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Peking Union Medical College Hospital
Chinese Academy of Medical Sciences
Peking Union Medical College
Beijing, China

November 30, 2022

Dear Editors

Re. Advancing the precision management of inflammatory bowel disease in the era of omics approaches and new technology

Please find the revised version of the above manuscript attached.

We are very grateful to the editor and reviewers for their positive comments and thorough feedback. We have now addressed all the reviewers' comments in full, and also added latest research results to the new version. Point-by-point responses are provided below.

We thank you for your considerations and look forward to publishing our review in *World Journal of Gastroenterology*.

Sincerely,

Xinyu Liu, MD, Bei Tan, MD, on behalf of all authors
Department of Gastroenterology, Peking Union Medical College Hospital
Chinese Academy of Medical Science & Peking Union Medical College

Point-by-Point Responses:

Reviewer #1:

Q1: The quantum of information provided in the manuscript entitled "Toward the precision management of inflammatory bowel disease in the era of omics and new technology" is very vast and the authors have tried to focus on nearly every aspect of IBD including the pathogenesis, prognosis, clinical manifestation, response to treatment and management. But in this quest to cover every aspect, the focus of the article has been lost and the write-up fails to provide a clear and concise message for the readers. It remains unclear why the sections on application of Artificial intelligence/machine learning and management of IBD during Covid-19 have been included in this manuscript. Ideally, they may be published separately to maintain the coherence of the present article and relevance to the title.

A1: Thank you so much for your comments and suggestions. Indeed, we tried to cover relevant contents to the best of our abilities, it's a pity that the review seemed somehow complex and unclear. Hence, we removed the COVID-19 section and reorganized the manuscript according to the following logical sequence. We first discussed the problems

underlying IBD precision management posed by its heterogeneity, then we discussed the methods to identify unique IBD populations e.g. clustering strategies and biomarkers etc. Since this problem has not been sufficiently solved by recent research, we proposed that multiomics might be the future direction. Finally, the integrated analysis of multiple omics strategies involves processing large volume of data, hence the artificial intelligence/machine learning is needed. Hope this modification made the manuscript clearer and more concise.

Q2: Furthermore, the manuscript needs to be organized better. For example, a category-wise list of biomarkers along with their merits and demerits may be provided in a Tabular form rather than as a text.

A2: Thank you so much for your suggestion. We organized and sorted all the biomarkers into "Table 1 Biomarkers of serum or feces identifying disease progression risk and activity" and "Table 2 Biomarkers predicting treatment response". (Pls see Table File)

Q3: All –omics should be discussed separately and not clubbed together.

A3: Thank you for your suggestion. We reconstructed the "Future of precision management in IBD: multiomics" SECTION, the gene expression section was organized in order of transcriptomics, proteomics and epigenomics, and the omics section was organized in order of gene, gene expression, environmental factors. (Pls see "Future of precision management in IBD: multiomics" SECTION)

Q4: There are several grammatical errors in the manuscript, especially related to the 'tense' which needs correction.

A4: Thank you for pointing this out. We have corrected and polished the language throughout the manuscript.

Reviewer #2:

Q1: This is the review regarding the management of inflammatory bowel disease (IBD) widely covering the topics for biomarkers, management precision by genetics, proteomics, microbiomics, and application of AI, and disease management during COVID-19 pandemic. Although the text of paper is interesting, no Figure or Table that help readers understand of the contents is provided, regrettably. Attractive Figures and Tables are quite important for the citation of review articles. Please provide some Figures and/or Tables.

A1: Thank you for pointing out this deficiency. We categorized the biomarkers into "Table 1 Biomarkers of serum or feces identifying disease progression risk and activity" and "Table 2 Biomarkers predicting treatment response". Also, we drew "Figure 1. Flow gram of the precision management strategies of inflammatory bowel disease" in order to outline and illustrate the main idea of this review.

Q2: I wonder the needs of description regarding the management during the COVID-19 pandemic. As COVID-19 pandemic is about to ending and the consideration for COVID-19 pandemic is different among countries, description regarding COVID-19 pandemic may be better to avoid.

A2: Thank you for your kind suggestion. We removed the "Disease monitoring and management during the COVID-19 pandemic" SECTION.

Reviewer #3:

Q1: Thank you for this review which updates the current knowledge.

A1: Thank you for your positive comments.