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Jayashree Kalpathy-Cramer

Editor

PeerJ

Subject: Manuscript article ID: 26404

Dear Jayashree Kalpathy-Cramer and Reviewers

Thank you for the thoughtful and constructive feedback you provided regarding our manuscript article ID: 26404, entitled "Accuracy of deep learning, a machine-learning technology, using ultra–wide-field fundus ophthalmoscopy for detecting idiopathic macular holes."

We are thankful for all your suggestions to improve our paper, and we have revised it accordingly and formatted it to conform to the PeerJ guidelines.

Please find enclosed detailed responses to each one of the reviewers' comments. We have aimed to explain our rationale in each case and hope our modifications and clarifications will render our revised manuscript suitable for publication.

We all agree to the revised version of our manuscript and hereby resubmit it for a secondary evaluation. Thank you once again for your

consideration of our paper.

Sincerely,

Reviewer 1 (Anonymous)

Basic reporting

1. line 61-

Please correct Optus to Optos and rewrite the sentence as “The study dataset included 910 Optos color images obtained at Tsukazaki Hospital (Himeji, Japan) and Tokushima University Hospital (715 normal images and 195 MH images).” because the original one was difficult to read.

Thank you for suggestion, we have changed “The study dataset included 910 Optos color images obtained at the Tsukazaki Hospital (Himeji, Japan) and Tokushima University Hospital (715 normal images and 195 MH images).”

2. line 111, ROV should be ROC.

Thank you for pointing this error out, we have changed “ROV→ROC”

3. line 125-

I don’t know what this sentence meant.

Thank you for pointing this out, we have changed our sentence: “We calculated the correct answer rate, specificity, sensitivity, and response times by CNN and six ophthalmologists were calculated.”

4. line 203

The authors wrote that "If surgical treatment is performed at an appropriate time in MH patients, a good prognosis can be obtained". How the Optos-based telemedicine system is used for the

determination of appropriate timing?

This is an interesting perspective. First of all, we believe that this system can be used in areas without access to an ophthalmologist. There is a potential for diagnoses to be made by optometrists to be able to reach patients in remote resions that might otherwise be missed.

Experimental design

1. As the authors commented, the limitation of this study was the inclusion of only normal and MH eyes.

You have raised an important issue. It is true that we included only normal and macular hole images for this proof-of-concept study, but in the future we want to experiment to assess whether more comprehensive diagnoses can be accomplished as well.

2. line 81-,

When did authors obtain the informed consent from each subject? Were all images used in this study collected for the purpose of this study after obtaining the informed consent from each subject? According to the clinical research ethical guidelines, the researchers can include the existent data after they disclose the research information.

Thank you for observation. We obtained consents forms from patients after explaining the research information to them. This information can be found in the methods section of the revised manuscript.

Validity of the findings

Although I admit the accuracy of the AI, the scores of ophthalmologists for the diagnosis of MH were low, especially the sensitivity. Were those ophthalmologists instructed 1:1 ratio of the normal and the MH image in the data set?

You have raised an important issue. We did not inform the ophthalmologists of the 1:1 ratio, as AI does not know about it either. We think this was a fair experimental setting.

Comments for the Author

1. There are eyes having “pseudo” MH. Please discuss whether the AI can differentiate true and pseudo MH.

Thank you for observation. In this study, we did not investigate the diagnosis of pseudo MH, because the number of cases is considered low, and the condition was not suitable for our deep learning study. We do not know whether the AI can differentiate true and pseudo MH at the moment.

2. The results discourage the "real" ophthalmologists. In addition to the speed, the accuracy of the diagnosis was superior in the AI than in the ophthalmologists. Please discuss the role of the ophthalmologists in the future.

Thank you for your commentary. The six ophthalmologists are in the study were not retinal specialists, and they diagnosed MH only from looking at the Optos images. In the actual clinical practice, ophthalmologist make a more comprehensive diagnosis, their expertise is invaluable, and they will still be needed in the near future.

Reviewer 2 (Anonymous)

Basic reporting

Comments for the Author

1. line 39; the authors emphasize that Optos dose not need mydriasis. In the current study, it is not clear all the Optos images were taken under the condition of non-mydriasis.

Thank you for pointing this out. We have explained that mydriasis is not required to obtain appropriate Optos images in general. However, we did not differentiate images taken under mydriasis in our study because the cases were mixed.

2. line 75; Images from patients, complications, such as vitreous hemorrhage, asteroid hyalosis, 76 intense cataract, and retinal photocoagulation scars, and other conditions, such as fundus diseases, were excluded. Additionally, images with poor clarity were excluded. Moreover, images from patients with stage 1 MHs and those with retinal detachment were excluded. The authors need to describe how many Optus images were excluded from all images.

Thank you for suggestion. During the data collection stage, orthoptists (non-ophthalmologist) excluded images with diabetic retinopathy, glaucoma, dense vitreous hemorrhage, fundus hemorrhage, and strong intrinsic vitreous opacity. We do not have the information on the number of images excluded at that stage. Ophthalmologists conducted the final checks after data collection, and they excluded one image with glaucoma.

3. Table 2; it is unclear what 32:80±7:36 and 13:58:00±3:19:16 actually mean.

Thank you for pointing this out. We have fixed the time unit in our revised version.

4. I am not sure why the authors use Optos to detect MH. OCT should be more accurate, easy, and more common.

We agree that OCT is more accurate, easy, and common. However, the retinal disease does not only involve the macula, peripheral retinal lesions are also important. If diagnosis using Optos and AI can comprehensively enabled in the future, it will lead to an improvement in the diagnosis rate. By examining the macular hole, we proved that it is possible to diagnose macular

disease even with the use of ultra-wide-field fundus ophthalmoscopy.

Reviewer 3 (Anonymous)

Basic reporting

In the table, it is not clear what format and units the time is reported in.

Thank you for pointing this out. We have now added a time unit, and changed “32：80±7:36, 13:58:00±3:19:16” to “32.80±7.36, 838.00±199.16” in the revised manuscript.

The figure legends should allow the figure to be read without referring to the original article – they may need to be made slightly more descriptive.

Thank you for your comments. We have added better descriptions.

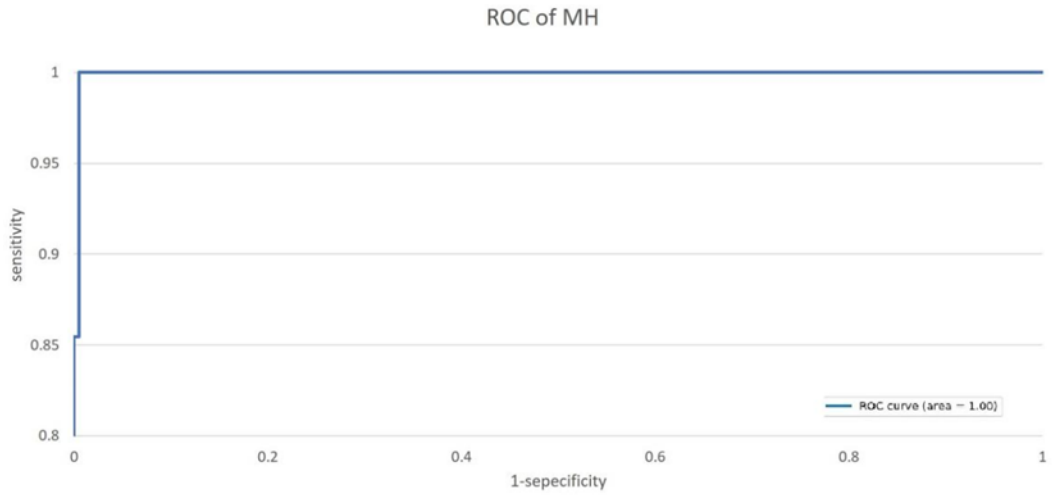
Figure 1: First, each dataset's image was reduced to 256 × 192 and was input into the model. Next, it was passed through all convolution layers and through the entire binding layer, and it was classified into 2 classes.

Figure 2: This is the first one out of 100 ROC curves. The average AUC of 100 ROC curves was almost 1, and all ROC curves were similar.

Figure 3: The dark blue color shows the point where the deep neural network is paying attention on the macula and from the point of view of an ophthalmologist.

I’m not sure ROC curve is necessary or helpful when the AUC is essentially 1.

Thank you for suggestion. Reviewer 4 suggested zooming in on the ROC curve figure, perhaps with the x and y axes at 0.5 or something. We tried, but it was rather confusing.



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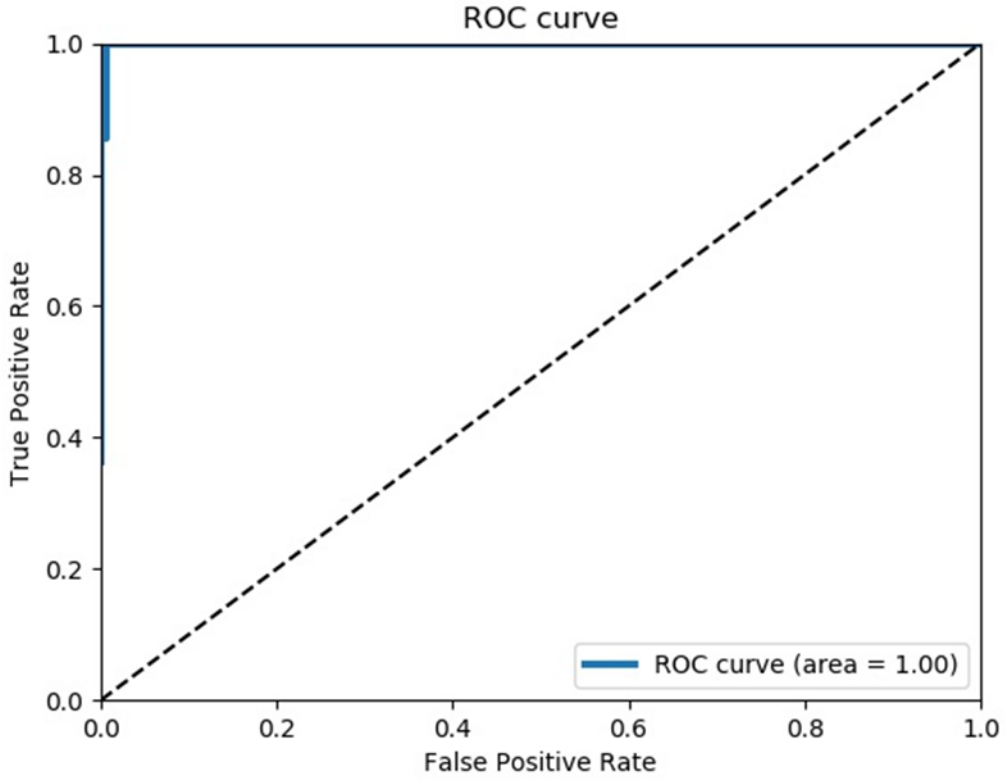


149

150 The image preprocessing is not well described. The images appear to have a circular crop

151 applied to the original image – this should be described.

152 Thank you for your comments. We did not pretreat all the images together. However, as stated,

153 we applied the same treatment to all of them:

→“The image amplification process comprised modifications of contrast adjustment, γ correction, histogram equalization, noise addition, and inversion. We used training on these learning images to train a deep convolutional neural network (CNN) and constructed a deep learning model.”

Was any effort made to center the images, align the disc, or flip left/right eyes to make the images appear similar to the CNN?

We did not attempt to center the images, align the disc, or flip left/right eyes to make the images appear similar to the CNN.

Comments for the Author

From an image processing perspective, assuming a good quality fundus image, the detection of a macular hole (a small dark circle in a larger fairly homogenous image) is not that complicated, and thus it is not surprising the CNN works as well as it does, but the results are nonetheless impressive.

From a clinical utility perspective, it is not clear that this is a solution to an existing clinical problem since macular holes always cause visual loss in the stages included in this study, the rationale for creating a screening program to detect them is less compelling. While perhaps not necessary for publication here, it may strengthen the paper to add some discussion as to how such a program might be used in the real world.

Reviewer 4 (Anonymous)

Basic reporting

Introduction

For me, the intro is far too short and doesn't really describe the problem in enough detail. There is almost no clinical background, and the discussion around deep learning is too brief. I would suggest expanding the Introduction to cover the following topics:

- What is a macular hole? How does it appear in a fundus photo vs. OCT?

Thank you for suggestions. We have limited our description to avoid extensive explanations for specific differences, in ophthalmic specialty fields. "The development of optical coherence tomography (OCT) and image resolution improvements have facilitated the diagnosis of macular diseases."

- What is the prevalence of macular holes? Some statistics might be helpful

Thank you for suggestion. We have now added a sentence to this effect: "The age and gender adjusted annual incidences of primary MH have been reported at 7.9 eyes and 7.4 respectively per 100 000 inhabitants, and the male to female ratio at 1:2.2 (Forsaa et al., 2017)."

- What are the complications associated with MH, if left undiagnosed?

Thank you for question. If the macular hole is not repaired, the visual prognosis is poor. We have not included this in the manuscript because it is obvious in the field of ophthalmology.

- Deep learning is not a machine learning algorithm; it's a sub-field of research within ML

Thank you for pointing this out. We have modified our statement from "a machine learning algorithm" to "a sub-field of machine learning algorithm studies".

- You state that DL is good generally, but you should give details of why DL is a good approach specifically to your problem. Have other methods been tried previously for MH? Are they inadequate?

You have raised an important point. In our previous research we proved that SVM (support vector machine) is inferior to Neural Network (Ohsugi et al., 2017); therefore, this time we did not assess the performance of SVM. Instead, we compared the performance of DL to diagnose

MHs with that of human ophthalmologists.

- Please cite some other recent DL papers in the context of ophthalmology, especially this one: https://www.nature.com/articles/s41551-018-0195-0

Thank you for suggestion. We have now added a citation to reference "(…Ryan et al., 2018)."

Methods

- It probably makes more sense to describe the FC dropout layer in the section "Deep learning model", rather than the "Training…" section.

Thank you for suggestion. We have made these changes to the revised manuscript:
"We performed dropout processing to mask the first total tie layer (FC1), with 50% probability."
"Training the deep convolutional neural network" section to "Deep learning model" section.

- Lines 132-135 do not make sense - please revise these sentences to be more clear

Thank you for observation. We have added "The time required by the ophthalmologists was set as the time taken to complete all answers in the Excel file. The time required for the deep neural network was measured by the internal clock of the computer."

- A citation is needed for the Grad-CAM method on line 141

Thank you for your suggestion. We have now cited a paper "(…Ryan et al., 2018)."

- What cost function did you use? Cross-entropy, or something else?

Thank you for your question. We used binary-cross-entropy.

Results

I am quite confused about the methods on page 9. Specifically, how (or why) is "deep-learning response time" calculated by the ophthalmologists (line 125)? The description on line 132-135

about data entry is also unclear, particularly the sentence: “In deep learning, a series of tasks was performed for all presented numbers as follows…”. My best guess is that the authors are trying to fairly compare the DL computation time with the ophthalmologists’ time taken to record the same information. Please revise this section to be more clear.

Thank you for comment. We have clarified the issue in the revised manuscript “The time required by the ophthalmologists was set as the time taken to complete all answers in the Excel file. The time required for the deep neural network was measured by the internal clock of the computer.”

Regarding the figures, I think there a few things that can be improved:

- In my opinion, the legends are too short. I personally try to provide enough information in the figures so that a reader could get the gist of the whole paper by reading the legends alone.

Thank you for suggestion. We have added more information to the legends for clarity.

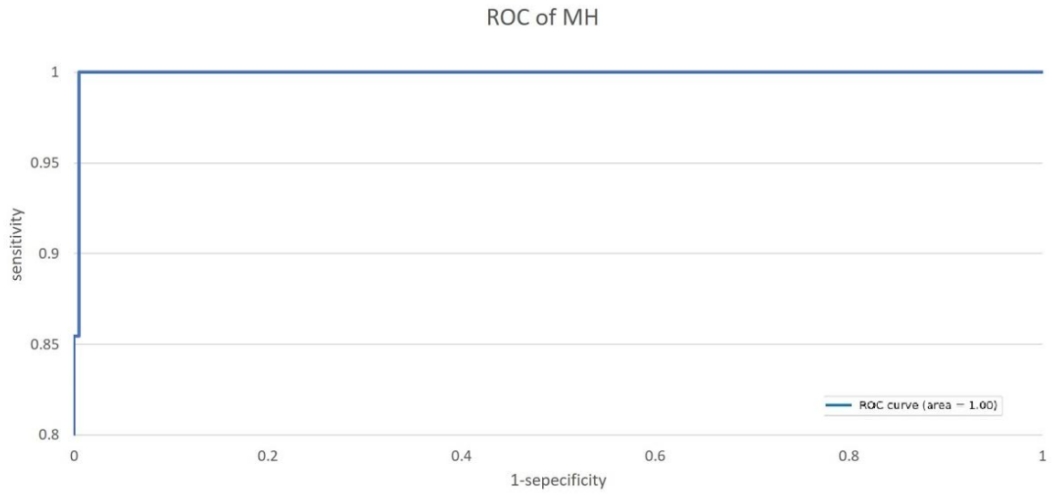
Figure 1: First, each dataset's image was reduced to 256 × 192 and was input into the model. Next, it was passed through all convolution layers and through the entire binding layer, and it was classified into 2 classes.

Figure 2: This is the first one out of 100 ROC curves. The average AUC of 100 ROC curves was almost 1, and all ROC curves were similar.

Figure 3: The dark blue color shows the point where the deep neural network is paying attention on the macula and from the same point of view of an ophthalmologist.

- For Figure 2, I’d suggest zooming in on the ROC curve figure, perhaps with the x and y axes at 0.5 or something. You really can’t make anything out otherwise. I’d suggest also including curves from several runs - perhaps the best, worst and average? It’ll give readers a better sense of the variability.

Thank you for suggestion. We have set the y coordinate to 0.8-1.



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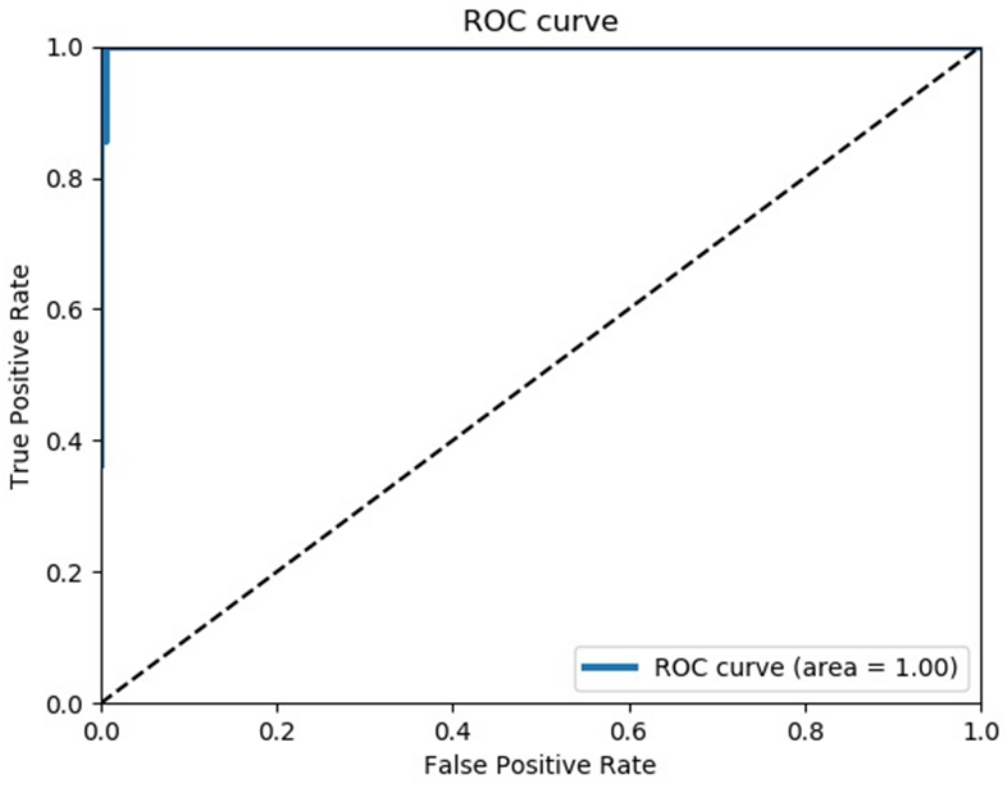

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256 - Figure 3 showing the heat map is not all that informative without a color bar. It also might be

257 useful to include a few examples rather than just one.

258 Thank you. We tried creating a color bar, but it was rather confusing.

259 - Table 2: “Accuracy” is a better term for “correct answer rate”. Also please state the unit of

measurement time.

We have changed the expression “correct answer rate” to “Accuracy” as recommended.

Other points:

- What is the “first” curve? The first experiment you ran? Why not the best curve?

You have raised an important question. The data evaluation was accomplished using 90% of images and excluding 10% randomly in 100 ways; therefore, using the best results introduces arbitrariness, so we chose the first one. However, since the AUC is 0.9993 on average and it is nearly 1, we think that any approach is valid in this specific case.

- On line 162, is this 13 minutes per image?

Thank you for question. We have changed the sentence in the revised manuscript; “Ophthalmologists carried out the test, and the mean (standard deviation) required time was 838.00 seconds (±199.16), the mean (standard deviation) accuracy rate was 80.6% (5.9%), sensitivity was 65.9% (15.7%), and specificity was 95.2% (4.3%). The same test was carried out with the CNN model, and the mean (standard deviation) required time was 32.8 seconds (±7.36), and accuracy rate, sensitivity, and specificity were all 100% (Table 2).”

Conclusions

- There’s no need to repeat that deep learning is an ML technology.

Thank you for suggestion. We have deleted “which is a machine-learning technology.”

- What are you going to do next?

Thank you for suggestion. We have added “Further research with increasing number of sheets, deepening the Layer structure, and using metastasis learning are necessary to confirm our results.”

Grammar, spelling and formatting

Overall the language is very good, though there are a few spelling/grammatical errors:

- Missing space after “macular holes” (line 19)

Thank you for your advice, we changed “macular holes(MHs)” to “macular holes (MHs)”

- Optus → Optos (line 61)

Thank you for your advice, we changed “Optus” to ”Optos.”

- Lots of unnecessary hyphens in the terms deep-learning and machine-learning (line 71, 88 and various other places)

Thank you for your advice, we erased the unnecessary hyphens.

- “...using a CNN” (line 88)

Thank you for your advice, we changed “using CNN” to “using a CNN”

- “The rectified linear unit (ReLU) activation function…” (line 89)

Thank you for your advice, we changed the expression “The activation function rectified linear unit (ReLU)” to“The rectified linear unit (ReLU) activation function”

- What is meant by a ‘tie layer’? Not sure what this means (line 92, 100)

Thank you for your advice, we have modified our sentences;

“two layers of the total tie layer called fully connection layer (FC 1, 2) were arranged” now reads “the two fully connected layers (FC 1, 2) were arranged”.

- “The network weights were optimized using stochastic gradient descent (SGD) with momentum…“ (line 101-102)

Thank you for your advice, we have made the proposed changes.

- ROV → ROC, and various grammatical errors afterward (line 111 onwards)

Thank you for your advice, we have changed “ROV” to “ROC”.

- Background data (line 147)

Thank you for your advice, we have now changed “Backgrounds data” to “Background data.”

- Probably better to describe the eye in terms of left/right or OD/OS (line 148)

Thank you for your advice, we have changed “side” to “left/right.”

- Resions → regions (line 201)

Thank you for your advice, we have changed “Resions” to “regions.”

Experimental design

The research question is not all that well defined in the introduction. Ultimately, the goal was to evaluate the performance of DL algorithm for detecting MH. However, the authors also do a good job of comparing the algorithm to multiple experts; something many papers do not do. I would therefore suggest adding a couple of sentences at the end of the introduction to state that this was also part of the study.

Thank you for your suggestion. We added “Deep neural networks have been used to diagnose skin cancer with as much accuracy as that attained by dermatologists (Esteva et al., 2017). We decided to assess the diagnostic capabilities of deep neural networks for macular holes as compared to ophthalmologists’ diagnoses.”

We changed, “in order to determine the accuracy of deep learning for MHs” to “to determine its accuracy based on the ophthalmologists’ diagnoses as the gold standards”

We added a cited paper;

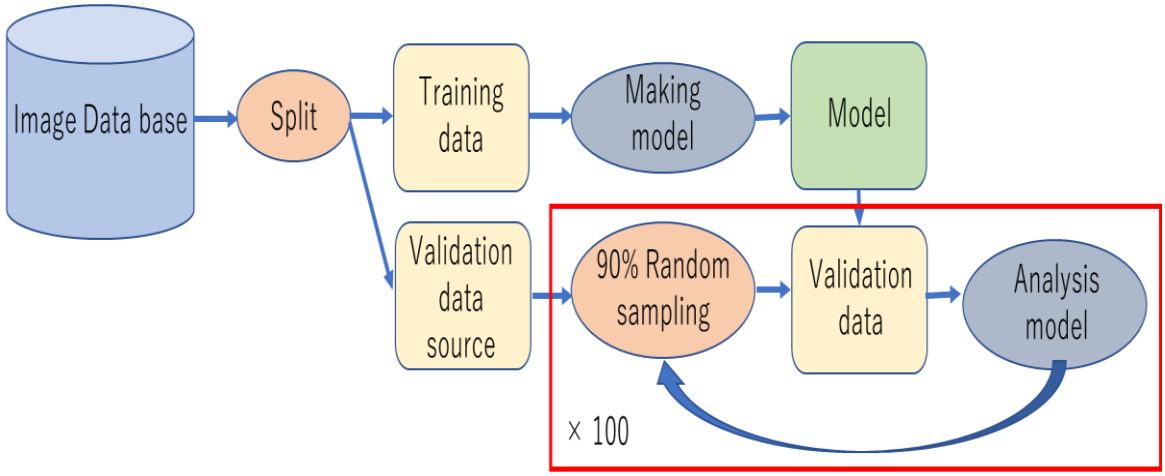
Esteva A, Kuprel B, Novoa RA, Ko J, Swetter SM, Blau HM, Thrun S. (2017) Dermatologist-level classification of skin cancer with deep neural networks. Nature 542:115-118 DOI: 10.1038/nature22985.

My main issue with the overall experimental design relates to how the final model for evaluation was selected. You shouldn’t use test accuracy as the basis, but instead use a validation set. Later, in the “Statistical analysis” section, I don’t really understand the authors’

description of the ROC analysis. I get that there should be one curve per model (100 overall) but I do not understand what is meant by: “We created 100 ROC curves by making 100 patterns, and 10% were thinned out”. Some clarification is needed. The authors also state the model was fitted to only 90% of the test data. Presumably this is an error, and the authors mean training data. This would suggest that the authors did indeed use a 10% validation set, but this is unclear. Please revise this section to better describe how the model was tested and evaluated.

Thank you for providing these thoughtful comments. We can explain better.

First, we divided the image data into 80% of training data and 20% of evaluation data. Next, out of the 20% of the evaluation data, 90% was randomly selected and evaluated in 100 different ways, and 100 ROC curves were derived. Finally, AUC, sensitivity and specificity were calculated for each. We used this method in our past publication (Ohsugi et al., 2017).



Some other points:

- It’s very common to pre-train networks on bigger datasets to boost performance and reduce the time needed to train. Did you try this out?

Thank you for suggestion. We did not try this for our study.

- Images from patients with various complications were excluded. How many? Why?

Thank you for questions. During the data collection stage, orthoptists (non-ophthalmologist) excluded images with diabetic retinopathy, glaucoma, vitreous hemorrhage, fundus hemorrhage, strong intrinsic vitreous opacity. We do not have the information on the number of images excluded at that stage. Ophthalmologists conducted the final checks after data collection, and they excluded one image with glaucoma.

- What was the criteria for “clarity”?

Thank you for your question. We comprehensively diagnosed from medical records and OCT, surgical images, etc.

- What is “stage 1” MH and why are they not included?

Because stage 1 MH has no surgical indications, the number of cases was very small.

- You state that 100 models were trained - what was the variability over the 100 runs?

Thank you for question. We did not train 100 models. After the learning cycle at the time of model adoption, we considered that no significant changes had occurred.

Validity of the findings

As described above, I am concerned about how the final model performance was evaluated. Running the algorithm 100 times and picking the best one based on testing accuracy is cheating a little bit, although it’s not clear from the methods whether this is how it was actually done. Furthermore, given the size of the dataset and near-perfect performance on the test set, I think that cross-validation is necessary to get true sense of algorithm generalizability. I think that given the authors can afford to do 100 repeats on the same data, performing K-fold cross validation should be feasible and would strengthen the reporting.

Thank you for your comments. Please refer to the explanations above.

Given that the authors went to the effort of making an application to capture six experts' gradings, it would be good if the authors could report metrics of interrater agreement (e.g. kappa coefficients). Furthermore, it's important that the authors discuss the limitations of the reference standard used, especially if it was based on the diagnosis of a single grader. This paper gives some good insight into why this is important: https://research.google.com/pubs/pub46802.html

Thank you for providing these insights. The purpose of this study was to examine whether DL can distinguish images with MH defined by a retinal specialist from normal images. From this point of view, we assumed that the physician's diagnoses were reliable in this research. To support this premise, we used the additional data such as OCT results and medical records to ensure accuracy of the diagnoses. We used data from six ophthalmologists because we thought that it was needed more than one to obtain a better estimate of the time required for reading an image, and to obtain ophthalmologists' sensitivity and specificity, etc. Please note that we did use data from six ophthalmologists to examine the consistency of their answers. Because of this, we do not consider the kappa coefficient and coincidence rate of the answers of six ophthalmologists as necessary.

Comments for the Author

Overall, the paper is well written and demonstrates that DL is a powerful approach for classifying MH in wide-angle retinal photographs. The choice of metric is appropriate and the comparison with multiple raters is great to see. Some more background information about MH would be useful for readers outside of the discipline, and would help to contextualize why this work is important.

Ultimately, I am concerned that the results do not reflect the realistic real-world performance

of the proposed method. With further clarification of how the model was tested and evaluated, I think that most of concerns will be addressed. However, I would maintain that cross-validation would be a more appropriate way of assessing the generalizabiltiy of the CNN.