Professor Lian-Sheng Ma

President and Company Editor-in-Chief,

Baishideng Publishing Group Inc,

Editorial Office,

Artificial Intelligence in Cancer

May 02, 2020

Dear Professor Lian-Sheng Ma,

Thank you for your email dated 22 April 2020 enclosing the reviewers' comments. We are grateful for the opportunity to revise our manuscript "Impact of blurs on machine-learning aided digital pathology image analysis" (Manuscript NO.: 54872) and we appreciate the helpful comments of your reviewers. We have carefully reviewed the comments and have revised the manuscript accordingly. Our responses are given in a point-by-point manner below.

We feel that the comments have allowed us to improve the paper and hope you will convey our gratitude to the reviewers.

Sincerely,

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Authors' Response to Reviewer 1:

Thank you for your positive assessment. We are grateful for the time and energy you expended on our behalf.

Authors' Response to Reviewer 2:

Thank you for your positive assessment. We have addressed all the comments by the reviewer and we hope that the explanations and revisions of our work are satisfactory. As indicated in the responses that follow, the manuscript has been improved according to the suggestions from the reviewer.

Comment #1. ML-aided classification model and criteria for both negative and positive classification should be briefly described.

Authors' Response:

Thank you for your comment. Accordingly, we added a brief description of ML-aided classification model and criteria for both negative and positive classification in the section *Digital image acquisition and automated image analysis* as follows: The procedure for classification of a cancerous areas in a given whole-slide image is as follows: (1) Identify the tissue regions at 1.25X. (2) The tissue area was then divided into several rectangular regions of interest (ROIs). (3) From each ROI, the structural and nuclear features are extracted at different magnification (10X and 20X). (4) After the feature extraction, all ROIs were classified as positive or negative using a pre-trained classifier (support vector machine, SVM). (5) The SVM-based classifier assigns a real number *t* to each ROI, where *t* takes value in the range [-1.0, 1.0]. A value of 1.0 indicates a positive ROI and a value of -1.0 indicates a negative ROI. [1] In this experiment, we interpreted the value of *t* >= 0.4 indicates a positive ROI.

[1] Yoshida H, Shimazu T, Kiyuna T, Marugame A, Yamashita Y, Cosatto E, Taniguchi H, Sekine S, Ochiai A Automated histological classification of whole-slide images of gastric biopsy specimens. *Gastric Cancer* 2018;21:249–57 [PMID: 28577229 DOI: 10.1007/s10120-017-0731-8]

Comment #2. Quantitative analysis of the degree of image blurring and its normalization should also be introduced.

Authors' Response:

Thank you for your comment. Accordingly, we added a brief description about how to calculate the degree of image blurring and its normalization in the section *Quantification of the degree of image blurring* as follows: The degree of image blurring is calculated and normalized as follows: (1) 2D convolution by neighboring fileter. (2) Local variance of a 5x5 area. (3) Captures local phase variations after convolution with wavelet filters, normalized by a sigmoid function to [0, 1] range.

Comment #3. May the authors propose potential solutions to avoid the discordance through excluding these disqualified slides?

Authors' Response:

Thank you for your comment. As suggested, we proposed a potential solution to avoid the discordance through excluding these disqualified slides in the last paragraph of the *Discussion* as follows: Since our method provides a quantitative measure for the degree of blurring, it is possible to avoid discordance through excluding these disqualified slides using this measure. However, further experiments are required to establish more reliable measure together with other factors, for instance, such as tissue area size and nuclear densities.

Authors' Response to Editorial Office's comments:

Comment #1. I found that the language qualities evaluated by peer-reviewers are Grade B and Grade B. The language needs a minor polishing.

Thank you for your comment. Accordingly, we requested native speakers of English to proofread our English writing. If there has already been any language problem in the revised manuscript, we would appreciate it if you could tell me a specific point.

Comment #2. The authors did not provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout.

Authors' Response:

Thank you for your comment. We added the PubMed numbers and DOI citation numbers to the reference and listed all authors.

Comment #3. The authors did not write the "article highlights" section at the end of the main text.

Thank you for your comment. Accordingly, we added the "article highlights" section at the end of the main text.