February 1, 2019

The Editor, *World Journal of Gastroenterology*

We thank the editor for the opportunity to resubmit our manuscript. We also thank the reviewers for their comments and insights. We have provided below a point-by-point response to the reviewers' comments, and we have shown the changes in the manuscript with tools tracking or with red font.

Sincerely,

Xiao Jing Wang, M.D.
Michael Camilleri, M.D.

Reviewer #1: Dr. Wang and Dr. Camilleri reviewed 'Personalized Medicine in Functional Gastrointestinal Disorders: Time to Tailor the Treatment on the Basis of the Pathogenesis? The manuscript is informative and well-presented. The reviewer has no comments. **Response: Thank you.**

Reviewer #2: In this review article Wang et al, has put together the recent developments in specific mechanisms and personalized treatment of functional gastrointestinal disorders. The article is informative and provides a nice overview. However, this reviewer has a few suggestions that the authors should consider addressing. 1. Recent information suggests that the association of functional gastrointestinal disorders and psychological impairment may be more fundamental than was previously believed. The rationale for psychological therapy in the treatment of functional gastrointestinal disorders should be also emphasized to give readers a wider view of the problem.
Response: Agreed. We have included a brief discussion of the association of FGIDs and psychologic impairment as part of the brain-gut interaction. We have also expanded on the role of central pain modulators and antidepressants in dyspepsia, as well as the role of cognitive behavioral therapy and hypnotherapy for treatment of concomitant conditions.

2. Functional gastrointestinal disorders are divided into functional upper gastrointestinal symptoms and functional lower gastrointestinal symptoms in the article, and related mechanisms have been listed. However, most of them are related to one or a type of symptom without mentioning possible mechanisms and treatments for multiple symptoms.
Response: We agree with the reviewer that most of the FGIDs are symptom complexes. Studies available in the literature are largely limited to specific symptom endpoints, often mandated by regulatory agencies like the FDA (e.g., pain and diarrhea in IBS-D; stool consistency or number of spontaneous bowel movements in constipation trials) and, thus, our review was limited to presenting data on a narrow symptom spectrum.

3. The authors mention that nutritional factors, including FODMAPs are associated with predominant pain or bloating, but miss out on dietary fibers. A couple of sentences regarding its association with functional gastrointestinal disorders should be included in the review.

Response: **We have added a brief discussion of dietary fibers as well as prebiotics in the treatment of FGIDs. We have noted, as well, that these are currently empiric treatments and do not have a clear way of being tailored to particular patient phenotypes.**

4. This review proposes an individualized approach to the management of functional gastrointestinal disorders on the basis of the pathogenesis. In fact, a table listing all the specific mechanisms and their personalized treatment of functional gastrointestinal disorders would be really informative.
Response: Agreed. We have added a review of the treatments available, their mechanisms of action, and phase of trial in Table 2 for the 4 main symptom complexes: functional dyspepsia, outlet dysfunction constipation, slow transit constipation, and bile acid diarrhea.

5. Accumulating studies have revealed the associations between gut dysbiosis and functional gastrointestinal disorders, and manipulating the microbial populations with therapeutic intent has become a hot topic of functional gastrointestinal disorders research. I would add some information about them.
Response: Agreed. We have included information on recent discussions of fecal microbiota transplant use in IBS.

Reviewer #3: This review looks written very well.
Response: Thank you.

Reviewer #4: This is an interesting review (see comments in the attached file—included below) This interesting review follows the lecture proposed by Michael CAMILLERI during the last Digestive Disease Week. We agree with the authors: tailored management of FGIDs need to be the main rule of a good medical management. There is no major criticism for this paper, but some points need to be underlined.

1. As indicated by the authors in the introduction section "*FGIDs encompass a group of gastrointestinal conditions characterized by chronic or recurrent GI symptoms without biochemical or structural abnormalities*", but in the following paragraphs, the authors pooled together disorders that associated digestive symptoms with physiological abnormalities as difficult defecation associated with pelvic floor dyssynergie or digestive symptoms associated with abnormal metabolic pathways like in bile acid induced diarrhea or disaccharidase malabsorption.
   It could be more interesting to separate disorders with a known etiology that mimics FGIDs and disorders of unknown origin that are named "functional". This inappropriate name, mainly by opposition to "organic", should be changed into "unknown origin".

Response: We agree with the reviewer that the use of "functional" diseases as an umbrella term is suboptimal, and the goal of our review is to push towards utilization of more specific disease diagnoses, which one could regard as "organic" diagnoses. However, current convention still bundles all of these disorders of motility and gastrointestinal function into "FGID" as illustrated by the fourth iteration of the Rome criteria. We have made note of this discrepancy in the Introduction and have recommended improved identification in the future in our conclusion.

2. Another important factor that could be emphasized in this review is the association between disorders in different segments like delayed gastric emptying associated with constipation or fecal incontinence associated with diarrhea. For these associated disorders, the regulation pathway are involved.

Response: Agreed. Although we have focused our discussion on specific symptoms for the purposes of this review, we have added this important caveat into the introductory paragraphs.

3. Finally, the importance of nutritional factors, not only FODMAPS, that interacts with the digestive microbiota or have a specific function must be mentioned like fibers or ultra processed food

Response: Agreed. We have added a brief discussion of dietary fibers, prebiotics, and ultra-processed foods in the treatment of FGIDs. We have noted, as well, that these are currently empiric treatments and do not have a validated way of being tailored to particular patient phenotypes.

Reviewer #5: 45797 Personalized Medicine in Functional Gastrointestinal Disorders: Time to Tailor the Treatment on the Basis of the Pathogenesis? by Wang & Camilleri, 2019. This is an interesting narrative review on the phenotypes of functional gastrointestinal disorders and the therapeutic application of its drug-related pharmacogenomics. After reviewing main types of functional gastrointestinal disorders, the authors report therapeutic advances of functional gastrointestinal disorders in pharmacogenomics and drug pharmacokinetics, mutations and genetic variants, mucosal gene expression of functional gastrointestinal disorders. They conclude that patient-based research can provide additional personalization of diagnosis and management for patients with gastrointestinal disorders, with the aid of better understanding of the pathophysiology and clinically-applicable diagnostic tests. The title is provocative, but does not reflect the global content of the article at all. In general, the type of review should be stated in the title.

Response: Agreed. We have edited our title to more closely reflect the content and have included the type of review in the submission.

The text is organized into a section of Background, Description of some functional gastrointestinal disorders (in terms of putative mechanism and the therapeutics), and indications of Precision Medicine. I would suggest a Table to summarize each type of gastrointestinal phenotype, along with a Table with recent advances of therapeutic alternatives.

Response: Agreed. We have added the pathogenesis of various disorders in Table 1 and a review of the treatments available in Table 2.

The authors can underscore the level of evidence for each treatment option. Because there is no critical assessment of the quality of existing evidence, I would replace the section of Conclusion by "Comments".

Response: Agreed, done.

A brief description of the limitations of the present review is welcome as well.

Response: Agreed. We have added a limitations section prior to our summary comments.