenomenon of cell necrosis and apoptosis with the production of circulating tumor DNA (ctDNA). This latter, infact, may enter the circulation in the early stage of the disease, suggesting that tumor markers based on ctDNA may play an important role in the early diagnosis of tumors. Among the DNA methylation markers, this meta-analysis chose to explore the value of BCAT1/IKZF1 for CRC. To do so twelve eligible studies were included with a search period from May 31, 2003 to June 1, 2023 for a total of 6561 partecipants. This study is very important for the improvement of the screening and post-treatment follow-up methods for CRC. It shows that methylated BCAT1/IKZF1 in plasma had a sensitivity of 64% (95%CI 59-69) and a specificity of 92% (95%CI 91-93) for CRC screening and a sensitivity of 54% (95%CI 42-67), and a specificity of 93% (95%CI 88-96) for CRC postoperative follow-up. Moreover, for his use as diagnostic value, some reports suggest that changes of methylated BCAT1/IKZF1 in plasma occur before imaging changes and, for the follow-up, researchers have found that methylated BCAT1/IKZF1 in plasma may also be valuable in the prognostic prediction of CRC, suggesting that methylated BCAT1/IKZF1 in plasma may be more likely to be found in patients with postoperative incisal margin deficiency, lymph node invasion or distant metastasis. In the end the role of this meta-analysis allows to make the difference in the diagnosis research field for CRC, showing how the detection of methylated BCAT1/IKZF1 in plasma, as a non-invasive detection method of circulating tumor DNA, has good diagnostic and prognostic accuracy, and is safe, convenient, fast, and economical, which is easy to be popularized. There were some limitations in this meta-analysis: the studies included were all conducted in Australia or the United States so the capability of methylated BCAT1/IKZF1 testing to diagnose CRC in other ethnic groups and regions needs to be further investigated. In addition, not all the studies clearly record the diagnostic sensitivity for patients with different stages. Neverthless,

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the value of this study is still high and define the necessity to continue the research in this field.

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Reviewer's code: 05345731
Position: Peer Reviewer
Academic degree: BSc, MD, MSc
Professional title: Doctor
Reviewer's Country/Territory: Kazakhstan
Author's Country/Territory: China

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Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
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	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The wide confidence intervals for sensitivity and specificity raise questions about the precision of the estimates. The authors should discuss the potential sources of heterogeneity among the included studies and consider conducting subgroup analyses to explore the reasons behind the variability. The conclusion states that the detection of methylated BCAT1/IKZF1 in plasma is "safe, convenient, fast, and economical." However, no evidence or rationale is provided to support this claim. The authors should either present relevant literature supporting their statement or modify the conclusion accordingly. The discussion of the results could be improved by comparing the findings of this study with other existing biomarkers for CRC screening and follow-up. This would provide a broader context for the significance of methylated BCAT1/IKZF1 in the field of CRC diagnosis. Overall, the article presents important findings on the diagnostic accuracy of methylated BCAT1/IKZF1 in CRC. However, addressing the mentioned concerns and incorporating the suggested improvements would further strengthen the validity and impact of the study. I recommend acceptance of the article pending the revisions mentioned above. The study has the potential to contribute significantly to the

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field of CRC diagnosis and would be of great interest to the readership of the journal. The authors conducted a systematic review of twelve eligible studies, involving a total of 6561 participants, to analyze the sensitivity, specificity, and diagnostic test accuracy of methylated BCAT1/IKZF1. The data analysis presented in the abstract indicates that the sensitivity of methylated BCAT1/IKZF1 for diagnosing CRC is 60%, with a specificity of 92%. The diagnostic odds ratio of 19 and area under the curve of 0.88 suggest good diagnostic accuracy for CRC detection. The study provides valuable insights into the potential of methylated BCAT1/IKZF1 as a biomarker for CRC diagnosis. The inclusion of multiple databases in the search strategy enhances the robustness of the results. The analysis of sensitivity and specificity for CRC screening and recurrence detection in the follow-up provides important information for clinical application.