

To the Editor-in-Chief of World Journal of Gastrointestinal Surgery

12th May 2021

Dear Editor,

We would like to thank the editor for the opportunity to resubmit a revised version of our manuscript (64229) entitled: *"Persistent bowel dysfunction after surgery for Hirschsprung's disease: a neuropathological perspective"*.

We would also like to thank the reviewer for his/her constructive and helpful comments in order to improve our manuscript. We have read the comments with interest, and we have tried to adjust the manuscript accordingly. Please find below our point-to-point responses to the reviewer comments.

On behalf of all authors,

Yours Sincerely,

Sanne J. Verkuijl

Peer review

Reviewer's code: 03252920. Well-written and very interesting review that addresses the most important aspects related to the topic. The review comprises a critical and current discussion on the main clinical and histopathological aspects related to the postoperative period of patients with Hirschsprung's disease. The only point I suggest reviewing by the authors is the statement on the use of calretinin immunohistochemistry for the diagnosis of Hirschsprung's disease (page 4/31, first paragraph). The absence of immunohistochemical expression of calretinin in ganglion cells and intrinsic nerve fibers in colorectal aganglionic segments has been routinely used and is part of the main guidelines for HD diagnostic management, as presented in the references: - Takawira C, D'Agostini S, Shenouda S, Persad R, Sergi C. Laboratory Procedures Update on Hirschsprung Disease. J Pediatr Gastroenterol Nutr. 2015; 60:598–605 [PMID: 25564805 DOI: 10.1097/MPG.0000000000000679] - Veras LV, Arnold M, Avansino JR, Bove K, Cowles RA, Durham MM, Goldstein AM, Krishnan C, Langer JC, Levitt M, Monforte-Munoz H, Rabah R, Reyes-Mugica M, Rollins MD, Kapur RP, Gosain A. Guidelines for synoptic reporting of surgery and pathology in Hirschsprung disease. Journal of Pediatric Surgery. 2019; 54:2017–23 [PMID: 30935730 DOI: 10.1016/j.jpedsurg.2019.03.010] Therefore, I suggest reviewing this aspect.

Answer: We would like to thank the reviewer for his/her thorough reading of our manuscript. As the reviewer suggests, we adapted the statement regarding the use of calretinin immunohistochemistry and we added the two proposed references to the manuscript (page 4, first paragraph): *“There is growing evidence that also immunohistochemistry against calretinin may be supportive in detecting aganglionic segments.^[12,13]”*

12. Veras LV, Arnold M, Avansino JR, Bove K, Cowles RA, Durham MM, Goldstein AM, Krishnan C, Langer JC, Levitt M, Monforte-Munoz H, Rabah R, Reyes-Mugica M, Rollins MD, 2nd, Kapur RP, Gosain A, American Pediatric Surgical Association Hirschsprung Disease Interest Group. Guidelines for

synoptic reporting of surgery and pathology in Hirschsprung disease. *J Pediatr Surg* 2019; **54**: 2017-2023 [PMID: 30935730 DOI:S0022-3468(19)30212-X]

13. **Takawira C, D'Agostini S, Shenouda S, Persad R, Sergi C.** Laboratory procedures update on Hirschsprung disease. *J Pediatr Gastroenterol Nutr* 2015; **60**: 598-605 [PMID:25564805 DOI:10.1097/MPG.0000000000000679]

Editorial Office Comments

A completed Conflict of Interest Disclosure Form and Copyright License Agreement are provided. Additionally, we revised the manuscript according to the following Editorial Office's comments and suggestions:

- Self-cited references: There are 11 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations that are closely related to the topic of the manuscript, and remove other improper self-citations.

Answer: We have deleted three self-cited references, which led to a current self-referencing rate of 9%.

- The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Answer: As requested, we uploaded the original images in a PowerPoint format, named "64229-Figures.ppt"

- PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references.

Answer: The references of the manuscript were adapted accordingly.