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Larissa, May ..., 2015

Dear Editor,

Thank you very much for your email dated May 19, 2015 concerning our original article by Norman et al, your Ref ESPS Manuscript No: 18263, entitled **"COMP: a novel non-invasive marker for assessing cirrhosis and risk of HCC"** that is kindly accepted for publication after minor revisions in *World Journal of Hepatology*.

Today, we submit our revised manuscript in Word format (**file name: 18263-edited-revised.docx**) following your and reviewers' instructions, with all changes precisely indicated in the text (yellow text highlight for the additions, strikethrough and red font for the deletions).

We also upload the **"Copyright Assignment"**, the current file **"18263_Answering Reviewers"**, the **audio_core_tip_18263** file and images files (**"figure1.jpg"**, **"figure2.pptx"**, **"figure3.jpg"**).

This work has not been published nor is under consideration elsewhere and I clearly state that all co-authors have seen and agreed with the contents of the manuscript. However, I should state that parts of this work have been presented as an abstract in the last AASLD Liver meeting (7-11 November, 2014, Boston, USA). In addition, all authors have substantially contributed to this work. Gary L Norman and Zakera Shums are employees of INOVA Diagnostics. However, all the other authors have not any financial, consultant or institutional conflict of interest.

We are very grateful to reviewers and you for the helpful and thoughtful recommendations. We believe that we addressed all of them satisfactorily. All of us feel that our paper has now been significantly improved.

Title: COMP: a novel non-invasive marker for assessing cirrhosis and risk of HCC

Author: Gary L Norman, Nikolaos K Gatselis, Zakera Shums, Christos Liaskos, Dimitrios P Bogdanos, George K Koukoulis, George N Dalekos

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 18263

Editor comments:

- An audio core tip file named **"audio_core_tip_18263.wav"** is uploaded according to your

instructions

- A decomposable file of figure 2 (as power point file) is attached, where parts are movable and words can be edited.
- Text format was changed (fonts size 10pt).

Reviewer 02861134

There was no comment to be addressed. We thank the reviewer for her/his positive comments.

Reviewer 02441174

First of all, we want to thank the reviewer for her/his supportive comments.

1. "In discussion the authors did not provide acronyms RA and OA."

Reply: These explanations had already been quoted in the fourth paragraph of the Introduction (*"Hence, measurement of serum COMP levels has been used diagnostically in the non-invasive estimation of the degree of cartilage damage in patients with inflammatory joint diseases such as rheumatoid arthritis (RA) and osteoarthritis (OA)"*^{[23-26]"}).

2. "As a general reference work contains too little of the literature from a last few years. The abstract, introduction are clear for the reader. The discussion is quite well planned. All issues raised by the authors are presented clearly and understandably. Charts in part A of Table 3 are not clear for reader."

Reply: We agree with reviewer that during the very last years, there is a substantial research and progress in non-invasive markers for the assessment of fibrosis, progression to cirrhosis and development of hepatocellular carcinoma. We now added new references (37 to 41) to further describe this progress.

Regarding "Chart A of Table 3", probably there is a misunderstanding, because our paper includes two tables and three figures. So, we suppose that this comment refers to "Chart A of Figure 3". We agree and really appreciate reviewers' comment, but we think that this is happening due to the very small number of patients (only three) that developed cirrhosis during follow-up period; all of them were COMP negative (see our statement in Page 9, First Paragraph of the revised version of our paper and also in Figure 2). In the revised paper, we added a relative comment in the footnote of Figure 3, in an attempt to further clarify this issue for the readers.

Reviewer 01588404

First of all, we want to express our thanks for the reviewer's comments.

1. This is an interesting study that has used COMP level as a marker for advanced cirrhosis and for identifying patients at risk of HCC development. A well planned study overall. The major criticism is a single point measurement. A serial / follow up measurement data may have added more mechanistic information regarding the utility of COMP level in following patients with Chronic liver disease.

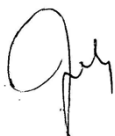
Reply: We absolutely agree with the reviewer suggestion that COMP will be of greater diagnostic value after its serial determinations. However, this very first study was designed in order to assess if serum COMP at one point time does makes any sense as a marker of cirrhosis and risk of progression to HCC. Of course, after our first encouraging results the investigation of serial determinations of COMP looks obligatory in future studies. In order to satisfy the reviewer, this minor limitation of our study has now been presented in the last paragraph of the manuscript (page 11 of the revised manuscript).

2. Language evaluation: Grade B - minor language polishing.

Answer: First author (Gary L Norman) along with Zakera Shums who are native speakers of English have constructed and approved the final draft of the paper.

Once again, I would like to thank you and the reviewers for your helpful suggestions. I really appreciate your kind invitation for contribution of high quality manuscripts and for permitting us the consideration for publication of our work to the *World Journal of Hepatology*.

Sincerely yours,



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