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Dear Editor Yan,

Thank you very much for reviewing our manuscript and pointing out a few questions. We also thank the reviewers for their suggestions on the manuscript. We have provided point to point answer to all reviewers, which are highlighted in green below. Besides, for several of the issues you pointed out, we reviewed and revised the manuscript. 1) we have checked the references section. There are no repeated references. We have completed all the PMID and DOI. 2) We have changed the abbreviation of the table title to a full spell word. We have also explained all the abbreviations of each table under each piece of table legends. 3) We will submit the certificate of the funding agency for the grant.

Thank you again, and I hope the revision is acceptable. I am looking forward to hearing from you soon.

Best wishes,

Lei Liu



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 47844

**Title:** Multiple “Omics” data based biomarker screening for HCC diagnosis

**Reviewer’s code:** 02944288

**Reviewer’s country:** Russia

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-04-10 09:31

**Reviewer performed review:** 2019-04-12 04:18

**Review time:** 1 Day and 18 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input checked="" type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer’s expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

### SPECIFIC COMMENTS TO AUTHORS

The manuscript does not contain conclusions and Conclusion section at all Dear authors. You have to write Conclusion section (see guidelines for manuscript preparation). Your conclusions are necessary to summarize your review and to answer scientific question. Plus there are many errors in the text.



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Thank you very much for your correction. We have added Conclusion section on page 15 of the manuscript. We have corrected some error on page 2, 4, 6.

#### INITIAL REVIEW OF THE MANUSCRIPT

##### *Google Search:*

- The same title
- Duplicate publication
- Plagiarism
- No

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- No



**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 47844

**Title:** Multiple “Omics” data based biomarker screening for HCC diagnosis

**Reviewer’s code:** 01806467

**Reviewer’s country:** South Korea

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-04-11 05:20

**Reviewer performed review:** 2019-04-14 13:41

**Review time:** 3 Days and 8 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer’s expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

I read your article with a great interest. This is a narrative review article which reviews biomarker screening for HCC diagnosis based on multiple “Omics” data. The authors divided the category into circulating tumor cells, exosomes, circulating tumor DNA, serum RNAs, metabolomics, and protein and summarized well about recent progress in



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devising biomarker for early stage HCC. While this is a well-organized narrative review, it leaves some issues that remain to be addressed. 1) Disruption of gut homeostasis and microbiome has been associated with different human diseases including HCC. Recent studies suggest that the development of HCC may be associated with the imbalance of the gut microflora. Thus, the authors are recommended to add recent studies of microbiome and metagenomics as an axis of multiple “Omics” related to HCC in the manuscript. 2) The authors divided and presented the related topics into the following categories: circulating tumor cells, exosomes, circulating tumor DNA, serum RNAs, metabolomics, and protein. I recommend to the authors to summarize recent phase 2 or 3 clinical trials regarding biomarkers for HCC diagnosis, if any, and present in the main text. In addition, it would be better if the related clinical trials are summarized and presented in a new table. 3) The most critical point is that there is a lack of content for each part and it is not sure whether all the important studies are presented or not.

Thank you for your suggestions. 1) 2) We have added the content of “INTESTINAL MICROORGANISMS” (see page 13 of the manuscript) and “BIOMARKS ENTERING CLINICAL TRIALS” (see page 14 of the manuscript). 3) Besides, we have added some content for some part (see “EXOSOMES” section on page 7 of the manuscript; see “PROTEIN” section on page 12 of the manuscript). We think we have shown all the important studies that were searched by us.

#### INITIAL REVIEW OF THE MANUSCRIPT

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## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 47844

**Title:** Multiple “Omics” data based biomarker screening for HCC diagnosis

**Reviewer’s code:** 02936306

**Reviewer’s country:** South Korea

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-04-11 14:02

**Reviewer performed review:** 2019-04-15 05:07

**Review time:** 3 Days and 15 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input checked="" type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer’s expertise on the
<input checked="" type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input checked="" type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input checked="" type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

### SPECIFIC COMMENTS TO AUTHORS

Dear Editor, I found a mistake in the uploaded file of the main manuscript. I sent this error to the Journal company, but did not receive any response. I hope you check the problem. Please, let the author re-upload the main manuscript.



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Thank you for finding a mistake. But we are sorry that we don't know what mistake is, so we don't know how to modify it.

#### INITIAL REVIEW OF THE MANUSCRIPT

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- Plagiarism
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**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 47844

**Title:** Multiple “Omics” data based biomarker screening for HCC diagnosis

**Reviewer’s code:** 02998194

**Reviewer’s country:** Greece

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-04-11 08:42

**Reviewer performed review:** 2019-04-16 12:34

**Review time:** 5 Days and 3 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input checked="" type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer’s expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

It is well-structured and comprehensive review about future biomarkers in HCC early diagnosis

Thank you so much for your positive remarks.



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- Plagiarism
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**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 47844

**Title:** Multiple “Omics” data based biomarker screening for HCC diagnosis

**Reviewer’s code:** 03261241

**Reviewer’s country:** Japan

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-04-12 07:10

**Reviewer performed review:** 2019-04-18 01:10

**Review time:** 5 Days and 18 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer’s expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

The authors reviewed the various HCC biomarkers derived from “omics” data and discussed the advantages and disadvantages for the diagnosis of HCC. In this study, the authors focused on circulating tumor cells, exosomes, circulating tumor DNA, serum RNAs, metabolomics, and protein and summarized recent progress in devising



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biomarker for early stage HCC. The authors presented effective biomarkers/panels/models that have been identified and validated at different clinical levels. They concluded that although further improvements are necessary, a large proportion of the "omics" data have a good diagnostic performance especially for early HCC. In general, this is a well-written paper that presents interesting data. It will be of interest to readers of this journal.

Thank you so much for your positive remarks.

#### INITIAL REVIEW OF THE MANUSCRIPT

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- No



**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 47844

**Title:** Multiple “Omics” data based biomarker screening for HCC diagnosis

**Reviewer’s code:** 00183029

**Reviewer’s country:** Reviewer\_Country

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-04-10 07:10

**Reviewer performed review:** 2019-04-27 00:31

**Review time:** 16 Days and 17 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer’s expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

Overall, the manuscript is a diligent study which is comprehensive and thorough. However, the novelty is not high. Redundant and repetitive information including basic introduction of HCC such as risk factors and classical diagnostic methods could be simplified. Discussion section should be revised to be more informative and add more



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explanation of the implications of the result, for further research and clinical practice.

Thank you for your suggestions. We have removed some content about risk factors and classical methods in the “Introduction” section (see page 4) We have also retouched the “Discussion” section to make it more informative and meaningful.

#### INITIAL REVIEW OF THE MANUSCRIPT

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