

Cover letter and point-to-point response to editors and reviewers

Title: Artificial intelligence and microbiome to promote precision medicine for gastric cancer

Authors:

ZML: lzmleo@xmu.edu.cn

XZ: zhuangxuan2006@aliyun.com

Tel: (86) 27- 83692651

Dear Editors,

Thanks for your valuable comments and consideration of our manuscript (65772), entitled as: **Artificial intelligence and microbiome to promote precision medicine for gastric cancer**, for publication in your journal.

We have revised the manuscript according to reviewer's commentaries below. The files were attached for your further reviewing.

Any further comments, please do not hesitate to let us know.

All the Best wishes,

Zhiming Li, Ph.D.

Institute of Reproductive Health,

Tongji Medical College,

Huazhong University of Science and Technology

Reviewers' Comments to Author:

Reviewer: 1

Abstract is low can be more

Response: The part of abstract was polished.

Reviewer: 2

There is no doubt that AI will contribute to progress of medical science, but the fields in which AI can be effective are limited. In this respect, AI is effective for analyzing a large amount of data on microbiome, and research to the relationship between diseases and the microbiome in the stomach is a promising frontier for AI. Unfortunately, this field is still developing, and has not yet produced enough research results to warrant a review. A review of this field is necessary, but at this point it would be more useful for newcomer researchers to summarize the methodological advances rather than the current state and prospects of the research. Please describe in more detailed descriptions about the progress of the analysis method of the microbiome due to the progress of the sequencer, the advances in methods to separate microbiome from host nucleotides, and the progress of the methods of AI.

Response: We supplemented the progress of the analysis method of microbiome, the advances in methods to separate microbiome from host nucleotide, and the progress of the methods of AI, which can be seen in Page 5.

16S rRNA gene fragments of >97% sequence identity is clustered into separate operational taxonomic units (OTUs) that reflect the phylogenetic boundaries of distinct bacterial species. Moreover, analysis of amplicon sequence variants (ASVs) provides improved sensitivity and specificity and reduces the problem of inflated microbiota datasets due to falsely identified distinct OTUs originating from mis-clustered sequences.

Reviewer: 3

This manuscript is a mini-review of how artificial intelligence can be applied to study microbiome to promote precision medicine for gastric cancer. The authors were very clear and concise in explaining how studying the microbiome in the gastric

environment can lead to new discoveries and at the same time have challenges, especially when the number of bacteria is low and there is contamination with the host's genome. However, they did not directly address how these studies can contribute to a decision by physicians to proceed with different treatments depending on the microbiota that is founded and characterized in the patient. Authors should add more practical examples of how AI contributes directly to therapy to complete the text and connect to what was proposed in the paper's title.

Response: We supplemented how these studies can contribute to a decision by physicians to proceed with different treatments depending on the microbiota that is founded and characterized in the patient, which can be seen in Page 8.

The tumor-immune environment is related to gastric microbiota in GC patients, providing a correlation of regulatory T cells and plasmacytoid dendritic cells within the tumor microenvironment with gastric microbiota dysbiosis.

We added more practical examples of how AI contributes directly to therapy, which can be seen in Page 7.

Microbiome composition can interfere in primary resistance to immune checkpoint inhibitors targeting programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1), recently introduced to GC therapeutic arsenal. One of the striking findings that distinguishes cancer patient responders from non-responders to PD-1 blockade immunotherapy is the ratio of putatively favorable to unfavorable bacteria.

Reviewer: 4

A well written manuscript, but missing parametric comparative analysis of state of the art methods.

Response: It is a very good advice. Unfortunately, this field is still developing, and has not yet produced enough research results to warrant a parametric comparative analysis.
