

February 19, 2014

Dear Editor,

Please find enclosed a second revision of 6621 in Word Format. On January 14th, I had submitted a first revision. I have not yet received feedback on the first revision, but am submitting a second revision to improve the graphics, and to add a Table. Nothing else has changed between the first and second revision.

The edited manuscript in Word format (file name 6621_edit).

The following is unchanged from the cover letter from the first revision:

Title: **Breath VOCs for the Gut-Fatty Liver Axis Promise, Peril, and Path Forward**

Author: Steven F. Solga

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 6621

The manuscript has been improved according to the suggestions of the reviewers:

1. Format has been updated
2. Revision has been made according to the suggestions of the reviewer:
 - a. Although the title is "Breath VOCs for the Gut-Fatty Liver Axis", the majority of the description was about other than "fatty liver." This review is better to be focused on the role of VOCs in NAFLD/NASH, because similar reviews papers have been recently published.I fully agree that multiple reviews focused on VOCs in NAFLD/NASH have recently been published. Indeed, this manuscript does not attempt to duplicate this effort. Rather, as noted in my original cover letter and core tip, this manuscript attempts to uniquely review the promise and peril of breath VOC research as applied to the gut-fatty liver axis. Accordingly, I hope it has broad appeal to multiple audiences, including engineers, breath researchers, and clinical researchers.
 - b. VOC is a new concept in the diagnosis of NAFLD/NASH, therefore, a lucent scheme for VOC is needed. I have expanded the section comparing and contrasting breath biomarker development to drug development on page 11.
 - c. Since this is a review paper, the authors better to provide the list of papers which studied on VOCs in patients with NAFLD/NASH as a Table. The graphics have been revised with additional references provided.
 - d. In the introduction, following paper regarding gut-liver axis better to be cited...These have been added. Thank you.
 - e. Some non-invasive diagnostic tools for NASH have been developed using biochemical tests, ultrasound, or MRI. Authors better to discuss advantage and disadvantage of VOC compared to these non-invasive tools. I fully agree that there are multiple non-invasive tools underdevelopment across a variety of testing modalities, and this point is acknowledged in the manuscript. However, I believe that a review of these, including a comparison with breath VOCs, is beyond the scope of this manuscript, and risks losing focus.
 - f. Spell out VOC at first appearance on page 2. Done.

- g. Need to add a table with advantage and disadvantage of each method: breath test by hydrogen, ammonia, VOC, etc. I have expanded section on page 4 regarding putative mechanisms of VOCs.
 - h. I suggest to use at least two methods always in order to increase yield of accuracy. A qualifying statement has been added to page 14.
3. References and typesetting were corrected

Thank you again for publishing our manuscript in the World Journal of Gastroenterology.

Sincerely yours,

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