

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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