Peer Review File

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Reviewer A

Comment 1: The manuscript is well written and tackles an interesting topic in ophtalmology and digital health. The authors evaluated two different and complementary approaches to diabetic retinopathy screening: a remote evaluation of retina images performed by humans (teleophthalmology) and the advent of AI based grading platform.

Response 1: We want to thank Reviewer A for taking the time to review our manuscript and the excellent suggestions which improved the manuscript by highlighting the newer facets of AI field, such as explainable AI, legal implications, and limitations. Please find the detailed response below regarding the changes that we have made to incorporate all your suggestions. Hopefully, the revised manuscript has provided a clear description about the advances in AI for DR screening for AES readers.

Comment 2: When describing advances and challenges of teleophthalmology (form line 225 to line 248), authors adopted an American-centric perspective that is not applicable to the European context, I would point this as a limitation of the reasoning provided.

Response 2: To address this, we added a sentence at the end of the Advantages and Challenges section on page 6: "*Notably, a limitation of this discussion of advantages and challenges is the reporting of findings within the United States; the field of teleophthalmology in Europe and other countries faces unique challenges that require separate consideration."*

Comment 3: It is not clear whether AI software have been used as a substitute for clinicians, autonomously grading images with no human supervision, or only as a support to clinicians in decision making (a human will always check the outcome of AI). Would appreciate clarification on this and some consideration about the legal aspects associated (medical liability).

Response 3: To address this, we added a section on *Legal Aspects of Remote and Automated Screening.* In this we have two paragraphs, one discussing the advancement of telemedicine law and one about the law surrounding AI, on pages 10 and 11:

An important consideration of advancements in teleophthalmology and artificial intelligence is the ethical and legal impact of new technology and workflow. Government regulations have not kept pace with advances in telemedicine(93), with only limited legislature passed addressing medical licensing, professional liability, accreditation, online prescription, informed consent/data security, and definition of the patient-doctor relationship in telehealth (94,95). For licensure and liability, the Federation of State Medical Boards approved the Interstate Medical Licensure Compact in 2014, which accelerates the licensure process to allow for physicians to provide care in other states(95). For online prescriptions, The Ryan Haight Online Pharmacy Consumer Protection Act of 2008 aims to prevent illegal distribution of medication via the Internet. Data confidentiality continues to be addressed via the Health Insurance Portability and Accountability Act (HIPAA)(96). During the COVID-19 pandemic, additional legislature was put into action - for example The Coronavirus Aid, Relief, and Economic Security (CARES) Act, that promoted the expansion of telemedicine(97). Ongoing global efforts are underway to regulate and standardize telemedicine care.

Despite the promise of AI in improving healthcare, concerns around transparency, misdiagnosis, exacerbation of socioeconomic biases, and patient privacy must be considered. There are limited regulations that address the use of AI in medicine (98). Most regulations exist as drafts, guidelines, or government initiatives. In 2018 the AMA adopted the Augmented Intelligence in Healthcare Policy (H-480.940) to ensure an emphasis on the ethical evolution, education, and of AI in clinical practice(99). This policy is based on two main criteria – first, that AI should be used only as a tool to aid clinical judgement rather than to replace it, and secondly, tool development must have clinically validated and ethically sensitive designs to safeguard patient privacy and safety(100). Additionally, the US Food and Drug Administration has approved AI tools for various clinical uses outside of ophthalmology such as stroke diagnosis, brain MRI interpretation, and atrial fibrillation detection, among other applications(101). The impact or sufficiency of these policies remains unclear.

Comment 4: It would be interesting for the author to mention the recent field of "explainable AI" compared to the "black box" approach as an attempt to overcome concerns over AI use.
Response 4: To address this, we added two sentences about 'explainable AI' on page 9: "*An ongoing effort in the field is 'explainable AI' (XAI) that focuses on increasing the users understanding by offering precise explanations for AI-generated output. By contextualizing the results, XAI provides more transparency and increases the users trust and understanding in the predictions.*"

Reviewer B
Comment 1: Overall, the work is well-written. There are some minor errors in punctuation that need to be fixed.
Response 1: We want to thank Reviewer B for taking the time to review our manuscript and for your recommendations to add a legal section. We agree that this has added a greater depth to the review. The errors in punctuation have been address within the text. Please find the detailed response below regarding the changes that we have made to incorporate all your suggestions. Hopefully, the revised manuscript has provided a clear description about the legal aspects of DR screening for AES readers.

Comment 2: The sentence in page 7 about figure 1 needs to be improved to correlate more with the figure caption (?student).
Response 2: To address this, we added a sentence to where Figure 1 is mentioned on page 5: "*Figure 1 shows a typical fundus camera used for remote screening*."

Comment 3: Recommend to add a section on legal aspects.
Response 3: To address this, we added a section on *Legal Aspects of Remote and Automated Screening.* In this we have two paragraphs, one discussing the advancement of telemedicine law and one about the law surrounding AI, on pages 10 and 11.