

November 24, 2015

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Editors-in-Chief  
*World Journal of Gastroenterology*  
e-Submission

Dear Editors-in-Chief:

My co-authors and I received a revise and resubmit decision regarding our manuscript, titled "The Healthcare and Economic Impact of Diarrhea among Patients with Carcinoid Syndrome" (Manuscript # 21973), submitted for publication in *World Journal of Gastroenterology*. We have addressed each comment raised by the two reviewers and made clarifications in the manuscript as requested. Our specific responses to the reviewers' comments are attached below. In response to the reviewers' comments, we have specified the sections for our corresponding revisions in the manuscript and quoted text where reviewers' comments were addressed. In the body of the manuscript, we have used track-changes and highlighted the edited and new text.

My co-authors and I would like to sincerely thank the *World Journal of Gastroenterology* Editors-In-Chief and the reviewers for their review of our manuscript.

Thank you for your time and consideration. We look forward to your decision.

Sincerely,

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## RESPONSE TO REVIEWERS

**Manuscript number:** #21973

**Title:** The Healthcare and Economic Impact of Diarrhea among Patients with Carcinoid Syndrome

### REVIEWER 00504462

1. **[Reviewer Comment]** Dear Sir, It was a pleasure reading your manuscript. And even though all the limitations that you already had described, your objectives and results are really interesting. Hopefully, new projects from your descriptions can be achieve for the future.

**[Authors' response]** My coauthors and I thank this review for the thorough assessment of our manuscript.

### REVIEWER 03441591

2. **[Reviewer Comment]** This analysis is informative and to the point and I enjoyed reading it. I think it is well executed methodologically and clearly described.

However, I had a feeling that some parts of the discussion section were too brief and it would be beneficial for both the manuscript and its readers, if you could elaborate on prevention and treatment of diarrhea in CS patients. You mention this multiple times, but always in very general terms, for example: "Effective preventive treatment of diarrhea in patients suffering from CS would be a reasonable approach to reducing healthcare resource utilization and costs in this population". or in the conclusion: "Reduction of health-care expenditures attributable to diarrhea may be achievable through preventive treatment and appropriate management of diarrhea in patients with CS."

Please provide specific (preferably evidence-based) preventive treatment and management strategies. What are the current treatment guidelines? Are there any systematic reviews about this topic? What are the recommendations? If this is not available, indicate that there's an urgent need for that.

**[Authors' response]** We appreciate this author's suggestions. We did not originally provide specific management strategies for diarrhea in CS patients since that was not the focus of our study. However, we have now reviewed the treatment recommendations for carcinoid diarrhea, and we have included the following statement in the Discussion section and cited the following new reference in the manuscript:

- "The NCCN Clinical Practice Guidelines in Oncology on NETs recommend the use of the long-acting somatostatin analogues, octreotide and lanreotide, should result in improvement of diarrhea and flushing symptoms of carcinoid syndrome.<sup>25</sup> Octreotide LAR dose and frequency may be further increased for symptom control as needed.<sup>25</sup>"
- Reference # 25: National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>): Neuroendocrine Tumors. Version 1.2015. Access at: [www.nccn.org](http://www.nccn.org)

3. **[Reviewer Comment]** Are there any related cost-effectiveness analyses? Please briefly review the relevant literature in this context and discuss the most important results and how this relates to your analysis. You could give some specific recommendations based on that.

**[Authors' response]** Cost-related analyses of diarrhea in CS are lacking. Hence, we have included the following statement at the end of the Background section to indicate motivation for our study:

- “The healthcare and economic burden of diarrhea in CS patients has not been previously quantified. The goal of the current study was to examine healthcare resource utilization (HRU) patterns and healthcare costs accrued by CS patients with and without diarrhea in an insured US population.”