PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Pathophysiology*

Manuscript NO: 64336

Title: Molecular and Genetic Markers in hepatocellular carcinoma; from Insilco analysis to clinical validation (current limitations and future promises)

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02992401

Position: Editor-in-Chief

Academic degree: PhD

Professional title: Professor

Reviewer's Country/Territory: China

Author's Country/Territory: Egypt

Manuscript submission date: 2021-03-21

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-03-23 03:13

Reviewer performed review: 2021-03-25 09:16

Review time: 2 Days and 6 Hours

Scientific quality	[　] Grade A: Excellent　[　] Grade B: Very good　[Y] Grade C: Good [　] Grade D: Fair　[　] Grade E: Do not publish
Language quality	[　] Grade A: Priority publishing　[　] Grade B: Minor language polishing [Y] Grade C: A great deal of language polishing　[　] Grade D: Rejection
Conclusion	[　] Accept (High priority)　[　] Accept (General priority) [　] Minor revision　[Y] Major revision　[　] Rejection
Re-review	[　] Yes　[Y] No

| **Peer-reviewer statements** | Peer-Review: [Y] Anonymous   [   ] Onymous |
| | Conflicts-of-Interest: [   ] Yes   [Y] No |

SPECIFIC COMMENTS TO AUTHORS

In this article, the authors presented a review regarding the discovering to clinical application of Molecular and Genetic Markers, which covered the areas from data mining to clinical validation of screened biomarkers. The authors also collected a large number of studies related to biomarkers including both coding and non-coding parts of human genome and point out the limitation of Insilco analysis and clinical validation and covered interesting topics such as Telomeres. However, this manuscript still needs to address following points before consideration of publication. 1. The structure of current manuscript is poorly organized, with different levels of titles mingling with each other, which make it difficult for readers to follow. Meanwhile, several parts of the manuscript lack proper description to help readers comprehend. For example, the part titled "Determining of the Genetic- epigenetic- phenotypic linkage through clinical studies" bring up Table 1 without giving an overall description of the topic, and further directly dive into "Autophagy" while other pathways such as "Proliferation" and "Cell growth and Angiogenesis" completely ignored. I understand that the authors want to focus on their own research area, however, a brief introduction of the larger picture will greatly ease the difficulty in reading and help deliver the points the authors desired. 2. When comes to specific subtopic, the manuscript lacked the necessary elaboration. While the article could still majorly focus one the authors' studies, research conducted by other groups in the same area is still needed to demonstrate the whole picture of the related field, which is the key point of a review article. Furthermore, in part "Important Qualities in Diagnostic and Prognostic Markers That Have To Be Met", the authors did not summary the important qualities of biomarkers. Meanwhile, the authors pointed out

the limitation of AFP and other biomarkers due to their unsatisfying sensitivity and specificity in this part, but when comes to the authors research, the authors also did not provide any detail regarding the performance of their biomarker, which make it very difficult for reader to understand the value of their studies. 3. The manuscript is titled as "Molecular and Genetic Markers in hepatocellular carcinoma; from Insilco analysis to clinical validation". However, the second part, i.e., clinical validation is much less discussed. A crucial part for a successful biomarker is clinical validation, during which different type of difficulty is presented. The authors should pay more focus to this part and fully discuss how clinical validation and Insilco analysis integrated. 4. I fully understand that the authors did not want to spoil their unpublished works, but in several part of the manuscript, the authors presented their work in process while still kept all the related information to themselves, which make some description meaningless and confusing. For example, when covering the autophagy pathway, the authors wrote: 'Also, we have another research completed, and on its way to being published linking another set of genetic, and epigenetic markers with autophagy through bioinformatics and confirmed by clinical validation.' Reading this did not help reader understand the importance of autophagy pathways nor deliver the significance of the to-be-published work.   Despite above problems, the writing of this manuscript still need great polishing, and the format of the manuscript also need further modification.

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Reviewer's code: 02929648

Position: Editorial Board

Academic degree: PhD

Professional title: Academic Research, Director

Reviewer's Country/Territory: China

Author's Country/Territory: Egypt

Manuscript submission date: 2021-03-21

Reviewer chosen by: Ya-Juan Ma

Reviewer accepted review: 2021-03-29 00:42

Reviewer performed review: 2021-03-29 00:49

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
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) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No

Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Good