

Peer Review File

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Reviewer A

The authors discuss an important paper by Mikhael et al that describes a novel deep learning model that predicts lung cancer risk over 6 years, using a single LDCT scan.

My concerns with this editorial are the following:

1. Line 29: “mortality” is incorrectly used in this sentence.

Response: The comment is resolved by changing “mortality” to “death”.

Action: The manuscript is modified accordingly.

2. Line 35: “low mortality” should be “decreased mortality”. Furthermore, the papers describing the results of reduced mortality observed in the NLST and Nelson trials should be cited.

Response: Thank you. The “low mortality” is changed to “decreased mortality”, as advised by the worthy review.

Action: The manuscript is modified accordingly.

3. Lines 36-38: the USPSTF recommends screening for lung cancer in adults from 50 to 80 years old. There is definitely an age cap for screening. Since there are several guidelines, the one discussed in this editorial should be referenced.

Response: Thank you very much. We have added the reference.

Action: The manuscript is modified accordingly.

4. Line 43: “increase” in what? Increase in lung cancer incidence? Please clarify.

Response: Thank you. The sentence is modified to “With a large increase in cancer among”.

Action: The manuscript is updated.

5. Lines 65-68: the term “feature engineering” should be explained for the reader not familiar with AI as well as why it “has a detrimental impact on models predictive performance”

Response: Thank you. The explanations regarding feature extraction and its importance are added to the revised manuscript.

Action: The manuscript is updated by adding new information.

6. Lines 66-72: The authors make a distinction between “machine learning” and “deep learning models”. These terms indeed represent different things, but not as the authors describe it. Machine learning can use deep learning methods (there are several deep learning type of methods), but also other non-deep learning types of methodologies to achieve the goal of allowing a computer to learn. The authors should therefore not contrast deep learning algorithms to machine learning, because machine learning

includes deep learning, but they should contrast it to a different category of algorithms used in machine learning.

Response: Thank you very much for your valuable suggestions. We have modified the statement as advised by the worthy review.

Action: The manuscript is updated accordingly.

7. Lines 79-80 and line 142: these sentences seem contradictory. In 79-80 it states that the approach used by Michael is one of its kind, while in 142 it talks about Michael's study and other, similar studies. Michael's study is unique in that it predicts lung cancer risk past 1 year, up to 6 years. There are other studies utilizing similar models to that used by Michael et al, but they do not go past the 1 year prediction. Perhaps the authors could clarify their statements a bit so that lines 79-80 and 142 do not seem to contradict each other.

Response: Lines 79-80 are modified to resolve the conflict, as suggested by the worth reviewer.

Action: The manuscript is updated.

8. Line 81: confirm is incorrectly used; it should be replaced with "test".

Response: Thank you. "Confirm" is replaced with "test".

Action: The manuscript is updated.

9. Line 97: "with" should be "within".

Response: Thank you. The "with" is replaced with "within".

Action: The manuscript is updated.

10. Line 118: "desired" should be "required" or "needed"

Response: Thank you. The "desired" is replaced with "needed".

Action: The manuscript is updated.

11. Lines 119-120: "...and do not provide equal spread or thorax". This part of the sentence is not understandable. It should be clarified so that the reader does not have to go to the paper under discussion.

Response: Thank you very much. We have added further details regarding the point raised by the worthy reviewer.

Action: The manuscript is updated by adding new information.

12. Lines 124-125: "... To mitigate such challenges to a greater extent." This part of the sentence is not understandable. Please clarify.

Response: Lines 124-125 are modified and further explanation is added.

Action: The manuscript is updated.

13. Line 131-132: "Validation on two recent datasets indicates hampered performance..." Table 1 of the manuscript by Mikhael et al shows the lung cancer predictions for 1 to 6 years as observed in the NLST data set as well as in the more

recent, independent test data sets from the MGH and the CGMH. The prediction numbers are really not that different between the NLST and the other two test data sets. Therefore, to state that the results (I am assuming?) of these recent data sets indicate a hampered performance seems not correct. Please clarify the statement.

Response: Thank you. The statement has been updated accordingly to avoid the confusion.

Action: The manuscript is updated.

14. Please consider working with a writer/editor to improve the quality of the English of the manuscript.

Response: Thank you very much for your valuable suggestions. English corrections have been performed.

Action: The manuscript is corrected regarding English grammar and typos.

Reviewer B

Ashraf et al. commented upon an impressive paper recently published on the Journal of Clinical Oncology presenting the results of a retrospective study indicating that a deep learning algorithm developed using cases from the NLST is capable to predict LC diagnosis from 1 to 6 years after the assessed LDCT.

Overall, the comment is equilibrated and can be shared. I found only some minor points for which the following suggestions are made.

1. Line 83 page 2. Reading carefully the original paper by Mikhael et al. the contribute of the presence of a nodule in improving the predictive values is apparent. Hence, I suggest to replace “other than” with “beyond lung nodules”.

Response: Thank you very much for your suggestions. We have modified it as suggested.

Action: The manuscript is updated.

2. Line 18 page 2. Please replace “desired” with “needed”.

Response: Thank you. The “desired” is replaced with “needed”.

Action: The manuscript is updated.

3. Line 142 page 2. Please remove “from”.

Response: Thank you. The “from” is removed.

Action: The manuscript is updated.

4. I feel that stating that “the adoption of AI for automated diagnosis and prognosis of LC is the need of the hour” is a bit exaggerated. Please down tune.

Response: Thank you. The sentence is modified as suggested by the worthy reviewer.

Action: The manuscript is updated accordingly.