March 17, 2021

Professor Subrata Ghosh & Professor Andrzej S Tarnawski
Editors-in-Chief
World Journal of Gastroenterology

Dear Editor:

We sincerely appreciate the careful review of our manuscript titled "**Requirements for implementation of artificial intelligence in the practice of gastrointestinal pathology**." **(ref. No: 63775)** and the helpful suggestions and comments made by the reviewers. These comments have contributed considerably to the improvement of our manuscript. Do note that all comments from both reviewers have been carefully considered and addressed and the manuscript has been revised accordingly. The detailed point-by-point responses to the individual comments are provided below.

We greatly appreciate your kind consideration of our revised manuscript and hope that this version is now suitable for publication in *World Journal of Gastroenterology*. However, we would be pleased to make further revisions if necessary. We look forward to hearing from you at your earliest convenience.

Sincerely yours,

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Responses to the reviewers' comments

Submission to *World Journal of Gastroenterology*

Manuscript ID: No: 63775 (Invited review)

Title: **Requirements for implementation of artificial intelligence in the practice of gastrointestinal pathology**.

Authors: Hiroshi Yoshida and Tomoharu Kiyuna

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Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Name of Journal: World Journal of Gastroenterology Manuscript Type: REVIEW Requirements for implementation of artificial intelligence in the practice of gastrointestinal pathology This review tries to present challenges in the process of AI development, validation, and regulation, and summarize the overcome for its implementation in real-life GI pathology practice. It is well written but the following should be clarified:

General response: Thank you for your encouraging assessment. We have addressed all the comments made by the reviewer and hope that our explanations and revisions are acceptable to you. As indicated in the responses below, the manuscript has been improved according to the reviewer's suggestions.

Specific comments:

1. The introduction should be shortened to make it concise and purpose driving.

Response to comment #1: Thank you for your suggestion; we completely agree with the reviewer. Accordingly, we have shortened the Introduction section by deleting some sentences.

2. Most of the contents of this review introduce and summarize the development, validation and application of different AI methods themselves, including machine learning, deep learning, CNNs and so on. However, the contents about those AI methods apply to gastrointestinal disease, such as gastric cancer and colon cancer are not comprehensive and thorough enough (The author simply listed the studies and did not discuss them). I suggest the authors to summarize roles of different AI methods in gastrointestinal disease diagnosis, staging, response evaluation and prognosis prediction, and discuss the advantages and disadvantages in each direction.

Response to comment #2: Thank you for your comment and valuable suggestion. As you pointed out, we would like to focus on obstacles and difficulties in the implementation of AI methods into GI pathology practice rather than a comprehensive literature review of published articles of each AI-based model because we believe the former is a fundamental issue and has been not fully discussed in the literature. The explosive development of AI-based models is expected to continue in the next decade. Simultaneously, issues on the implementation of AI methods into the real-life world would be more important.

According to the reviewer's valuable suggestion, we have summarized both advantages and

disadvantages of representative machine-learning methods in the development of an AI-model for gastrointestinal pathology (Table 3).

Table 3. Advantages and disadvantages of representative machine-learning methods in the development of AI-models for gastrointestinal pathology

AI model	Advantages	Disadvantages
Conventional ML (supervised)	▪User can reflect domain knowledge to features	▪Requires hand-crafted features ▪Accuracy depends heavily on the quality of feature extraction
Conventional ML (unsupervised)	▪Executable without labels	▪Results are often unstable ▪Interpretability of the results
Deep Neural Networks (CNN)	▪Automatic feature extraction ▪High accuracy	▪Requires a large dataset ▪Low explainability (Black box)
Multi-instance Learning	▪Executable without detailed labels	▪Requires a large dataset ▪High computational cost
Semantic Segmentation (FCN, U-Net)	▪Pixel-level detection gives the position, size, and shape of the target	▪High labeling cost
Recurrent Neural Networks (RNN)	▪Learn sequential data	▪High computational cost
Generative Adversarial Networks (GAN)	▪Learn to synthesize new realistic data	▪Complexity and instability in training

Abbreviations: ML, machine learning; CNN, convolutional neural network; FCN, fully convolution network

Furthermore, we have added the description on this point to the revised manuscript as follows: "All of the current ML methods have their advantages and disadvantages, and it is necessary to select an appropriate method according to the purpose of image analysis. DL-based methods are most used in current image analysis of GI pathology; however, they have limitations of requiring substantial data sets and insufficient interpretability. In the future, the development of new ML methods that can compensate for the disadvantages of current ML methods will further accelerate the development of AI- models." (Page 6, lines 19-25).

Science editor:

1 Scientific quality: The manuscript describes a review of the requirements for implementation of artificial intelligence in the practice of gastrointestinal pathology. The topic is within the scope of the WJG. (1) Classification: Grade B; (2) Summary of the Peer-Review Report: This review tries to present challenges in the process of AI development, validation, and regulation, and summarize the overcome for its implementation in real-life GI pathology practice. It is well written. The questions raised by the reviewers should be answered; (3) Format: There are 2 tables and 2 figures; (4) References: A total of 94 references are cited, including 54 references published in the last 3 years; (5) Self-cited references: There are 4 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations (i.e. those that are most closely related to the topic of the manuscript) and remove all other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated; and (6) References recommendations: The authors have the right to refuse to cite improper references recommended by the peer reviewer(s), especially references published by the peer reviewer(s) him/herself (themselves). If the authors find the peer reviewer(s) request for the authors to cite improper references published by him/herself (themselves), please send the peer reviewer's ID number to editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately.

2 Language evaluation: Classification: Grade B. A language editing certificate issued by Editage was provided.

3 Academic norms and rules: No academic misconduct was found in the Bing search.

4 Supplementary comments: This is an invited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJG.

5 Issues raised: (1) 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; and (2) If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.

6 Recommendation: Conditional acceptance.

General response: Thank you for your positive assessment. Accordingly, we have provided the original figures as a ppt file.

Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

General response: Thank you for your positive assessment. We have addressed all the comments made by the reviewer and updated the manuscript in accordance. We hope that you find our explanations and revisions acceptable.

Thank you again for your valuable comments. We are grateful for the time and energy spent making these observations and recommendations.