Author’s response to reviews

Title: The challenges of colposcopy for cervical cancer screening in LMICs and solutions by artificial intelligence

Authors:

Peng Xue (xuepeng_pumc@foxmail.com)
Man Tat Alexander Ng (alexng@post.harvard.edu)
You-Lin Qiao (qiaoy@cicams.ac.cn)

Version: 1 Date: 21 Apr 2020

Author’s response to reviews:

Aprial 21, 2020

BMC Medicine
Dear Editor,

Thank you very much for your letter and the accompanying reviewers’ comments on our paper “The challenges of colposcopy for cervical cancer screening in LMICs and solutions by artificial intelligence” (BMED-D-20-00570). We are submitting a revised manuscript that incorporates the reviewers’ comments. All alterations within the manuscript have been highlighted in blue for your convenience.

Below we have provided a detailed point-by-point response to each comment made by the reviewers and a description of changes that we have made to the manuscript to address the concerns.

We hope that our paper has been revised satisfactorily and will be published in the journal of BMC Medicine.

Thank you for your consideration!

Sincerely,

Youlin Qiao, M.D., Ph.D.
Senior Professor, Department of Cancer Epidemiology
Cancer Hospital, Chinese Academy of Medical Sciences
and Peking Union Medical College
17 South Panjiayuan Lane, Old Research Building Suite 1317
Beijing 100021, China
Phone: +86-10-8778-8489, Fax: +86-10-6771-3648;
Email: qiaoy@cicams.ac.cn

Formatting checks
- Please include a 'Declarations' heading within your Manuscript. This should be placed after your 'Abbreviations' and just before 'Acknowledgements'.
- Please remove the Figure caption and note from the actual Figure file. Figure files should only include the image graphics. The Figure caption with its note should be placed within the main Manuscript text, after the References, under 'Figure legends' heading.

Response:
Thank you for your comments. The above two formatting checks has been adjusted in terms of your suggestions in the manuscript, (line 316-333, page 13-14) figure caption with its note, (page 18) and separate figure file.

Point-by-point response to the reviewers’ comments
Reviewers’ Comments:
Reviewer #1
Comment #1.1

Background and the challenges of diagnostic performance of colposcopy in LMICs sections. In these two sections, I would recommend that the author first make a comparison of what screening strategies are used for cervical cancer in different countries, what are the advantages and disadvantages of each, and identify what are the most important challenges with screening strategies in low-income countries. This could help readers better understand what a key role AI can play in cervical cancer screening.

Response:
Thank you so much for your valuable suggestion. Actually, cervical cancer has a standardized or uniform screening procedure/strategy-that is primary screening, colposcopy, and biopsy in that order, as shown in WHO guidelines for cervical cancer prevention (ISBN 978 924 154869 4), maybe there is minor differences in choice of testing method. For high-resource settings, the incidence of cervical cancer has decreased substantially due to cytology screening and colposcopy. However, they are subjective, and their accuracy to a great extent relies on the experienced physicians which are shortage in low- and middle-income countries (LMICs). Fortunately, HPV testing, due to its more objective and higher performance compared with cytology, has been developed as a primary screening tool. Therefore, the most important challenge falls to colposcopy, and is hard to overcome as expressed in our article. We spend a great deal of effort distinguishing the underlying population with high risks of cervical precancer from the screened population and referred them to colposcopy for further confirmation. However, the poor performance of colposcopy in LMICs causes potentially false-negative and false-positive findings, which lead to a considerable burden for affected women. Considering these challenges are generally consistent in low- and middle-income countries (LMICs), our article summarizes the current challenges of colposcopy for cervical cancer screening in LMICs and possible solution by AI.
Comment #1.2
The advancements in computer algorithms applying to cervical images. This section should discuss the strengths and limitations of existing reported studies.

Response:
Thank you for the comment. Currently, limited studies of AI guided digital colposcopy are reported due to this is a new territory. We discuss the strengths and limitations of existing reported studies that edited the description as below:
These studies indicate an encouraging trajectory, but they could not be generalized due to the relatively small training set and lack of external validations/prospective clinical trials to confirm the results in clinical settings. (line 196-198, page 8)

Comment #1.3
The challenges to development and application of AI guided digital colposcopy. How to improve AI technology is also a challenge.

Response:
Thank you for the suggestion. We added the description into the manuscript below:
Another reasonable strategy is to further improve the AI algorithms to enable them to deal with images of different origins and qualities. (line 211-213, page 9)

Reviewer #2
Comment #2.1
Page 5, line 108-114. the author should provide relevant references to support the corresponding opinions, such as the specific difference on CIN diagnosis ability between expert colposcopists and junior colposcopists, and the reported intra-operator and inter-operator variabilities based on current published data. These published data would be better to illustrate the application value of AI.

Response:
Thank you for the comment. We provide relevant references and current published data in the manuscript as below:
Thus, there are substantial inter-, and intra-operator variabilities in the agreement of colposcopic impressions and pathology, ranging from 52% to 66% [12-14]. (line 114-116, page 5)
Comment #2.2
Page 6 line 126-127, it will be difficult to build a high-quality AI diagnostic model due to lack of uniform diagnostic standard and strict quality control for colposcopy practice. This problem should be the first solved by professional organization or alliance of colposcopy screening or diagnosis. We cannot rely on AI to solve all problems.

Response:
Thank you for the comment. Actually, we have uniform diagnostic standard and strict quality control for colposcopy practice released by the International Federation for Cervical Pathology and Colposcopy (IFCPC), the American Society for Colposcopy and Cervical Pathology (ASCCP), and the Chinese Society for Colposcopy and Cervical Pathology(CSCCP), etc. However, colposcopic practitioners of LMICs due to limited diagnostic ability and lacking of professional training in clinical practice are hard to follow standardized recommendations based on the mentioned official organizations.
We revised the description as below:

Although uniform diagnostic standard and strict quality control for colposcopy practice are released by relevant official organizations, many colposcopic practitioners due to limited diagnostic ability and lacking of professional training from LMICs are hard to follow standardized recommendations to practice colposcopy examination, resulting in discrepant reporting and documentation of colposcopy impressions.(line 127-132, page 6)

Comment #2.3
Page 7, line 150-152, AI interpretation depends on the accuracy of the "gold standard", which is usually based on the CIN diagnosis of the expert colposcopists. If there is high inter- and intra-colposcopists variability in the diagnosis of CIN between expert colposcopists, it will be hard to build a stable and reliable AI guided digital colposcopy model.

Response:
Thank you for the comment. Actually, the gold standard for development and validation of AI guided digital colposcopy is generally based on pathological results which were stable and reliable. Therefore, we can build AI guided digital colposcopy model according to patients’ pathological results as the ground truth.

Comment #2.4
Page 8, line 183-185, Sato's study only achieves an accuracy of 50% for CIN2+ detection. This is a very worrying result. The author should preliminarily summary the reasons for the different accuracy obtained by different AI analysis techniques, so as to clarify the possible risks of applying AI technology to population screening.

Response:
Thank you for the comment. As rightly pointed out the accuracy for CIN2+ was 50% is a very worrying result. we observe that the reason is the relatively small training and validation set (158 patients with 485 images) from the Sato's study, and it is hard to build a robust and accurate AI model. As our article described that development of AI guided digital colposcopy need a large-
scale datasets of annotated colposcopy images by experienced colposcopists in terms of pathological results, we decided to delect this reference of Sato's study.

Comment #2.5
Page 9, line 216-218, at present, AI can analysis of dynamic imaging, so the challenge for AI analysis of dynamic imaging is how to embed the AI interpretation system in the existing image imaging equipment.

Response:
Thank you for the comment. We have added the description as following:
Also, how to embed the AI models in the existing colposcopy imaging equipment becomes the challenge for AI analysis of dynamic imaging.(line 219-221, page 9)

Comment #2.6
Page 10, line 242-244, due to the requirement of large amount of data to develop AI model, in addition to the risk of data privacy disclosure, data sharing could be an equally important solution to the lack of large amount of data.

Response:
Thank you for the comment. We have added the description as following:
Due to the requirement of large amount of data to develop AI model, the risk of data privacy disclosure and data sharing becomes an important concern. (line 244-245, page 10)

Comment #2.7
Page 10, line 247-248, we strongly agree with the author's opinion that the target positioning of AI guided digital colposcopy is to assist colposcopists rather than replace them. Meanwhile, the author should emphasize that colposcopists should not rely on AI guided digital colposcopy, especially for junior colposcopists. Otherwise, junior colposcopists may still have the risk of being replaced. Meanwhile, it should be emphasized that colposcopists should continuously improve their ability from AI-assisted model, and can find the problems in AI interpretation, rather than simply apply the AI-assisted technology.

Response:
Thank you so much for the comment. We revised the description as following:
The AI guided digital colposcopy aims to assist colposcopists rather than replace them. Also, colposcopists should not rely on AI guided digital colposcopy, especially for junior colposcopists. Otherwise, junior colposcopists may still have the risk of being replaced. Meanwhile, colposcopists should continuously improve their ability from AI-assisted model, and could find the problems in AI interpretation, rather than simply apply the AI-assisted technology.(line 251-255, page 11)

Comment #2.8
Page 11, line 269-271, the team of AI guided digital colposcopy should emphasize the communication between colposcopists and AI engineers. Only when colposcopists can find the problems existing in the current AI-assisted model, can they really promote the development of AI guided digital colposcopy.
Response:
Thank you so much for the comment. We revised the description as following:
Also, when colposcopists can find the problems existing in the current AI-assisted model in clinical application, the frequent communication between colposcopists and AI engineers can promote the development of AI guided digital colposcopy.(line 279-282, page 12)