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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 47672

Title: Biomarkers and subtypes of deranged lipid metabolism in non-alcoholic fatty liver disease

Reviewer's code: 02702057

Reviewer's country: Italy

Science editor: Ruo-Yu Ma

Reviewer accepted review: 2019-03-22 12:32

Reviewer performed review: 2019-03-22 14:50

Review time: 2 Hours

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[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High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

SPECIFIC COMMENTS TO AUTHORS

The manuscript entitled "Biomarkers and subtypes of non-alcoholic fatty liver disease" deals an important issue of medical liver diseases. Please improve the aim of this study in the abstract and in the introduction section to help better readers understanding.

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Please add the following recent and interesting references to improve the NONALCOHOLIC FATTY LIVER DISEASE paragraph: Fatty liver disease and lifestyle in youngsters. Diet, food intake Frequency, exercise, sleep shortage and fashion. Liver International. 2016 Mar;36(3):427-33. Early effects of high-fat diet, extra-virgin olive oil and vitamin D in a sedentary rat model of non-alcoholic fatty liver disease. Histology and Histopathology. 2018, 33(11), 1201-1213 Echocardiography and NAFLD (non-alcoholic fatty liver disease). Int J Cardiol. 2016 Oct 15;221:275-9. Please strengthen and improve the conclusion, adding the clinical relevance of your work and some important suggestions for the scientific community. Please refresh and update the reference list section.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 47672

Title: Biomarkers and subtypes of deranged lipid metabolism in non-alcoholic fatty liver disease

Reviewer's code: 00053423

Reviewer's country: Brazil

Science editor: Ruo-Yu Ma

Reviewer accepted review: 2019-03-22 10:47

Reviewer performed review: 2019-03-24 13:28

Review time: 2 Days and 2 Hours

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

SPECIFIC COMMENTS TO AUTHORS

It is an interesting review regarding the possible role of lipid metabolism and lipidomic signatures allowing identifying different subtypes of NAFLD. Lipidomic may be helpful to identify severity, risk of progression and possible response to treatment. I suggest

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the authors down tone the isolated importance of these lipidomic signatures. Based on currently knowledge, although there are recent advances in the field of genomics, transcriptomics, proteomics, and metabolomics that may contribute to the diagnosis and risk prediction of NAFLD progression and response to therapy. However, there are still no uniform metabolites which could be used as the diagnostic markers of NAFLD. Some studies showed that metabolomic patterns are different in patients with NAFLD, compared to healthy controls. (Gitto, S et al; Metabolites 2018, 8, 17) However, the discrimination between NAFL and NASH remains a true challenge. (Carulli L; Metabolites 2019, 9, 25; doi: 10.3390/metabo9020025) Further, data derived from single-omics analysis are not enough to explain the complexity of liver diseases. Integration of multiomics data with biological network models may allow advances in our understanding of the complex biochemical processes and pathophysiological responses in liver diseases. (Mardinoglu A et al; Nat. Rev. Gastroenterol. Hepatol. 2016, 13, 439–440; Mardinoglu A et al Nat. Rev. Gastroenterol. Hepatol. 2018, 15, 365–377) Moreover, it is also important to integrate gene products, mRNA, proteins, and metabolites, as well as their molecular interactions with the environmental factors (such as diet).(Maldonado EM et al; NPJ Syst. Biol. Appl. 2018, 4, 33 ; Mardinoglu A et al . Cell Metab. 2018, 27, 559–571.e5).

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 47672

Title: Biomarkers and subtypes of deranged lipid metabolism in non-alcoholic fatty liver disease

Reviewer's code: 01805809

Reviewer's country: United States

Science editor: Ruo-Yu Ma

Reviewer accepted review: 2019-03-22 17:53

Reviewer performed review: 2019-03-29 12:15

Review time: 6 Days and 18 Hours

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

SPECIFIC COMMENTS TO AUTHORS

Authors review experimental and clinical advances that may help distinguish the large and heterogeneous population affected with NAFLD based on lipidomics profiling. The review is heavily focused on authors prior work (published in Gastroenterology 2017;

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152:1449) revealing the association of methionine adenosyltransferase 1a (MAT1A) deficiency with NAFLD in mice and establishing a corresponding metabolic signature among patients with NAFLD, which may result in more targeted therapeutic interventions, primarily by efforts to correct S-adenosylmethionine levels and using new drugs that aim at correcting deranged lipid metabolism in NAFLD. In this regard, authors make the important (and most likely correct) notion that partial success of all pharmaceuticals tested so far in NAFLD may stem from the fact that NAFLD subgroups need targeted intervention to maximize therapeutic efficacy. I have several remarks that will hopefully improve the quality of this manuscript. 1. The background of MAT1A-based phenotype and intricate details of associated changes in lipid metabolism are perhaps overwhelming in a primarily translational paper. Most these issues have been laid out already in the original Gastro publication and this review could streamline this part and refer to those earlier discussions. 2. The original paper used an 'indeterminate' M subtype, which is missing in the current discussion. Since it was not negligible (19%), it would be reasonable to discuss this issue here, unless interim advances better clarified the status of these patients. 3. It is somewhat disappointing that the M phenotype is equally distributed among patients with steatosis and NASH according to the original paper, indicating that it may have little or no impact on the natural history of NAFLD. Of course this would not take away the importance of administering drugs that appropriately exploit the underlying metabolic deficiency, but the fact that this particular constellation has little to do with progression should be more clearly pointed out. 4. Authors showed in the earlier report that the non-M subtype in humans differs in several ways such as age, ALT, and 1-carbon metabolism, and one wonders if there are additional clinical/laboratory parameters that may help distinguish and explain the impact of this subtype in human NAFLD. Authors could also address the problematics of lean NAFLD in this context. 5. There are many different metabolic

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functions in NAFLD based on which we hope to find subtypes for targeted prognosis and therapy. A review on biomarkers and subtypes could presumably embrace these efforts. Deficiency in 1-carbon metabolism is probably just one of these phenotypic differences and - as mentioned above - regrettably it may not distinguish less from more advanced forms (i.e., steatosis vs. NASH) very well. It may be therefore appropriate to consider a more specific title for this review manuscript, just to reflect that it will not discuss any other efforts in this area (.e.g., Biomarkers and subtypes of deranged lipid metabolism in NAFLD' or 'Biomarkers and subtypes of NAFLD based on hepatocellular one-carbon metabolism' etc.) 6. It may be counterintuitive to discount the importance on de novo lipid synthesis in NAFLD as authors do here, since increased DNL rates may just as well overwhelm a deficient VLDL exporting system as it is presumably caused by increased hepatocellular lipid uptake. In this regard, authors may consider mentioning Vidal-Puig's lipoexpediency concept. Also, the pathophysiologic importance of increased vs. deficient FA oxidation as mentioned on page 8 may need a bit more clarification for the average reader.

INITIAL REVIEW OF THE MANUSCRIPT

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