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Title: Multiomics Biomarkers for the Prediction of Nonalcoholic Fatty Liver Disease Severity

We would like to thank the Editors and the reviewers for the insightful and constructive comments regarding our manuscript. The revised version has been clarified, and we the authors are very grateful for their helpful evaluation of our paper.

Reviewer 00199807:
Dear Editor, I reviewed the manuscript titled "Multiomics Biomarkers for the Prediction of Nonalcoholic Fatty Liver Disease Severity". I think this paper can be accepted in this current form. Sincerely yours.
Answer: Thank you very much for your kind comments.

Reviewer 01560058:
In this review article, the authors summarized novel findings obtained from various omics studies on the pathogenesis of nonalcoholic fatty liver disease (NAFLD). The Reviewer considers that this article allow readers to gain new insights into the molecular pathogenesis of NAFLD.
Answer: Thank you very much for your kind comments.

Reviewer 02942798:
Dear sir, thank you to select me for reviewing manuscript: Pirola JC, Sookoian S. Multiomics Biomarkers for the Prediction of Nonalcoholic Fatty Liver Disease Severity. Paper is well written. Only 2 technical changes are needed: 1) I can not open Figure 3 2) Please edit the references as recommended by World Journal of Gastroenterology. My final decision is acceptation for publication in World Journal of Gastroenterolotgy.
Answer: Thank you very much for your kind comments. We apologize the reviewers because the information in Figure 3 could not be entirely appreciated. We uploaded a more explicative version of Figure 3, which contains detailed information of the nodes we considered as important according to the content of the paper. In addition, we confirm that references are in the form that is required for publishing in WJG.

Reviewer 02861277:
In the manuscript, entitled "Multiomics Biomarkers for the Prediction of Nonalcoholic Fatty Liver Disease Severity" the authors provided an exhaustive overview concerning biomarkers and their integrative analysis in predicting NASH severity. In my opinion, they focused on a very promising clinical tool that in the era of personalized medicine might have a huge scientific relevance. Comments I think that it should be always kept in mind that NAFLD/NASH is an inflammatory disease involving both innate and adaptive immune responses and for these latter their interplay with the oxidative stress. Indeed some potential therapeutic options are directed against these pathogenetic mechanisms such as Vitamin E and Cenicriviroc (CVC) etc. Considering the relevance of these molecular targets, we cannot exclude in the near future to use additional biomarkers immunity-related such as circulating levels of cyto/chemokines, antibodies etc. in predicting NASH progression toward advanced phases. Taking into account these premises, I would suggest for a compelling analysis to give some hints (in the introduction

section) to the role of innate and adaptive immunity in NASH (see for instance: Therapeutic Inhibition of Inflammatory Monocyte Recruitment Reduces Steatohepatitis and Liver Fibrosis. Hepatology. 2017 Sep 21. doi: 10.1002/hep.29544 and Is there a role for adaptive immunity in nonalcoholic steatohepatitis? World J Hepatol. 2015 Jul 8; 7(13):1725-9.). I did not succeed to visualize the Figure 3

Answer: We sincerely appreciate the comments raised by the reviewer. We agree with the point that NAFLD/NASH is an inflammatory disease involving both innate and adaptive immune responses. According to the reviewer suggestion, we have included a paragraph and a new reference that both highlight this point. In addition, as explained above, we have edited Figure 3.

Reviewer 02942902:

The authors summarized the OMICS-based findings regarding NAFLD/NASH. I consider this paper is interesting and informative. Comments: 1) They mentioned that "Rigorous steps that must include validation and replication are mandatory before utilizing OMICs biomarkers in diagnostics to identify patients at risk of advanced disease, including liver cancer." I would like to know whether they consider that the risk of disease severity (fibrosis) was equal to that of HCC development. (Is it unnecessary to take into account some additional conditions in relation to the development of NASH-related HCC?) 2) Perhaps due to the capacity of my PC, I could not visualize the Figure 3. Kindly scale down the file size.

Answer: We appreciate the reviewer comment. Indeed, this review is not specifically focused on HCC; then, as the reviewer highlighted, the risk of HCC development must be specifically monitored by additional biomarkers that are out of the focus of this paper. In addition, as explained above, we have edited Figure 3.