**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.

Comment: Thanks for these kind recommendations. The structure is modified to a clearer format, and a small explanation is written in the "Background".

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.

Comment: Thank you for this important note. A brief introduction was added. Also parts explaining other molecular pathways as mentioned by the reviewer are added.

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.

Comment:  Many thanks to the reviewer's important comment. The author thinks that the qualities of the biomarkers were implied in the problems faced with AFP, but a paragraph was added to clarify this part.

Also, Sensitivity and specificity of the biomarkers are added from the author's work.
The summary of the important qualities for diagnostic and prognostic biomarkers is presented in figure 1, and to avoid repetition, they weren't mentioned in the text.

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.
Comment: Thank you for this valuable comment. This part is discussed in the respective subtitle, in addition to figure 2 to show the clinical validation and steps of integrating clinical and Insilco validation. An added introductory part is added, with restructuring of the manuscript to avoid repetition of explaining the existing biomarkers.

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.
Comment: Thanks. This sentence is removed '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'

Despite above problems, the writing of this manuscript still need great polishing, and the format of the manuscript also need further modification. ⌊SEP⌋
Comment: Thank you. The manuscript was revised for grammatical errors, syntax and flow.

**(1) Science editor:** 1 Scientific quality: The manuscript describes a frontier of the molecular and Genetic Markers in hepatocellular carcinoma. The topic is within the scope of the WJG.

(1) Classification: Grade C and Grade C;

(2) Summary of the Peer-Review Report: 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. However, the questions raised by the reviewer should be answered; and

(3) Format: There is 1 table and 5 figures.

(4) References: A total of 73 references are cited, including 26 references published in the last 3 years;

(5) Self-cited references: There are 3 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations that are closely related to the topic of the manuscript, and remove other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated; and

Comment: We thank the editor for this important note. As recommended by the editor; in this revised manuscript, all the work mentioned is related and didn't exceed the 10% limit; there were 6 self-cited references in a manuscript with ***81 references.*** The self-citation was intended to demonstrate the author's contribution to the topic in question (HCC biomarkers), as this is a "**Frontier Article**", but of curse if the reviewers or editors insist on removing any of the references due possible unsuitability to the topic, the author would immediately remove the references with the explanatory paragraphs or the work done in this area.

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2 Language evaluation: Classification: Grade C and Grade B. 3 Academic norms and rules: No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJG. 5 Issues raised:

(1) The language classification is Grade C. Please visit the following website for the professional English language editing companies we recommend: https://www.wjgnet.com/bpg/gerinfo/240;

Comment: The article was revised for native English and fluency.

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